

AHA STATISTICAL UPDATE

2025 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association

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BACKGROUND: The American Heart Association (AHA), in conjunction with the National Institutes of Health, annually reports the most up-to-date statistics related to heart disease, stroke, and cardiovascular risk factors, including core health behaviors (smoking, physical activity, nutrition, sleep, and obesity) and health factors (cholesterol, blood pressure, glucose control, and metabolic syndrome) that contribute to cardiovascular health. The AHA Heart Disease and Stroke Statistical Update presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, brain health, complications of pregnancy, kidney disease, congenital heart disease, rhythm disorders, sudden cardiac arrest, subclinical atherosclerosis, coronary heart disease, cardiomyopathy, heart failure, valvular disease, venous thromboembolism, and peripheral artery disease) and the associated outcomes (including quality of care, procedures, and economic costs).

METHODS: The AHA, through its Epidemiology and Prevention Statistics Committee, continuously monitors and evaluates sources of data on heart disease and stroke in the United States and globally to provide the most current information available in the annual Statistical Update with review of published literature through the year before writing. The 2025 AHA Statistical Update is the product of a full year's worth of effort in 2024 by dedicated volunteer clinicians and scientists, committed government professionals, and AHA staff members. This year's edition includes a continued focus on health equity across several key domains and enhanced global data that reflect improved methods and incorporation of ≈3000 new data sources since last year's Statistical Update.

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

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RESULTS: Each of the chapters in the Statistical Update focuses on a different topic related to heart disease and stroke statistics.

CONCLUSIONS: The Statistical Update represents a critical resource for the lay public, policymakers, media professionals, clinicians, health care administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions.

Key Words: AHA Scientific Statements □ cardiovascular diseases □ epidemiology □ risk factors □ statistics □ stroke

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SUMMARY

Each year, the American Heart Association (AHA), in conjunction with the National Institutes of Health and other government agencies, brings together in a single document the most up-to-date statistics related to HD, stroke, and cardiovascular risk factors in the AHA's Life's

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and includes the CVH framework to incorporate kidney health was developed by the AHA and called CKM health.^{2,3} The CKM syndrome includes stages 0 to 4, which represent the pathophysiological progression from optimal CKM health to prevalent CVD.

The AHA Heart Disease and Stroke Statistical Update represents a critical resource for the lay public, policymakers, media professionals, clinicians, health care administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions. CVD produces immense health and economic burdens in the United States and globally. The Statistical Update also presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, congenital HD, rhythm disorders, subclinical atherosclerosis, CHD, HF, VHD, venous disease, and PAD) and the associated outcomes (including quality of care, procedures, and economic costs).

Each annual version of the Statistical Update undergoes revisions to include the newest nationally and globally representative available data, add additional relevant published scientific findings, remove older information, add new sections or chapters, and increase the number of ways to access and use the assembled information. This year-long process, which begins as soon as the previous Statistical Update is published, is performed by

Outcomes

the

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Figure. AHA's My Life Check–Life's Essential 8.
AHA indicates American Heart Association.

highlights from this year's Statistical Update. Please see each chapter for references for these highlights, CIs for statistics reported, and additional information.

Cardiovascular Health (Chapter 2)

- The AHA Life's Essential 8 scores among NHANES (National Health and Nutrition Examination Survey) 2007 through 2018 participants were significantly associated with the prevalence of CVD. For every increasing 1-SD increment of the AHA Life's Essential 8 score, there was a lower odds of CVD (OR, 0.64).
- CVH score, as measured by the AHA Life's Essential 8, and components were also shown

mortality risk (HRs, 2.3 and 1.45) compared with those who had high AHA Life's Essential 8 scores above the examination median at both examinations 2 and 6.

Smoking/Tobacco Use (Chapter 3)

- The prevalence of cigarette use in the past 30 days among middle and high school students in the United States was 1.1% and 1.9%, respectively, in 2023.
- Although there has been a consistent decline in adult and youth cigarette use in the United States in the past 2 decades, significant disparities persist. In 2023, the prevalence of past 30-day cigarette use was comparable between NH White youths (1.6%) and NH multiracial prevalence of use in the past 30 days among mid- to predict MACEs (first occurrence of IHD, MI, stroke, and HF) within the UK Biobank. Individuals in the lowest quartile (least healthy) compared with the highest quartile (healthiest) had a greater risk for MACEs (HR, 2.07), which was strongest for HF. The authors estimated that a 10-point improvement in the AHA Life's Essential 8 score could have prevented 9.2% of MACEs.
- CVH measured at multiple times across the life course can be used to assess the cumulative exposure to CVH. In the FHS (Framingham Heart Study), participants who maintained a low AHA Life's Essential 8 score (below the median at each examination; AHA Life's Essential 8 scores at examination 2, 69; median at examination 6, 66) scores over an average of 13 years had the highest CVD and

dle and high school students in the United States was 4.6% and 10.0%, respectively, with 89.4% of adolescent users reporting use of flavored products and 25.2% reporting daily use.

Physical Activity and Sedentary Behavior (Chapter 4)

- The percentage of high school students who were physically active for ≥ 60 minutes on all 7 d/wk decreased over the past decade from 28.7% in 2011 to 23.9% in 2021. The percentage of high school students participating in muscle-strengthening activities on ≥ 3 d/wk decreased over the past decade from 55.6% in 2011 to 44.9% in 2021.
- According to the NHIS (National Health Interview Survey), the percentage of adults meeting the aerobic and muscle-strengthening Physical Activity Guidelines for Americans changed little from 2020 to 2022. The percentage reporting engaging in ≥ 150 min/wk of moderate-intensity aerobic activity, 75 min/wk of vigorous aerobic activity, or an equivalent combination was 47.9% in 2020 and 48.1% in 2022. The percentage reporting engaging in muscle-strengthening activities of at least moderate intensity and including all major muscle groups ≥ 2 d/wk was 31.9% in 2020 and 31.5% in 2022. The percentage of adults meeting both aerobic PA and muscle-strengthening guidelines was 25.2% in 2020 and 25.3% in 2022. It is important to note that each of these population prevalence estimates

remains below the goals set 2030.

- In the PROPASS consortium Activity, Sitting, and Sleep), a cross-sectional mated that replacing less sedentary time, standing, and 4 to 12 min/d of moderate- to PA was associated with

health benefits. For example, the minimum reallocation associated with a statistically significant reduction in body mass index was replacing 7 min/d of sedentary behavior with moderate to vigorous PA. In addition, replacing 4 min/d of light-intensity PA with moderate- to vigorous-intensity PA was associated with a significantly lower hemoglobin A1c.

Nutrition (Chapter 5)

- The evidence for benefits of healthful diet patterns on a range of cardiometabolic and other disease outcomes is strong. The core elements of a healthy dietary pattern are (1) vegetables of all types; (2) fruits, especially whole fruits; (3) grains, of which at least half are whole grains; (4) dairy, including fat-free or low-fat milk, yogurt, and cheese or lactose-free versions and fortified soy beverages and yogurt as alternatives; (5) protein foods, including lean meats, poultry and eggs, seafood, beans, peas, lentils, nuts, seeds, and soy products; and (6) oils, including vegetable oils and oils in food such as seafood and nuts. A healthy dietary pattern is also limited in foods and beverages high in added sugars, saturated fat, sodium, and alcoholic beverages. • Most of the American population does not consume a healthy dietary pattern, as measured by the Healthy

below prices seen in January fresh vegetables increased by 2024 but was almost 1% in January 2023, at which elevated after a peak in in the first quarter of each experience a seasonal peak fresh vegetables are 2024 (prediction interval,

Eating Index, which is a measure of diet quality and compliance with the Dietary Guidelines for Americans. Although average diet quality has slightly improved in the past 10 years, the current average score is 59 (on a scale from 0–100).

Differences in overall Healthy Eating Index scores are observed across subgroups characterized by age, sex, race and ethnicity, income, pregnancy status, and lactation status.

- Social and environmental factors observed to be associated with diet quality include education, income, race and ethnicity, neighborhood availability of supermarkets, and cost of food. The US Department of Agriculture reported that food-at-home prices will increase by 2.9% (prediction interval, 0.5%–5.3%) in 2024. This is a deceleration relative to the reported increase of 8.6% (prediction interval, 5.6%–11.8%) in 2023. The retail price of eggs increased 1.8% in January 2024, after an increase of 8.9% in December 2023, albeit 28.6%

Overweight and Obesity (Chapter 6)

- According to US data from 2017 to 2020, the prevalence of obesity in adults was 41.8% for males and 41.8% for females; among youths 2 to 19 years of age, the prevalence of obesity was 20.9% for males and 18.5% for females.
- In 2022, all US states had an obesity prevalence >20%, 22 states had an obesity prevalence between 30% and 35%, 19 states had a prevalence of 35% to 40%, and 3 states had a prevalence of ≥40%.
- In 2022, it was estimated that among adults ≥18 years of age globally, 16% (890 million) were obese and 43% adults (2.5 billion) were overweight.

High Blood Cholesterol and Other Lipids (Chapter 7)

- Elevated lipoprotein(a), which is defined as ≥125 nmol/L or ≥50 mg/dL and is present in up to 20% of the population, is associated with increased risk of a range of CVD conditions. Recent recommendations call for measuring lipoprotein(a) at least once in every adult, although screening rates remain low in US adults.
- Among US adults with severe dyslipidemia (low-density lipoprotein cholesterol ≥190 mg/dL), 78.0% reported cholesterol evaluation in the preceding 5 years, with no significant change in screening rates between 2011 to 2012 and 2017 to March 2020. • The landmark CLEAR outcomes trial (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) testing bempedoic acid versus placebo among statin-intolerant patients showed an overall 13% relative risk reduction in the primary end point; however, recent analyses among the primary prevention patient subgroup showed a 30% relative risk reduction.

High Blood Pressure (Chapter 8)

- In 2022, the prevalence of high BP in US adults was highest in Mississippi (40.2%) and lowest in Colorado (24.6%). The prevalence of hypertension increases with age and was 28.5% among those 20 to 44 years of age, 58.6% among those 45 to 64

years of age, and 76.5% among those ≥ 65 years of age.

- A systematic review and meta-analysis of 136 studies with 28 612 children and young adults (4 and 25 years of age) showed that the prevalence of masked hypertension was 10.4%.
- A reanalysis from the Spanish Ambulatory Blood Pressure Registry with 10-year follow-up data reported that 24-hour systolic BP was more strongly associated with all-cause mortality (HR, 1.41 per 1-SD increment), which remained robust after adjustment for clinic BP. Elevated all-cause mortality risk was also reported with masked hypertension (HR, 1.24) but not with white-coat hypertension.

Diabetes (Chapter 9)

- CVDs remain the leading causes of death in individuals with diabetes.
- Composite risk factor control in those with diabetes remains suboptimal, with $\leq 20\%$ at recommended levels of hemoglobin A1c, BP, and lipids.
- In a meta-analysis of 45 cohort studies, a systolic BP of ≥ 140 mm Hg (but not ≥ 130 mm Hg) compared with below this number was associated with a greater risk of cardiovascular outcomes (HR, 1.56). The risk was greater for each 10-mm Hg increment in systolic BP (HR, 1.10).

present in 17.35%, 5.45%, and 1.80%, respectively, and risk factors and subclinical CKM (stages 1–3) were present in 80.94%, 85.95%,

Adverse Pregnancy Outcomes (Chapter 11)

- The US national prevalence of gestational diabetes was 8.3% in 2021, an increase of 38% from 2016 according to birth data from the National Vital Statistics System.⁴ Rates of gestational diabetes rose steadily with maternal age: In 2021, the rate for mothers ≥ 40 years of age was almost 6 times higher compared with that for mothers < 20 years of

Metabolic Syndrome (Chapter 10)

- A meta-analysis including 28 193 768 participants showed that the global metabolic syndrome prevalence varied from 12.5% to 31.4% according to the definition considered. The prevalence was significantly higher in the Eastern Mediterranean region and Americas compared with other global regions and was directly related to the country's level of income.
- In the United States, according to data from NHANES 2001 to 2020, the prevalence of metabolic syndrome among youths 12 to 18 years of age was 3.73% for Hispanic youths, 1.58% for NH Black youths, and 2.78% for NH White youths. In 2017 to 2018, Mexican American adults generally

- Among 51 685 525 live births between 2007 and 2019, age-standardized hypertensive disorders of pregnancy rates doubled (38.4 to 77.8 per 1000 live births). An inflection point was observed in 2014, with an acceleration in the rate of increase of hypertensive disorders of pregnancy (from +4.1%/y before 2014 to +9.1%/y after 2014).
Rates of preterm delivery and low birth weight increased significantly when co-occurring in the same pregnancy with hypertensive disorders of pregnancy. Absolute rates of adverse pregnancy outcomes were higher in NH Black individuals and in older age groups. However, similar relative increases were seen across all age and racial and ethnic groups.
- A meta-analysis of 20 studies up to 2019 showed the effectiveness of lifestyle intervention and bariatric surgery on reduced risk of hypertensive disorders of pregnancy (OR, 0.45), gestational hypertension (OR, 0.61), and preeclampsia (OR, 0.67).

Kidney Disease (Chapter 12)

- In 2021, the age-, race-, and sex-adjusted prevalence of ESKD in the United States was 2219 per million people, a decrease of 3.5% from its peak in 2019. The overall prevalence count increased slightly from 807 920 in 2020 to 808 536 in 2021, after having almost doubled from 409 226 in 2001 to 806 939 in 2019.
had the highest prevalence of metabolic syndrome at 52.2%, followed by NH Black adults (47.6%), Asian/other adults and multirace adults (46.7%), NH White adults (46.6%) and other Hispanic adults

- The adjusted ESKD incidence decreased in all racial and ethnic groups from 2001 to 2019. After 2019, ESKD incidence increased among Black (45.9%).
- CKM syndrome was defined as a health disorder attributable to connections among obesity, diabetes, chronic kidney disease, and CVD, including individuals but not among members of other race HF, AF, CHD, stroke, and PAD. In the NHANES 2011 to 2018 database, among individuals 20 to 44, 45 to 64, and ≥ 65 years of age, stage 0 CKM was

and ethnicity groups. In 2021, the incidence of ESKD among Black individuals was 3.8 times the incidence of NH White individuals; the incidence among Native American individuals was 2.3 times as high, and it was twice as high among Hispanic individuals.

- There is a strong and consistent reduced estimated glomerular higher urine albuminuria range with incident and tion of estimated glomerular urine albumin-to-creatinine prediction of CVD beyond and they are included in the Association Predicting Risk of tion. Furthermore, in an

from 35 cohorts, inclusion of estimated glomerular filtration rate and albuminuria significantly improved prediction for CVD mortality beyond the Systematic Coronary Risk Evaluation and atherosclerotic CVD beyond the Pooled Cohort Equations in validation datasets (ΔC statistic, 0.027 and 0.010) and categorical net reclassification improvement (0.080 and 0.056, respectively).

Sleep (Chapter 13)

- Females have ≈ 1.5 to 2.3 higher odds of reporting insomnia symptoms than males.
- Risks of developing obstructive sleep apnea and reporting a sleep disorder are lower in

(HR, 0.82), which held true for except subarachnoid

- Among 6214 participants in the ELSA (English dataset, over 8 years of good sleep quality, poor associated with long-term Worsened sleep quality was risk among those with good mediate (HR, 2.15) sleep individuals who consume a healthy diet.
- Obstructive sleep apnea severity is associated with higher odds of white matter hyperintensities (mild: OR, 1.70; moderate to severe: OR, 3.9; severe: OR, 4.3).

Total Cardiovascular Diseases (Chapter 14)

- According to national data, 39.5% of deaths in 2022 attributable to CVD in the United States were

quality was associated with decreased stroke risk among those with poor sleep quality (HR, 0.31).

Brain Health (Chapter 16)

- Young-onset dementia, defined as symptoms before 65 years of age, was estimated in a meta-analysis to have a prevalence globally of 1.1 per 100 000 at 30 to 34 years of age, 1.0 per 100 000 at 35 to 39 years of age, 3.8 per 100 000 at 40 to 44 years of age, 6.3 per 100 000 at 45 to 49 years of age, 10.0 per 100 000 at 50 to 54 years of age, 19.2 per 100 000 at 55 to 59 years of age, and 77.4 per 100 000 at 60 to 64 years of age, although data for some age groups were limited in lower- and middle-income countries.
- In a nationally representative cohort study of US veterans (N=1 869 090; individuals ≥55 years of age receiving care in the Veterans Healthcare System between 1999 and 2019), there were significant differences in the incidence of dementia by race and ethnicity. The age-adjusted incidence of dementia was higher among underrepresented racial and ethnic groups than White racial and ethnic groups: 14.2 per 1000 person-years in American Indian or Alaska Native participants, 12.4 in Asian participants, 19.4 in Puerto Rico (1.8%) and South Dakota (2.1%) and the highest prevalence in Arkansas (4.8%).
- In 2022, the age-adjusted mortality rate attributable to CVD in the United States was 224.3 per 100 000. The highest rate was in NH Black males (379.7 per 100 000), and the lowest rate was in NH Asian females (104.9 per 100 000).
- A population-based cohort study from Ontario, Canada, followed up 9.2 million adults for a median of 15 years (2003–2018) and observed 280 197 incident stroke or transient ischemic attack events. Women had an overall lower adjusted hazard of stroke or transient ischemic attack than men.

Stroke (Cerebrovascular Diseases) (Chapter 15)

- According to BRFSS (Behavioral Risk Factor Surveillance System) 2022 data, stroke prevalence in adults was 3.4% (median) in the United States, with the lowest prevalence in

in Black participants, and 20.7 in Hispanic participants compared with 11.5 in White participants.

- Among 316 669 participants in the UK Biobank with 4238 incident cases of all-cause dementia (mean, 56 years of age) over a median 12.6 years of follow-up, an optimal AHA Life's Essential 8 score (score, 80–100 on a 100-point scale) was associated with a 14% lower risk of incident all-cause dementia (HR, 0.86) and 30% lower risk of vascular dementia (HR, 0.70) compared with a poor AHA Life's Essential 8 score (score of 0–49).

Congenital Cardiovascular Defects and Kawasaki Disease (Chapter 17)

- Novel technology such as remote cardiac monitoring during the interstage might help to reduce disparities in outcome. Among families from low, mid, and high socioeconomic groups enrolled in a Cardiac High Acuity Monitoring Program, survival

was no different among the highest- and mid-socioeconomic status groups (mortality OR, 0.997; and OR 1.7, respectively).

- Gaps in care are common among youths with congenital cardiovascular defects. According to results from a single-center study, roughly one-third of youths with congenital cardiovascular defects experience a >3-year gap in clinical care. Factors associated with gaps in clinical care include 14 to 29 years of age (OR, 1.20), Black race (OR, 1.50), a distance of >150 miles from the hospital (OR, 1.81), mother's education of high school or less (OR, 1.17), and low neighborhood-level opportunity (eg, high deprivation; OR, 1.22).
- Risk of multisystem inflammatory syndrome in children is higher in children who have not been vaccinated. The pooled OR for multisystem inflammatory syndrome in children in vaccinated

Disorders of Heart Rhythm (Chapter 18)

- A nationwide, time-stratified case-crossover study using air pollution data from 322 cities in China observed an increased incidence of symptomatic AF and supraventricular tachycardia in the 24 hours after higher pollutant exposure. The change in the odds of onset of symptomatic AF associated with a 10- $\mu\text{g}/\text{m}^3$ (1 mg/m^3 for carbon monoxide) increase in air pollutant concentrations during lag 0 to 24 hours was 0.6% for fine particulate matter <2.5- μm diameter, 1.6% for NO_2 , and 5.7% for carbon monoxide.
- An analysis of the UK Biobank (N=201 856) combined dietary recall of fruit juice and soft drink consumption with the polygenic risk score for AF developed in the cohort. Over a median of 9.9

avoidance of 12 236 strokes with a gain of 59 577 quality-adjusted life-years (0.02 per patient) over the

Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies (Chapter 19)

- Cardiac arrest secondary to poisoning/overdose continues to rise with a recent study from Sweden highlighting the international concern about polysubstance use as a rising cause of cause of out-of-hospital cardiac arrest. In this recent study, 5.2% of out-of-hospital cardiac arrests were secondary to poisoning primarily secondary to polysubstance use. • Studies continue to show worse outcomes for individuals with lower socioeconomic at-risk individuals and communities internationally. years of follow-up, consumption of >2 L/wk of sugar-sweetened beverages and artificially sweetened beverages was associated with increased risk of AF in multivariable-adjusted analyses including demographic, social, clinical, and genetic risk factors (HR, 1.10 and 1.20, respectively) compared with nonconsumption of sugar-sweetened beverages or artificially sweetened beverages. Consumption of >2 L/wk of fruit juice was not associated with increased risk of AF (HR, 1.05) compared with nonconsumption. However, consumption of ≤ 1 L/wk of fruit juice was associated with reduced risk of AF (HR, 0.92) compared with nonconsumption.
- In Canada's single-payer health care environment, screening for AF with a single-lead ECG was determined to improve health outcomes and cost savings. A model indicated that screening 2 929 301 individuals identified 127 670 cases of AF and estimated

ally. A recent study showed worse outcomes on all reportable measures for Black individuals with out-of-hospital cardiac arrest, including survival to hospital discharge (OR, 0.81), return of spontaneous circulation (OR, 0.79), and good neurological outcomes (OR, 0.80).

- Data from Get With The Guidelines–Resuscitation have shown a modest improvement in survival in pre-COVID-19 data. Results indicated that both return of spontaneous circulation (unadjusted rate, 55.0%–65.4%; aOR per year, 1.04) and survival to hospital discharge (unadjusted rate, 16.7%–20.5%; aOR per year, 1.03) improved in an analysis of in-hospital cardiac arrest from 2006 through 2018.

Subclinical Atherosclerosis (Chapter 20)

- In a harmonized data set analysis of 19 725 Black individuals and White individuals 30 to 45 years of age from CARDIA (Coronary Artery Risk Development in Young Adults), the CAC Consortium (Coronary Artery Calcium), and the Walter Reed Cohort, the prevalence of CAC >0 among White males, Black males, White females, and Black females was 26%, 16%, 10%, and 7%, respectively. In an analysis of 4511 participants without known coronary artery disease who were compared with 438 individuals with a prior atherosclerotic CVD event in the CONFIRM international registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry), there was a similar MACE rate of ≈53 per 1000 patient-years for individuals with CAC >300 and those with a history of atherosclerotic CVD. Over a median of 4 years of follow-up, there was a similar

cumulative incidence of
CAC >300 or a prior
($P=0.329$).

- Compared with traditional risk for CVD ($C=0.756$) and CHD the most by the addition of $C=0.776$; CHD: $C=0.784$;

Coronary Heart Disease, Syndrome, and Angina

- An analysis of data on 17 266 adults with a history of CHD from NHIS 2006 to 2015, the prevalence of premature CHD (<65 years of age for females and <55 years of age for males) was higher among Asian Indian adults (aOR, 1.77) and other Asian adults (aOR, 1.68) than White adults.
- In a study of the 2010 to 2019 National Readmission Database, among 592 015 thirty-day readmissions and 787 008 ninety-day readmissions after index acute MI hospitalization, 30-day and 90-day all-cause readmission rates after acute MI decreased from

Venous Thromboembolism Thrombosis and Pulmonary Venous Insufficiency, (Chapter 24)

- In 2021, there were an of pulmonary embolism. ≈756 vein thrombosis, and ≈1 280 thromboembolism cases in inpatient settings. Moreover, 2011 and 2018 involving 12.8% to 11.6% ($P=0.0001$) and 20.6% to 18.8% ($P=0.0001$), respectively.
- In a meta-analysis of 4 retrospective, nonrandomized, observational cohort studies among 184 951 patients ≥18 years of age diagnosed with non-ST-segment-elevation MI, early treatment (administered within 24 hours) with β -blockers was associated with a significant reduction in in-hospital mortality compared with no β -blocker treatment

thromboembolism diagnosis observed that 37.6% of all patients were treated as outpatients.

- Data from Pulmonary Embolism Response Team Consortium Registry revealed a mortality rate of 20.6% in high-risk patients and 3.7% in intermediate-risk patients. Among the high-risk individuals, in-hospital mortality rate was 42.1% for those admitted with a catastrophic pulmonary embolism.
- Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research revealed a progressive increase in pulmonary hypertension-related mortality from 2003 to 2020.

The age-standardized mortality rate per 1 000 000 patient-years rose from 17.81 in 2003 to 23.89 in 2020, driven by a pronounced increase in deaths in pulmonary hypertension groups 2 through 5.

Peripheral Artery Disease and Aortic Diseases (Chapter 25)

- The prevalence of PAD in the United States is (OR, 0.43).

increasing and was estimated at >12.4 million

Cardiomyopathy and Heart Failure (Chapter 22)

- According to recent Global Burden of Disease 2021 estimates, the prevalence of cardiomyopathy or myocarditis was 5.26 million and that of HF was 55.50 million.
- In the United States, 6.7 million people (2.3%) lived with HF in 2017 to 2020, and 87 941 people died of HF in 2022.
- Treatments that improve survival are underused in HF, and age- and population-adjusted

mortality in the United States has continued to rise over time, reaching 21.0 per 100 000 people in 2022.

Valvular Diseases (Chapter 23)

- The global prevalence of nonrheumatic VHD in 2021 was 28.4 million.

- Social determinants of health, including low socio-economic status and living in rural communities, are associated with worse outcomes for patients with PAD. For example, lower socioeconomic status (defined as living in a ZIP code with a median household income <\$40 000) was associated with greater risk for amputation (HR, 1.12).
- PAD was the underlying cause of death for 11 596 individuals in 2022.

Quality of Care (Chapter 26)

- Among 237 549 survivors of acute MI in the US Nationwide Readmissions Database, sex differences in HF hospitalization risk were explored. In a propensity-matched time-to-event analysis, females had a 13% higher risk of 6-month HF readmission compared with males (6.4% versus 5.8%; HR, 1.13).
 - Globally, the prevalence of nonrheumatic calcific aortic valve disease was 13.32 million in 2021.
 - In 2021, there were 40 000 nonrheumatic degenerative mitral valve deaths globally.

- A multicenter, nationwide cross-sectional analysis of Medicare claims data (2012–2018) examined receipt of TAVR among beneficiaries of

fee-for-service Medicare who were ≥ 66 years of age living in the 25 largest metropolitan core-based statistical areas. When analyzed by ZIP code, every 1-unit increase in the Distressed Communities Index score was associated with 0.4% fewer TAVR procedures performed per 100 000 Medicare beneficiaries.

- Recent work within a large US registry demonstrated that Black individuals and Hispanic individuals were 27% less likely to receive bystander cardiopulmonary resuscitation at home (38.5%) than White individuals (47.4%; aOR, 0.74) and 37% less likely to receive bystander cardiopulmonary resuscitation in public locations than White individuals (45.6% versus 60.0%; aOR, 0.63).
nic composition of the location of the arrest.

and globally to provide the most current information available in the Statistical Update. The 2025 Statistical Update is the product of a full year's worth of effort by dedicated volunteer clinicians and scientists, committed government professionals, and AHA staff members, without whom publication of this valuable resource would be impossible. Their contributions are gratefully acknowledged.

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Medical Procedures (Chapter 27)

- Percutaneous coronary intervention was the most common cardiovascular procedure in the United States from 2016 to 2021, followed by angioplasty and related vessel procedures (endovascular, excluding carotid) and saphenous vein harvest and other therapeutic vessel removal.
- In 2019, TAVR volumes (n=72 991) exceeded the volumes for all forms of SAVR (n=57 626). Patients undergoing TAVR in 2019 had a median of 80 years of age (interquartile range, 73–85 years of age) compared with 84 years of age (interquartile range, 78–88 years of age) in the initial years after US Food

and Drug Administration approval of TAVR. • In 2023, 4545 heart transplantations were performed in the United States, the most ever.

Economic Cost of Cardiovascular Disease (Chapter 28)

- The average annual direct and indirect costs of CVD in the United States were an estimated \$417.9 billion in 2020 to 2021.
- The estimated direct costs of CVD in the United States increased from \$189.7 billion in 2012 to 2013 to \$233.3 billion in 2020 to 2021.
- Direct costs of hypertension by percentage of event type were largest for prescription medicines (30%) and office-based events (30%).

ARTICLE INFORMATION

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; the US Department of Health and Human Services; or the US Department of Veterans Affairs.

The AHA makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Conclusions

The AHA, through its Epidemiology and Prevention Statistics Committee, continuously monitors and

Anokhi Dahya, Olivia Larkins, Kathie Thomas, Holly Picotte, Tian Jiang, Chandler Beon, Haoyun Hong, Sophia Zhong, and Shen Li from the AHA Data Science

evaluates sources of data on HD and stroke in the United States

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

REFERENCES

1. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhanc-ing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078

2. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, Coresh J, Mathew RO, Baker-Smith CM, Carnethon MR, et al; on behalf of the American Heart Association. Cardiovascular-kidney-

[published correction appears in *Circulation*. 2024;149:e1023]. *Circulation*. 2023;148:1606–1635. doi: 10.1161/CIR.0000000000001184

3. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, Coresh J, Baker-Smith CM, Carnethon MR, Despres JP, et al; on behalf of the American Heart Association. A synopsis of the evi- dence for the science and clinical management of cardiovascular- kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation*. 2023;148:1636–1664. doi: 10.1161/CIR.0000000000001186

4. QuickStats: percentage of mothers with gestational diabetes, by

ABBREVIATIONS TABLE

[Click here to return to the Table of Contents](#)

4D	Die Deutsche Diabetes Dialyze Studie	ADRD	Alzheimer disease
AAA	abdominal aortic aneurysm	ADVANCE	Action in Diabetes and Cardiovascular Control Controlled Evaluation
AAMR	age-adjusted mortality rate	AF	atrial fibrillation or a
AASM	American Academy of Sleep Medicine	AFFINITY	Assessment of Fluid
ABC-ACS	Age-Related Biomarkers, Clinical History, Acute Coronary Syndrome Score		Age, Gene/Environment
ABI	ankle-brachial index		American Heart Ass
ACC	AIM-HIGH		Alternative Healthy
ACCORD	American College of Cardiology		apnea-hypopnea in
ACE	Action to Control Cardiovascular Risk in Diabetes		apnea-hypopnea in
ACR	alRR		adjusted hazard rat
ACS	angiotensin-converting enzyme		Adventist Health St
ACT	AIS		Atherosclerosis In
ACTION	albumin-to-creatinine ratio		HDL/High Triglycer
AD	ALL HAT		
	acute coronary syndrome		acute ischemic stro
	Adult Changes in Thought		Antihypertensive an
	Acute Coronary Treatment and Intervention Outcomes Network		Attack Trial
	ANGEL-		acute myocardial in
	ASPECT		Endovascular Thera
			Occlusive Patients

ANP	atrial natriuretic peptide
aOR	adjusted odds ratio
AP	angina pectoris
APACE	Advantageous Predictors of Acute Coronary Syndromes Evaluation
APO	adverse pregnancy outcome
app	application
ARB	angiotensin receptor blocker
ARGEN- IAM-ST	Pilot Study on ST Elevation Acute Myocardial Infarction
ARIC	Atherosclerosis Risk in Communities
ARIC-NCS	Atherosclerosis Risk in Communities–Neurocognitive Study
ARIC-PET	Atherosclerosis Risk in Communities–Positron Emission Tomography
aRR	adjusted relative risk
ARVC	arrhythmogenic right ventricular cardiomyopathy
ASB	artificially sweetened beverage
ASCOD	atherosclerosis, small vessel disease, cardiac pathology, other causes, dissection
ASCVD	atherosclerotic cardiovascular disease
ASCVD-PCE	Atherosclerotic Cardiovascular Disease Pooled Cohort Equation
ASD	atrial septal defect
ASPECTS	Alberta Stroke Program Early CT Score
ASPIRE	Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre Registry
ASPREE	Aspirin in Reducing Events in the Elderly
ATP III	Adult Treatment Panel III
ATTENTION	Endovascular Treatment for Acute Basilar-Artery Occlusion
AUC	area under the curve
AVAIL	Adherence Evaluation After Ischemic Stroke Longitudinal
AVATAR	Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis
AWHS	Aragon Workers Health Study
AXADIA– AFNET 8	Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease
BAOCHE	Basilar Artery Occlusion Chinese Endovascular
BASIC	Brain Attack Surveillance in Corpus Christi
BASICS	Basilar Artery International Cooperation Study
BEST	Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease

BEST	Acute Basilar Artery Occlusion: Endovascular	CHOICE-MI
BEST-CLI	Best Surgical Therapy in Patients With Chronic	CHS
BEST-MSU	BEnefits of Stroke Treatment Delivered Using a Mobile Stroke	CI
BiomarCaRE	Biomarker for Cardiovascular Risk	CKD
BMI	body mass index	CKiD
BNP	B-type natriuretic peptide	CKM
BP	blood pressure	CLARIFY
B_PROUD	Berlin PREhospitaL Or Usual Delivery of Acute Stroke Care	CLEAR
BRAVO	Building, Relating, Assessing, and	CLEAR Outcomes
BRFSS	Behavioral Risk Factor Surveillance	CLTI
BWHS	Black Women's Health Study	CNSR
CABANA	Catheter Ablation vs Antiarrhythmic Drug Therapy	COAPT
CABG	coronary artery bypass graft	COAST
CAC	coronary artery calcification	COMBINE-AF
CAD	coronary artery disease	COMPASS
CAIDE	Cardiovascular Risk Factors, Aging	CONFIRM
CARDIA	Coronary Artery Risk Development	CORAL
CARDIo-GRAM-plusC4D	Coronary Artery Disease Genome Wide Replication and Meta-Analysis Plus Coronary Artery	CORE- Thailand
CARES	Cardiac Arrest Registry to Enhance	COSMIC
CARPREG	Cardiac Disease in Pregnancy	COVID-19
CASCADE	Cascade Screening for Awareness	CPAP
CASI	Cognitive Abilities Screening	CPR
CASQ2	calsequestrin 2	CPVT
CAVIAAR	Conservation Aortique Valvulaire dans les Insuffisances Aortiques	CrCI
CCD	congenital cardiovascular defect	CRCS-K-NIH
CCTA	coronary computed tomography	CREOLE
CDC	Centers for Disease Control and	CRIC
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for	CRP
CERAD-TS	Consortium to Establish a Registry for Alzheimer's	CSA
CGPS	Copenhagen General Population	CSPPT
CHA2DS2-VASc	clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes, and sex (1 point each); age ≥75 years and stroke/transient ischemic	CT
CHAP	Chicago Health and Aging Project	CTEPH
CHARGE-AF	Cohorts for Heart and Aging Research in Genomic	CVD
CHARLS	China Health and Retirement	CVD PRE-DICT
CHARM	Candesartan in Heart Failure—Assessment of Reduction in	CVH
CHD	coronary heart disease	CVI
		DALY
		DANISH

DASH	Dietary Approaches	FAST-MAG	Field Administration of Stroke Therapy
DBP	diastolic blood pressure	FDA	US Food and Drug Administration
DCCT/EDIC	Diabetes Control and Trial/Epidemiology	FDRS	Framingham Dementia Risk Score
DCM	dilated cardiomyopathy	FH	familial hypercholesterolemia
DEBATS	Discussion on the Benefits	FHS	Framingham Heart Study
DHA	docosahexaenoic acid	FIDELIO-DKD	Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic
DIAL2	DIABetes Lifetime perspective	FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and
DIAMANTE	Diabetes Meta-Analysis Trans-Ethnic Association	FinnDiane	Finnish Diabetic Nephropathy
DII	Dietary Inflammatory Index	FINRISK	Finnish Population Survey on Risk Factors for Chronic, Noncommunicable Diseases
DNA	deoxyribonucleic acid	FIT	Henry Ford Exercise Testing Project
DOAC	direct oral anticoagulant	FOURIER	Further Cardiovascular Outcomes Res With PCSK9 Inhibition in Subjects With
DPP	Diabetes Prevention Program	FPG	fasting plasma glucose
DREAM-LDL	Diabetes (Fasting Blood Level), Rating (National Health Stroke Scale), Education, Age, Blood	FPL	federal poverty level
DR's EXTRA	Dose Responses to Exercise Training	FRS	Framingham Risk Score
DVT	deep vein thrombosis	FVE	factor V Leiden
EAGLES	Study Evaluating the Efficacy of Varenicline Bupropion for Smoking	GARFIELD-VTE	Global Anticoagulant Registry in the Field–Venous Thromboembolism
e-cigarette	electronic cigarette	GBD	Global Burden of Diseases, Injuries, and
ECG	electrocardiogram	G-CHF	Global Congestive Heart Failure
ED	emergency department	GCKNSS	Greater Cincinnati/Northern Kentucky
EDIC	Epidemiology of Diabetes Intervention	GDMT	guideline-directed medical therapy
EF	ejection fraction	GDP	gross domestic product
EFFECTS	Efficacy of Fluoxetine Randomized Controlled	GLORIA-AF	Global Registry on Long-Term Oral Antithrombotic Treatment in Patients
eGFR	estimated glomerular filtration rate	GLP1-RA	glucagon-like peptide 1 receptor agonist
ELSA	English Longitudinal Study of Ageing	GRACE	Global Registry of Acute Coronary Events
EMS	emergency medical services	GRS	genetic risk score
EPA	eicosapentaenoic acid	GWAS	genome-wide association studies
EPIC	European Prospective Investigation Into Cancer	GWTC	Get With The Guidelines
EQ-5D-5L	European Quality of Life	GWTC-AFIB	Get With The Guidelines–Atrial Fibrillation
ERICA	Study of Cardiovascular	GWTC-R	Get With the Guidelines-Resuscitation
ERP	early repolarization pattern	HANDLS	Health Aging in Neighborhoods of Diversity Across the Life Span
ESC-HFA EORP	European Society of Cardiology Heart Failure Association	HAPIEE	Health, Alcohol and Psychosocial Factors in Eastern Europe
ESKD	end-stage kidney disease	HAPPO	Hyperglycemia and Adverse Pregnancy
EUCLID	Examining Use of Ticagrelor in PAD	HARMS2-AF	hypertension, age, raised body mass index, male sex, sleep apnea, smoking
EVEREST	Endovascular Valve	HbA1c	hemoglobin A1c (glycosylated total
EVITA	Evaluation of Varenicline Smoking Cessation	HBP	high blood pressure
EVT	endovascular thrombectomy	HCHS/SOL	Hispanic Community Health Study/Study
EXAMINE	Examination of Cardiovascular Outcomes With Alcohol	HCM	hypertrophic cardiomyopathy
FAMILIA	Family-Based Approach to Minority Communities	HCUP	Healthcare Cost and Utilization Project
		HD	heart disease
		HDL	high-density lipoprotein
		HDL-C	high-density lipoprotein cholesterol
		HDP	hypertensive disorders of pregnancy

HeartScore	Heart Strategies Concentrating on	IRR
HEI	Healthy Eating Index	ISCHEMIA
HELENA	Healthy Lifestyle in Europe by	
HF	heart failure	IVIG
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of	JHS
HFpEF	heart failure with preserved ejection	KD
HFREF	heart failure with reduced ejection	KFRT
High-STEACS	High-Sensitivity Troponin in the Evaluation of Patients With	KHANDLE
HIV	human immunodeficiency virus	Kuakini HHP
HLHS	hypoplastic left-heart syndrome	LA
HPFS	Health Professionals Follow-Up	LAO
HPS	Heart Protection Study	LASI
HR	hazard ratio	LBW
HRRP	Hospital Readmissions Reduction	LDL
HRS	Health and Retirement Study	LDL-C
HUNT	Trøndelag Health Study	LEAD
HYVET	Hypertension in the Very Elderly	LEADER
i3C	International Childhood	LIBRA
ICD	implantable cardioverter defibrillator	LODESTAR
ICD	<i>International Classification of</i>	
ICD-9	<i>International Classification of</i>	Look AHEAD
ICD-9-CM	<i>International Classification of Diseases, 9th Revision, Clinical</i>	LOOP
ICD-10	<i>International Classification of</i>	LQTS
ICD-10-CM	<i>International Classification of Diseases, 10th Revision, Clinical</i>	LTPA
ICH	intracerebral hemorrhage	LV
ICU	intensive care unit	LVAD
ICU-RESUS	ICU Resuscitation Project	LVEF
IDF	International Diabetes Federation	LVH
IE	infective endocarditis	MACE
IE After TAVI	Infective Endocarditis After Transcatheter Aortic Valve	MAP
IHCA	in-hospital cardiac arrest	MAPT
IHD	ischemic heart disease	MASALA
IHM	interstage home monitoring program	MASLD
ILCOR	International Liaison Committee on	MCI
IMPROVE	Carotid Intima–Media Thickness (IMT) and IMT Progression as Predictors of	MDCS
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy	MEPS
IMT	intima-media thickness	MESA
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory	MET
IPPIC	International Prediction of	MetS
IPSS	International Pediatric Stroke Study	MHAS
IQ	intelligence quotient	MI
IRAD	International Registry of Acute	MIDA
		MIDUS
		MIMS
		MIND-China
		MIS-C

MITRA-FR	Percutaneous Rep MitraClip Device fo	ODYSSEY Outcomes	Evaluation of Cardiovascular Outcome After an Acute Coronary Syndrome Du
MMSE	Mini-Mental State Exam	Offspring	Offspring Study of Racial and Ethnic Disparities in Alzheimer Disease
MoCA	Montreal Cognitive Assessment	OHCA	out-of-hospital cardiac arrest
MONICA	Monitoring Trends Determinants of Ca	ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial and to Telmisartan
MR	mitral regurgitation	OPACH	Objective Physical Activity and Cardiovascular Health in Older Women
MRI	magnetic resonance imaging	OR	odds ratio
mRS	modified Rankin Scale	ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
MSU	mobile stroke unit	ORION-1	Trial to Evaluate the Effect of ALN-PC: Treatment on Low Density Lipoprotein
MTF	Monitoring the Future	ORION-3	An Extension Trial of Inclisiran in Participants With Cardiovascular
MUSIC	Muerte Súbita en Ir	ORION-9	Trial to Evaluate the Effect of Inclisiran Treatment on Low-Density Lipoprotein Cholesterol (LDL-C) in Subjects With
MVP	Million Veterans Program	ORION-10	Inclisiran for Participants With Atherosclerotic Cardio-vascular Disease and Elevated Low-Density Lipoprotein
NACC	National Alzheimer	ORION-11	Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-Density Lipoprotein Cholesterol
NAFLD	nonalcoholic fatty liver disease	OSA	obstructive sleep apnea
NAMCS	National Ambulator	OVER	Open Versus Endovascular Repair
NCDR	National Cardiovas	PA	physical activity
NCHS	National Center for Health Statistics	PACE	Impact of Right Ventricular Pacing in F
neuro-COVID-19	neurological disorders associated with COVID-19	PAD	peripheral artery disease
NFHS-4	National Family Health Survey	PAF	population attributable fraction
NH	non-Hispanic	PAGE	Placental Abruption Genetic Epidemiology
NHAMCS	National Hospital A	PAH	pulmonary arterial hypertension
NHANES	National Health and	PAPE	Peruvian Abruptio Placentae Epidemiology
NHATS	National Health and	PAR	population attributable risk
NHDS	National Hospital Discharge Survey	PARADIGM	Progression of Atherosclerotic Plaque Determined by Computed Tomographi
NHIRD	National Health Ins	PARTNER	Placement of Aortic Transcatheter Valve
NHIS	National Health Interview Survey	PATH	Population Assessment of Tobacco an
NHLBI	National Heart, Lur	PE	Pooled Cohort Equations
NIH	National Institutes of Health	PCI	percutaneous coronary intervention
NIH-AARP	National Institutes of American Associat	PCP	proprotein convertase subtilisin/kexin type 9
NIHSS	National Institutes of	PE	pulmonary embolism
NINDS	National Institutes of	PESA	Progression of Early Subclinical
NIS	National (Nationwid	PH	pulmonary hypertension
NNT	number needed to treat	PHIRST	Pulmonary Arterial Hypertension and Response to Tadalafil Study
NOMAS	Northern Manhattan Study	PINNACLE	Practice Innovation and Clinical Excellence
NOTION	Nordic Aortic Valve Intervention	PLATO	A Comparison of Ticagrelor [AZD6140] Clopidogrel in Patients With Acute Cor
NRI	net reclassification improvement	PME3	fine particulate matter <2.5-µm diameter
NSDUH	National Survey on	POISE	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
NSHDS	Northern Sweden H		
NSTEMI	non-ST-segment		
NT-proBNP	N-terminal pro-B-ty		
nuMoM2b	Nulliparous Pregnant Outcomes Study: N		
nuMoM2b-HHS	Nulliparous Pregnant Outcomes Study: N		
NVSS	National Vital Statistics System		
NYTS	National Youth Tobacco Survey		
OBSERVANT-II	Observational Study of TAVI With New C		

PORTRAIT	Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease:	RE-SPECT ESUS
POUNDS	Preventing Overweight Using Novel	
POUNDS Lost	Toward Precision Weight-Loss Dietary Interventions: Findings	RIVANA
PPCM	peripartum cardiomyopathy	ROSC
PPSW	Prospective Population Study of	RR
PQSI	Pittsburgh Sleep Quality Index	RV
PR	prevalence ratio	RYR2
PRECOMBAT	Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using	S.AGES
PREDIMED	Prevención con Dieta Mediterránea	SADHS
PreDIVA	Prevention of Dementia by Intensive	SAFEHEART
PREMIER	Lifestyle Interventions for Blood	SAGE
PREVEND	Prevention of Renal and Vascular	SAH
PREVENT	American Heart Association Predicting Risk of CVD Events	SARS-CoV-2
ProDiGY	Progress in Diabetes Genetics in	SAVR
PROFESS	Prevention Regimen for Effectively Avoiding Second	SBP
PROGRESS	Perindopril Protection Against	SCA
PROMINENT	Pemafibrate to Reduce Cardiovascular Outcomes by	SCAPIS
PROPASS	Prospective Physical Activity,	SCD
PRS	polygenic risk score	SCORE
PTB	preterm birth	SCORE2
<i>P</i> trend	<i>P</i> for trend	SD
PTS	postthrombotic syndrome	SDB
PUFA	polyunsaturated fatty acid	SDI
PURE	Prospective Urban Rural	SE
PWV	pulse-wave velocity	SEARCH
PY	person-years	SELECT
QALY	quality-adjusted life-year	SELECT-2
QTc	corrected QT interval	SEMI-COVID-19
RACECAT	Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With	SES
RCT	randomized controlled trial	SFA
REDINSCOR	Red Española de Insuficiencia	SGA
REGARDS	Reasons for Geographic and Racial	SGLT-2
RENAL-AF	Renal Hemodialysis Patients Allocated Apixaban Versus	SHEP
RENIS-T6	Renal Iohexol Clearance Survey in	SHIP
REPLACE	Riociguat Replacing PDE5i Therapy Evaluated Against	SHIP AHOY
RESCUE Japan-LIMIT	Recovery by Endovascular Salvage for Cerebral	SHS
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease	SILVER-AMI
		SMARRT
		SMD
		SNAC-K
		SND

SNP	single-nucleotide polymorphism	top-down	Treatment Options for Type 2 Diabetes in Adolescents and Youth
SpecTRA	Spectrometry for T Ischemic Attack Risk	TOF	tetralogy of Fallot
SPHERE	Stroke Prevention With Hydroxyurea Enabled	T1D Exchange Clinic Registry	Type 1 Diabetes Exchange Clinic Registry
SPIN	Stroke Prevention in Niger	TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone
SPRINT	Systolic Blood Pressure	TOPMed	Trans-Omics for Precision Medicine
SPRINT MIND	Systolic Blood Pressure Intervention Trial Mind	tPA	tissue-type plasminogen activator
SPS3	Secondary Prevention	TRILUMINATE Pivotal	Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System
SSB	sugar-sweetened beverage	TRIUMPH	Treprostinil Sodium Inhalation Used in Management of Pulmonary Arterial
STABILITY	Stabilization of Atherosclerotic Plaque by Initiation	TVT	transcatheter valve therapy
START	South Asian Birth Cohort	TyG	Triglyceride-glucose
STEMI	ST-segment-elevation	UDS	Uniform Data Set
STEP	Semaglutide Treatment	UI	uncertainty interval
STEP 1	Research Study Involving Well Semaglutide V	UK	United Kingdom
STEP-HFpEF	Effect of Semaglutide Weekly on Function in Subjects With Ob	UNICEF	United Nations Children's Fund
STOP-COVID	Study of the Treatment Outcomes in Critic	USRDS	US Renal Data System
STROKE-AF	Rate of Atrial Fibrillation Months in Patient	VF	ventricular fibrillation
STROKE-STOP	Systematic ECG Screening for Atrial Fibrillation Among Old Subjects in the	VHD	valvular heart disease
STS	Society of Thoracic Surgeons	VIPS	Vascular Effects of Infection in Pediatric
SUN	Seguimiento Universidad de Navarra	VISP	Vitamin Intervention for Stroke Prevention
SURMOUNT-1	Efficacy and Safety of Once Weekly Versus Participants Who A	VITAL	Vitamin D and Omega-3 Trial
SURTAVI	Surgical Replacement Transcatheter Aortic	VITAL-HF	Vitamin D and Omega-3 Trial–Heart Failure
SVT	supraventricular tachycardia	Vmax	aortic valve peak jet velocity
SWAN	Study of Women's	VOYAGER	Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization
Swiss TAVI	Swiss Transcatheter	VSD	ventricular septal defect
SYNTAX	Synergy Between F	VTA	ventricular tachycardia
SYST-EUR	Systolic Hypertension in Europe trial	VTE	venous thromboembolism
TAA	thoracic aortic aneurysm	WATCH-TAVR	WATCHMAN for Patients With Atrial Fibrillation Undergoing TAVR
TAVI	transcatheter aortic	WC	waist circumference
TAVR	transcatheter aortic	WHI	Women's Health Initiative
TC	total cholesterol	WHICAP	Washington Heights-Hamilton Heights-Inwood Community Aging
TdP	torsade de pointes	WHO	World Health Organization
TEER	transcatheter-edge-to-edge repair	WHS	Women's Health Study
TGA	transposition of the great arteries	WIC	Special Supplemental Nutrition Program for Women, Infants, and Children
TGF	transforming growth factor	WMD	weighted mean difference
TIA	transient ischemic attack	WMH	white matter hyperintensity
TICS	Telephone Interview	WPW	Wolff-Parkinson-White
TIMI	Thrombolysis in Myocardial Infarction	YLD	years of life lived with disability or injury
TIPS-3	International Polycap Study 3	YLL	years of life lost to premature mortality
TOAST	Trial of ORG 10172	Young ESUS	Young Embolic Stroke of Undetermined
		YRBS	Youth Risk Behavior Survey

2025

1. ABOUT THESE STATISTICS

[Click here to return to the Table of Contents](#)

[Click here to return to the Abbreviations](#)

The AHA works with the NHLBI of the NIH to derive the annual statistics in the AHA Statistical Update. This chapter describes the most important sources and the types of data used from them. For more details, see Chapter 30 of this document, the Glossary.

The surveys and data sources used are the following:

- ARIC—CHD and HF incidence rates
- BRFSS—ongoing telephone health survey system
- CARES—OHCA
 - GBD—global disease prevalence, mortality, and healthy life expectancy
 - GCNKSS—stroke incidence rates and outcomes within a biracial population
- GWTG—quality information for AF, CAD, HF, resuscitation, and stroke
- HCUP—inpatient discharges and procedures
- MEPS—data on specific health services that Americans use, how frequently they use them, the cost of these services, and how the costs are paid
- NAMCS—physician office visits
- NHANES—disease and risk factor prevalence and nutrition statistics
- NHIS—disease and risk factor prevalence
- NVSS—mortality for the United States
- USRDS—kidney disease prevalence
- WHO—mortality rates by country
- YRBS—health-risk behaviors in youth and young adults

NHIS because in Questionnaire: hypertension is views: and an cluding MI, AP, A maior present the latest the United States tions to provide a mates based on on data collected to census population sible trends in based on lection period by estimates. prevalence rates different years. In the 2025 on health equity estimates are nrovided when view surveys that provide estimates of the prevalence of diseases and risk factors. In this Statistical Update, the health interview part of the NHANES is used for the prevalence of CVDs. NHANES is used more than the

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths,

Disease Prevalence

Prevalence is an estimate of how many people have a condition at a given point or period in time. The CDC/ NCHS conducts health examination and health inter-

Risk Factor Prevalence

The NHANES 2017 to 2020 data are used in the 2025 Statistical Update to present estimates of the percent-age of people with high LDL-C, high TC, elevated triglyc-erides, low HDL-C, hypertension, overweight, obesity, and diabetes. BRFSS 2022 and NHIS 2022 data are used for the prevalence of sleep issues. The NHIS 2021 data, BRFSS 2022, and NYTS 2022 are used for the prevalence of cigarette smoking. The prevalence of PA is obtained from the National Survey of Children’s Health 2022, YRBS 2021, and NHIS 2022.

Incidence and Recurrent Events

An incidence rate refers to the number of new cases of a disease that develop in a population per unit of time. The unit of time for incidence is not necessarily 1 year, although incidence is often discussed in terms of 1 year. For some statistics, new and recurrent events or cases are combined. Our national incidence esti-mates for the various types of CVD are extrapolations to the US population from the FHS, the ARIC study, and the CHS, all conducted by the NHLBI, as well as the GCNKSS, which is funded by the NINDS. The rates change only when new data are available; they are

not
Native American patients, White females).
computed annually.

As the AHA continues its focus on health equity to address
racism, we are working to reconcile language used in previously published data
sources and studies when this information is compiled in the annual Statistical Update. We
strive to use terms from the original data sources or published

Mortality

studies (mostly from the past 5 years) that may not be as inclusive as the
terms used in 2025. As style guidelines for scientific writing evolve, they will
serve as guidance for data sources and publications and how
they are cited in future Statistical Updates.

Mortality data are generally presented according to the underlying cause of death. “Any-mention” mortality means that the condition was nominally selected as the

underlying cause or was otherwise mentioned on the death certificate. For many deaths classified as attributable to CVD, selection of the single most likely underlying cause can be difficult when several major comorbidities are present, as is often the case in the elderly population. Therefore, it is useful to know the extent of mortality at underlying cause or a contributing cause (ie, the “any-mention” status). The number of deaths in 2022 with any mention of specific causes of death was tabulated by the NHLBI from the NCHS public-use electronic files on mortality.

The first set of statistics for each disease in the 2025 Statistical Update include the number of deaths for which the disease is the underlying cause. Three exceptions are Chapter 8 (High Blood Pressure), Chapter 19 (Sudden Cardiac Arrest), and Chapter 22 (Cardiomyopathy and Heart Failure). HBP, or hypertension, increases the mortality risks of CVD and other diseases, and HF should be selected as an underlying cause only hypertension, SCA, and HF death rates are presented in 2 ways: (1) as nominally classified as the underlying cause and (2) as any-mention mortality.

National and state mortality data presented according to the underlying cause of death were obtained from the CDC WONDER website or the CDC NVSS mortality file.^{1,2} Any-mention numbers of deaths were tabulated from the CDC WONDER website or CDC NVSS mortality file.^{1,2}

Population Estimates

In this publication, we have used national population estimates from the US Census Bureau³ for 2020 in the computation of morbidity data. CDC/NCHS population estimates for 2022 were used in the computation of death rate data. The Census Bureau

the HCUP 2021 National Emergency Department Sample. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *ICD-9* to *ICD-10*. This should be kept in mind because coding changes could affect some statistics,

International Classification of Diseases

Morbidity (illness) and mortality (death) data in the United States have a standard classification system: the *ICD*. Approximately every 10 to 20 years, the *ICD* codes are revised to reflect changes over time in medical technology, diagnosis, or terminology. If necessary for comparability of mortality trends across *ICD-9* and *ICD-10*, comparability ratios computed by the CDC/NCHS are applied as noted.⁴ Effective with mortality data for 1999, *ICD-10* is used.⁵ Beginning in 2016, *ICD-10-CM* is used for

website contains these data, as well as information on the file layout.

Hospital Discharges and Ambulatory Care Visits

Estimates of the numbers of hospital discharges and numbers of procedures performed are for inpatients discharged from short-stay hospitals. Discharges include those discharged alive, dead, or with unknown status. Unless otherwise specified, discharges are listed according to the principal (first-listed) diagnosis, and procedures are listed according to all-listed procedures (principal and secondary). These estimates are from the HCUP 2021 NIS. Ambulatory care visit data include patient visits to primary health care professionals' offices and EDs. Ambulatory care visit data reflect the primary (first-listed) diagnosis. Primary health care professional office visit estimates are from the NAMCS

Age Adjustment

Prevalence and mortality estimates for the United States or individual states comparing demographic groups or estimates over time are either age specific or age ad-justed to the year 2000 standard population by the direct method.⁶ International mortality data from the WHO in Chapter 14 (Total Cardiovascular Diseases) are age ad-justed to the European standard population. Unless oth-erwise stated, all death rates in this publication are age adjusted and are deaths per 100 000 population.

Data Years for National Estimates

In the 2025 Statistical Update, we estimate the an-nual number of new (incidence) and recurrent cases of a disease in the United States by extrapolating to the US population in 2014 from rates reported in a community- or hospital-based study or multiple studies. Age-adjusted incidence rates by sex and race are also given in this report as observed in the study or studies. For US mortality, most numbers and rates are for 2022. For disease and risk factor prevalence, most rates in this report are calculated from NHANES 2017 to 2020. Be-cause NHANES is conducted only in the noninstitution-alized population, we extrapolated the rates to the total US resident population on July 1, 2020, recognizing that this probably underestimates the total prevalence given the relatively high prevalence in the institutionalized population. The numbers of hospital inpatient discharg-es for the United States are for 2021. The numbers of visits to primary health care professionals' offices are for 2019. Except as noted, economic cost estimates are for 2019 of the CDC/NCHS. 2020 to 2021. ED visit estimates are

Cardiovascular Disease

For data on hospitalizations, sional office visits, and mortality, according to *ICD* codes given in Cardiovascular Diseases) of the definition includes all diseases of Unless otherwise specified, not include congenital CVD. cludes people with hypertension

which was co-led by the American Study of Liver Diseases. It was NAFLD carries multiple limitations, potentially stigmatizing language, ture of the diagnosis, and the lack root cause of the condition. limitations and is the preferred forward.

Race and Ethnicity

Data published by governmental agencies for some racial and ethnic groups are considered unreliable because of the small sample size in the studies. Because we try to provide data for as many racial and ethnic groups as possible, we show these data for informational and comparative purposes.

Global Burden of Disease

The AHA collaborates with the Institute for Health Metrics and Evaluation to report statistics for the AHA Statistical Update from the GBD. This is an ongoing global effort to quantify health loss from hundreds of causes and risks from 1990 to the present for all countries. GBD produces consistent and comparable estimates of population health over time and across locations, including summary metrics such as DALYs and healthy life expectancy. Results are made available to policymakers, researchers, governments, and the public with the over-arching goals of improving population health and reducing health disparities.

The 2025 AHA Statistical Update uses GBD estimates that were produced for 1990 to 2021 for 204 countries and territories and stratified by age and sex.^{7–9} These estimates reflect improvements in

Genetics

demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. PAH has been added to the GBD study as a cause of disease burden. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in results across GBD cycles for both the most recent and earlier years.

For more information about the GBD and to access GBD resources, data visualizations, and most recent publications, please visit the study website.¹⁰

The 2025 Statistical Update includes additional global and regional CVD statistics.

Liver Disease Terminology

Beginning in the 2025 Statistical Update, MASLD is used instead of NAFLD. This updated terminology is consistent with the global Delphi consensus statement,¹¹

Genetic studies are reported in many chapters of the Statistical Update and are useful in identifying CVD heritability, risk factors, diagnoses, therapeutic targets, and patterns among high-risk groups. However, the current literature predominantly reflects data from White European populations, which constitute nearly 80% of genetic studies despite making up only 16% of the global population.¹² Moreover, studies done among underrepresented racial and ethnic populations consist largely of individuals of East Asian ancestry, with individuals of African, Latin American, and Indigenous ancestry less represented.¹³ Data-sharing limitations attributable to privacy issues and identification risk also affect the availability of diverse genetic datasets.¹⁴ The underrepresentation of diverse racial and ethnic groups within genetic and genomics research¹⁵ underscores a critical gap that warrants consideration when reviewing the Statistical Update.

Gender Identity/Sex

The Statistical Update recognizes the important differences between sex and gender identity. The authors therefore use the following definitions, based on statements of the AHA and National Academies,^{16,17} to distinguish sex and gender. Sex is used to describe the biological characteristics determined by chromosomes, gonads, sex hormones, or genitals and categorized as male or female. Gender is recognized as a multidimensional construct that may have cultural, social, and linguistic dimensions and reflects an inner sense of being such as being a girl/woman, a boy/man, a combination of girl/woman and boy/man, or something else or having no gender at all. Historically, the terms sex, male, and female have been used throughout the Statistical Update for consistency and because most studies have assessed sex as opposed to gender. Recognizing the need to evolve in our approach, beginning in 2025, the Statistical Update reports gender when collected specifically by studies and when self-identified individually by study participants. The writing group acknowledges that the terms sex and gender are commonly used interchangeably in the referenced literature, and the terminology in a primary publication may not accurately reflect the important distinction between sex and gender. In the Statistical

Update, we strive to use language that reflects our interpretation of the underlying study methodology and is attentive to the fundamental differences between these 2 terms. When explicit language to indicate evaluation of gender methodology is not reported, we presume that the authors intended the biological variable of sex and use that term consistently in the Statistical Update.

Contacts

If you have questions about statistics or any points made in this Statistical Update, please contact the AHA Na-tional Center, Office of Science, Medicine and Health. Direct all media inquiries to News Media Relations at .

7. GBD Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2024;403:2100–2132.

doi: 10.1016/S0140-6736(24)00367-2

8. GBD Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational 2024;403:2133–2161. doi: 10.1016/S0140-6736(24)00757-8

9. GBD Risk Factors Collaborators. Global burden and strength of

The AHA works diligently to ensure that the Statistical Update is error free. If we discover errors after publication, we will provide corrections at and in the journal *Circulation*.

11. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP, et al; NAFDL Nomenclature Consensus Group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023;79:1542–1556. doi: 10.1016/j.jhep.2023.06.003

12. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet*. 2019;51:584–591. doi: 10.1038/s41588-019-0379-x

13. Popejoy AB, Fullerton SM. Genomics is failing on diversity. *Nature*. 2016;538:161–164. doi: 10.1038/538161a

14. Sollis E, Mosaku A, Abid A, Buniello A, Cerezo M, Gil L, Groza T, Gunes O, Hall P, Hayhurst J, et al. The NHGRI-EBI GWAS Catalog: knowledgebase and deposition resource. *Nucleic Acids Res*. 2023;51:D977–D985. doi: 10.1093/nar/gkac1010

15. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.

16. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.

17. US Census Bureau. US Census Bureau population estimates: historical data: 2000s. Accessed May 29, 2024.

REFERENCES

15. Mudd-Martin G, Cirino AL, Barcelona V, Fox K, Hudson M, Sun YV, Taylor JY, Cameron VA; on behalf of the American Heart Association Council on Genomic and Precision Medicine; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Considerations for cardiovascular genetic and genomic research with marginalized racial and ethnic groups and indigenous peoples: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2021;14:e000084. doi: 10.1161/CIRCGEN.120.000084. Accessed May 29, 2024.
4. Anderson RN, Minino AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. *Natl Vital Stat Rep*. 2001;49:1–32.
6. Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. *Natl Vital Stat Rep*. 1998;47:1–16, 20.
5. Centers for Disease Control and Prevention and National Center for Health Statistics. ICD-10-CM official guidelines for coding and report-

10.1161/HCG.0000000000000084

16. Caceres BA, Streed CG Jr, Corliss HL, Lloyd-Jones DM, Matthews PA, Mukherjee M, Poteat T, Rosendale N, Ross LM; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Hypertension; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Stroke Council. Assessing and addressing cardiovascular health in LGBTQ adults: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e321–e332. doi: 10.1161/CIR.0000000000000914
17. Becker T, Chin M, Bates N, eds. *Measuring Sex, Gender Identity, and Sexual Orientation*. National Academies Press; 2022.

2. CARDIOVASCULAR

*See Tables 2-1 through 2-10 and
through 2-8*

[Click here to return to the Table](#)

[Click here to return to the](#)

In 2010, the AHA released its
cluded 2 objectives that would
ities over the next decade: “by
of all Americans by 20%, while
CVDs and stroke by 20%.”¹ The
roduced in this goal and
(Life’s Simple 7) that include
ity, PA, smoking) and health
BMI, BP, blood glucose). For an
CVH overall, they must not have
and also have optimal levels of all

including not smoking, a healthy diet pattern,
sufficient PA, normal body weight, and normal levels
of TC, BP, and FPG in the absence of medication
treatment.

To update the construct of CVH metrics on the
basis of extensive evidence and insights
accumulated over the decade after introduction of
Life’s Simple 7, the AHA released a presidential
advisory in 2022 to introduce an enhanced approach
to measuring CVH: AHA’s Life’s Essential 8.² The
components of AHA’s Life’s Essential 8 include
updates for the original 7 CVH components to
provide metrics that more broadly recognize the
scope of current health behaviors and practices with
a more refined and continuous scale for better
contrasting inter-individual differences in CVH at a
given point in time and improved tracking of
intraindividual changes in CVH over time.
Furthermore, sleep health was added into the CVH
metrics, given its important role in human biology and
sustainability of life, as well as its impact on
cardiometabolic health. Table 2-1 summarizes the
definitions and scoring algorithms for each of the
CVH components under this new approach in both

tes) may be able to estimate the
8 score, offering the potential to
Essential 8 framework even when
behavioral metrics are missing.³ It
that the AHA presidential advisory

logical health and well-being and
health not merely as individual
one of the AHA’s Life’s Essential 8
ditional factors underlying all 8

With this updated approach to
chapter now provides statistical
newer CVH metrics as the health
practice fields migrate toward the
Essential 8, with attention also
tional influences on CVH. Changes
and risk factors for YLDs and YLLs
2019, first added to the 2021
light the influence of the
ture death and disability in

adults and youths. Recent meth-
odological work has demonstrated that
statistical models using demographics and
those factors often available in routinely
collected data such as EHR systems
(BMI, smoking, hypertension,
hypercholesterolemia and diabe-

The 2025 AHA Statistical Update uses language that
conveys respect and specificity when referencing race and
ethnicity. Instead of referring to groups very broadly with
collective nouns (eg, Blacks, Whites), we use descriptions of
race and ethnicity as adjectives (eg, Asian people, Black
adults, Hispanic youths, Native American patients, White
females).

As the AHA continues its focus on health equity to
address structural racism, we are working to reconcile
language used in previously published data sources and
studies when this information is compiled in the annual
Statistical Update. We strive to use terms from the original
data sources or published studies (mostly from the past 5
years) that may not be as inclusive as the terms used in
2025. As style guidelines for scientific writing evolve, they
will serve as guidance for data sources and publications and
how they are cited in future Statistical Updates.

Relevance of Ideal CVH

(See Table 2-2 and Charts 2-1 through 2-8)

- Multiple independent investigations have confirmed the importance of having ideal levels of CVH components, along with the overall concept of CVH, based on the original Life's Simple 7 metrics and updated to include AHA's Life's Essential 8. Findings include strong inverse, stepwise associations in the United States and in recent meta-analyses of the number of CVH components at ideal levels with all-cause mortality, CVD mortality, IHD mortality, CVD, and HF; with subclinical measures of atherosclerosis such as carotid IMT, arterial stiffness, the number of carotid artery plaques, and CAC prevalence and progression; with physical functional impairment and frailty; with cognitive decline and depression; and with longevity.⁴⁻⁸ CVH has also been shown to be associated with various diseases and conditions, including periodontitis,⁹ depression¹⁰, osteoarthritis,¹¹ MASLD,¹² and cancer.¹³ These associations were observed in all populations in the United States, including underrepresented racial and ethnic populations.¹⁴ Similar relationships have also been seen in different populations internationally and in certain patient populations such as cancer survivors.^{7,15-25}
- AHA's Life's Essential 8 scores among NHANES 2007 through 2018 participants were significantly associated with the prevalence of CVD. For every increasing 1-SD increment of AHA's Life's Essential 8 score, there was a lower odds of CVD (OR, 0.64 [95% CI, 0.60–0.69]).²⁶
- The strength of the association between AHA's Life's Essential 8 score and CVD was strongest in younger individuals (20–59 years of age) and women. Recent work to elucidate the molecular mechanisms underlying the

association between CVH and CVD events found that metabolomic profiles were associated with CVH and partially mediated the relationship between CVH and HF in the Framingham cohort.²⁷ Other biomarkers considered have included early kidney dysfunction; urinary ACR in the normal range moderated the impact of CVH on all-cause mortality.²⁸

- Ideal health behaviors and ideal health factors behaviors, having a greater number of ideal health factors is associated with a graded decrease in risk of incident CVD, and conversely, across any level of health factors, having a greater number of ideal health behaviors is associated with a graded lowering of incident CVD risk.^{29,30} Use of technology has been shown to be differentially associated with health factors compared with behaviors.³¹ Data from the JHS found that among these older adults, 88% of participants used internet and mobile technology.

This study demonstrated that although no association of internet and mobile technology was seen with overall CVH score, using technology to track health was associated with having ideal BP, BMI, and cholesterol (all $P < 0.05$), and having ideal PA was associated with using smart devices ($P = 0.012$).[•] Many studies have been published in which investigators have assigned individuals a CVH score ranging from 0 to 14 on the basis of the sum of points assigned to each component of the original Life's Simple 7 CVH metrics (poor=0, intermediate=1, ideal=2 points). With

study, a biracial community-based population, over a median follow-up of 12 years.³⁶

- By combining the 7 CVH component scores and categorizing the total score to define overall CVH (low, 0–8 points; moderate, 9–11 points; high, 12–14 points), a report pooled NHANES 2011 to 2016 data and individual-level data from 7 US

this approach, data from the REGARDS cohort were used to demonstrate an inverse stepwise association between a higher CVH score component and a lower incidence of stroke.

On the basis of this score, every 1-unit increase in CVH was associated with an 8% lower risk of incident stroke (HR, 0.92 [95% CI, 0.88–0.95]), with a similar effect size for White participants (HR, 0.91 [95% CI, 0.86–0.96]) and Black participants (HR, 0.93 [95% CI, 0.87–0.98]).³² A similar association between CVH score and incidence of stroke was also observed in a large Chinese cohort.³³ Arterial stiffness mediates almost 10% of the relationship between CVH and stroke risk.³⁴

- CVH score, as measured by AHA's Life's Essential 8, and components were also shown to predict MACEs (first occurrence of IHD, MI, stroke, and HF) within the UK Biobank.³⁵ Individuals in the lowest quartile (least healthy) compared with the highest quartile (healthiest) had a greater risk for MACEs (HR, 2.07 [95% CI, 1.99–2.16]), which was strongest for HF. The authors estimated that a 10-point improvement in AHA's Life's Essential 8 score could have prevented 9.2% of MACEs. Similar findings were seen in the Heart SCORE

ciated with CVH and found that 70.0% (95% CI, 56.5%–79.9%) of major CVD events in the United States were attributable to low and moderate CVH.³⁷ According to the authors' estimates, 2.0 (95% CI, 1.6–2.3) million major CVD events could potentially be prevented each year if all US adults attain high CVH, and even a partial improvement in CVH scores to the moderate level among all US adults with low overall CVH could lead to a reduction of 1.2 (95% CI, 1.0–1.4) million major CVD events annually.

- A report from the CARDIA study observed a very low rate of CVD (aHR, 0.14 [95% CI, 0.09–0.22]) and CVD mortality (aHR, 0.17 [95% CI, 0.03–0.19]) over 32 years of follow-up being associated with a high (12–14 of 14 points) versus low (<8 points) level of CVH in late adolescence or early adulthood, as classified by Life's Simple 7.³⁸
- CVH, as measured at multiple times across the life course, can be used to assess the cumulative exposure to CVH. In the FHS, participants who maintained low AHA's Life's Essential 8 scores (below the median at each examination; AHA's Life's Essential 8 scores at examination 2=69 and median at examination 6=66) over an average of 13 years had the highest CVD and mortality risk (HRs, 2.3 [95% CI, 1.75–3.13] and 1.45 [95% CI, 1.13–1.85]) compared with those who had high AHA's Life's Essential 8 scores above the examination median at both examinations 2 and 6.³⁹
- A report from the Framingham Offspring Study showed increased risks of subsequent hypertension, diabetes, CKD, CVD, and mortality associated with having a shorter duration of ideal CVH in adulthood.⁴⁰ Another report from the ARIC study estimated CVD risk and all-cause mortality associated with patterns of overall CVH level (classified as poor, intermediate, and ideal to correspond to 0–2, 3–4, and 5–7 of the original CVH metrics at ideal levels) over time. The authors observed that participants attaining ideal CVH at the first follow-up visit had the lowest levels of CVD risks and mortality regardless of subsequent change in CVH level, and improvement from poor CVH over time was consistently associated with lower CVD risk (aHR, 0.67 [95% CI, 0.59–0.75]) and mortality (aHR, 0.80 [95% CI, 0.72–0.89]) subsequently compared with

remaining in poor CVH over risk associated with was also observed in the populations without CVD.⁴²

- Ideal CVH in parents was CVD-free survival in offspring. (0–4 versus 10–14 CVH be a more robust predictor of free survival (aHR, 2.09 [95% paternal CVH (aHR, 1.30

Furthermore, better maternal CVH at 28 weeks' gestation during pregnancy was significantly associated with better offspring CVH in early adolescence: Having just 1 poor maternal CVH metric (versus all ideal) in pregnancy was associated with a 33% lower chance of offspring

volume,⁵⁴ and lower hazard of tia.^{55–57} Among participants of favorable CVH was lower risk of dementia (HR, 1.01).⁵⁵ A recent systematic CVH is associated with ear manner; however, the ship differs, depending on are measured, with a linear risk factors and a more J-

attaining ideal CVH (aRR, 0.67 [95% CI, 0.58–0.77]) between 10 and 14 years of age.⁴⁴ Long-term data from the FHS show that parental CVH affects offspring DALYs such that

older-age risk factors.⁵⁸ At 5 years of age, children with better CVH have greater neurodevelopment as measured by the intelligence quotient.⁵⁹ Data from the longitudinal study ELSA-Brazil found that higher baseline AHA's Life's Essential 8 scores were associated with slower decline in global cognition, memory, verbal fluency, and the Trail-Making Test B.⁵³ Apolipoprotein E carrier status⁵⁴ and acculturation⁶⁰ have been demonstrated to modify the effects of CVH on cognition.

offspring of mothers in ideal compared with poor CVH had an additional 3 healthy life-years, although no association was seen with paternal CVH.⁴⁵

- The Cardiovascular Lifetime Risk Pooling Project showed that adults with all optimal risk factor levels (similar to having ideal CVH factor levels of cholesterol, blood sugar, and BP, as well as not smoking) have substantially longer overall and CVD-free survival than those who have poor levels of ≥ 1 of these CVH factors. For example, at an index of 45 years of age, males with optimal risk factor profiles lived on average 14 years longer free of all CVD events and 12 years longer overall than people with ≥ 2 risk factors.⁴⁶ A large community-based prospective study in China showed that greater CVH was associated with lower lifetime risk of CVD and that improvement in CVH could lower the lifetime risk of CVD and prolong the years of life free of CVD.^{47,48} Another report based on a large dataset from the UK Biobank found that having ideal CVH compared with poor CVH attenuated the all-cause and cardiovascular metabolic disease-related

mortality for males and females and was associated with life expectancy gains of 5.50 years (95% CI, 3.94–7.05) for males and 4.20 years (95% CI, 2.77–5.62) for females at an index of 45 years of age among participants with cardiometabolic diseases and correspondingly 4.55 years (95% CI, 3.62–5.48) in males and 4.89 years (95% CI, 3.99–5.79) in females for people without cardiometabolic diseases.⁴⁹

- Better CVH as defined by both the Life's Simple 7 and AHA's Life's Essential 8 scores is associated with less subclinical vascular disease,^{8,18} better global cognitive and domain-specific performance and cognitive function,⁵⁰ higher incidence of MCI,⁵¹ slower cognitive decline,⁵³ greater total brain volume, lower WMH volume, greater hippocampal

• Better CVH is also associated with fewer depressive symptoms,^{61–63} lower risks of proteinuria⁶⁴ and chronic obstructive pulmonary disease,⁶⁵ lower risk of AF,⁶⁶ and lower odds of having elevated resting heart rate.⁶⁷ Using the CVH scoring approach, the FHS demonstrated significantly lower odds of prevalent hepatic steatosis associated with more favorable CVH scores, and the decrease of liver fat associated with more favorable CVH scores was greater among people with a higher GRS for MASLD.⁶⁸ In addition, a study based on NHANES data showed significantly decreased odds of ocular diseases (OR, 0.91 [95% CI, 0.87–0.95]), defined as age-related macular degeneration, any retinopathy, and cataract or glaucoma, and odds of diabetic retinopathy (OR, 0.71 [95% CI, 0.66–0.76]) associated with each 1-unit increase in CVH among US adults.⁶⁹

• CVH has consistently been associated with frailty and multimorbidity in later life.⁷⁰ Better CVH in midlife was associated with a lower prevalence of frailty in a large community-based cohort study, ARIC,⁷¹ such that for every 1-unit greater midlife Life's Simple 7 CVH score, there was a 37% higher relative prevalence of being in robust health as opposed to being frail (relative PR, 1.37 [95% CI, 1.30–1.44]). It is important to note that the UK Biobank has also shown that frailty and poor psychosocial health modify the relationship of CVH with CVD such that individuals who are both frail or in poor psychosocial health (social isolation and loneliness) and in poor CVH have the greatest risk of CVD.^{70,72} Having ≥5 ideal Life's Simple 7 metrics was associated with a lower odds of having multiple disabilities within the 2017 to 2019 BRFSS data.⁷³ Among adults ≥65 years of age with ≥5 ideal CVH components, 78.8% (95% CI, 77.6%–79.9%) had

no disabilities compared with only 61.2% (95% CI, 60.1%–61.9%) among those with <5 ideal metrics. According to NHANES 1999 to 2006 data, several social risk factors (low family income, low education level, underrepresented racial groups, and single-living status) were related to lower likelihood of attaining better CVH as measured by Life's Simple 7 scores.⁷⁴ A recent report from the ARIC study found that people of 0.71 [95% CI, 0.57–0.87]), or with low education (OR, 0.65 [95% CI, 0.53–0.79]) were at higher odds of having worsening CVH over time,⁷⁵ whereas analysis of NHANES data from 2013 to 2016 found that the association between educational attainment and likelihood of ideal CVH differed by race and ethnicity, underscoring the need for elucidating specific barriers preventing achievement of CVH across different racial and ethnic subgroups in the population.^{76,77}

A recent publication from the MESA study found that greater social disadvantage as measured by an aggregated score across 5 social determinants of health domains was associated with greater odds of unfavorable CVH risk factors, including hypertension, diabetes, smoking, and obesity, and higher risk of CVD, consistent with the notion of social determinants of health as a foundational factor for CVH.⁷⁸ The MESA study also found that health literacy, which is highly disparate by race and ethnicity and SES, was associated with Life's Simple 7 scores in older age such that limited personal health literacy had a

more affluent being more likely to have ideal CVH.⁸² In addition to these broad markers of SES, NHANES data shows disparities in CVH among those who have lower household food security even among those that participate in Supplemental Nutrition Assistance Program with Life's Simple 7 mean CVH scores for those with high, marginal, low and very

31% lower odds of optimal Life's Simple 7 score (OR, 0.69 [95% CI, 0.50–0.95]).⁷⁹

Other recent reports on CVH disparity include a study focused on people with serious mental illness, which found that individuals of underrepresented races and ethnicities had significantly lower CVH scores based on 5 of the Life's Simple 7 components.⁸⁰ Data from BRFSS identifying racial and ethnic and geographic disparities in CVH among females of childbearing age in the United

States showed that NH Black females were found to have lower adjusted odds (OR, 0.54 [95% CI, 0.46–0.63]) of attaining ideal CVH compared with NH White females, whereas 5 spatial clusters in the Southwest, South, Midwest, and Mid-Atlantic regions were identified as having significantly lower prevalence of ideal CVH.⁸¹ A systematic review and meta-analysis summarized the finding on demographic differences and socioeconomic disparities in ideal CVH in the literature through June 2020, with females having a significantly higher prevalence of ideal smoking (81% versus 60% in males), BP (41% versus 30% in males), and overall CVH (6% versus 3% in males) and people with higher education and individuals who were economically

have been linked to health disparities in CVH, but more research is needed to better understand these complex relationships.⁸⁴ A cross-sectional study from REGARDS found that neighborhood characteristics mediated a portion of the racial disparities in ideal CVH such that neighborhood physical environment, neighborhood safety, neighborhood social cohesion, and discrimination explained 5%, 6%, 1%, and 11%, respectively, of the racial disparities in CVH.⁸⁵ This and other recent reports on the association between better neighborhood perceptions and higher CVH score in Black communities^{86,87} and the relationship between greater perceived social status and higher CVH score in the Hispanic/Latino population in the United States⁸⁸ are some examples of effort toward identifying complex relationships between demographic and socioeconomic factors and attaining ideal CVH. A recently published narrative review⁸⁹ described knowledge gaps and outlined potential steps toward equity in CVH, which is the objective of the interim⁹⁰ and longer-term⁹¹ Impact Goals set forth by the AHA.

- Reproductive factors, including higher BMI in pregnancy, greater gestational weight gain, and a history of infertility, have been associated with worse CVH in middle-aged females.^{92,93} Among Project Viva participants, 34% of female individuals had experienced infertility, and those with a history of infertility had an average CVH score that was 2.94 points lower (95% CI, −5.13 to −0.74) compared with those without a history of infertility after adjustment for demographics, SES, and reproductive factors.⁹³• Having more ideal CVH components in middle age has been associated with lower non-CVD and CVD health care costs in later life.⁹⁴ An investigation of 4906 participants in the Cooper Center Longitudinal Study reported that participants with ≥5 ideal CVH components in the original metrics exhibited 24.9% (95% CI, 11.7%–36.0%) lower median annual non-CVD costs and 74.5% (95% CI, 57.5%–84.7%) lower median CVD costs than those with ≤2 ideal CVH components.⁹⁴ A report from a large, ethnically diverse insured population found that people with 6 or 7 and those with 3 to 5 of the CVH components in the ideal category had a \$2021 and \$940 lower annual mean health care expenditure, respectively, than those with 0 to 2 ideal health components.⁹⁵

- The 2022 AHA presidential Essential 8 also provided gained on CVH since 2010 in psychological health and as social determinants, as CVH.² Since the publication of advisory on AHA's Life's et al⁹⁶ reported CVH United States, analyzing to 2018 using the updated

another report using 6 cycles of NHANES data from 2007 to 2018 focused on trajectories of overall and component CVH scores under the updated metrics for US adults between 18 and 44 years of age by sex and race and ethnicity subgroups, over 3 periods in time, each with 2 cycles, 4 years of NHANES data combined.⁹⁷ Similar statistics produced by the AHA using NHANES data are presented in the next section (Table 2-2 and Charts 2-1 through 2-8).

- Two additional reports used NHANES data from 2005 to 2018 to quantify CVH using the AHA Life's Essential 8 metrics and linked the NHANES participants to the National Death Index mortality file through 2019 to study the association between CVH and life expectancy, as well as all-cause and CVD-specific mortality. From 23 003 US adults 20 to 79 years of age, the life expectancy at 50 years of age, for example, the average number of years of life remaining after age 50, was estimated to be 27.3 years (95% CI, 26.1–28.4) in the low-CVH group, defined as CVH overall score <50, 32.9 (95% CI, 32.3–33.4) in the moderate-CVH group (CVH overall score between 50 and 79), and 36.2 (95% CI, 34.2–38.2) years in the high-CVH group, defined as overall CVH score of ≥80.⁹⁸ With 19 951 US adults between 30 and 79 years of age over a median

group (defined as overall CVH with the low-CVH group

- Several reports using UK produced with the updated CVH participants observed over a years. people in the lowest score had 2.1- (95% CI, 2.0–MACEs (including IHD, MI, with participants in the highest HF was the MACE

follow-up of 7.6 years, the second report found a 58% reduction (HR, 0.42 [95% CI, 0.32–0.56]) in all-cause mortality rate and a 64% reduction (HR, 0.36 [95% CI, 0.21–0.59]) in CVD-specific mortality rate when the high-CVH (score, 75–100) was compared with the low-CVH (score <50) group and a 40% reduction (HR, 0.60 [95% CI, 0.51–0.71]) in all-cause mortality rate and 38% reduction (HR, 0.62 [95% CI, 0.46–0.83]) in CVD-specific mortality rate when the moderate-CVH group (score, 50–74) was compared with the low-CVH group.⁹⁹ In a third report analyzing 23 110 US adults ≥20 years of age from NHANES between 2005 and 2014, also matching with the National Death Index data through 2019, the authors reported a 40% reduction (HR, 0.60 [95% CI, 0.48–0.75]) in all-cause mortality rate and a 54% reduction (HR, 0.46 [95% CI, 0.31–0.68]) in CVD-specific mortality rate over a median follow-

ended the greatest elevated risk (HR, 2.7 [95% CI, 2.4–2.9]).³⁵ The mean difference in life expectancy at 45 years of age between these 2 groups of people was estimated as 7.2 years (95% CI, 5.5–8.9) in favor of people with ≥ 4 ideal components in the CVH metrics. According to data from 135 199 participants, the life expectancy free of 4 major chronic diseases, namely CVD, diabetes, cancer, and dementia, at 50 years of age was estimated to be 6.9 years (95% CI, 6.1–7.7) longer for males with high CVH level (overall score, 80–100) compared with males at the low CVH level (overall score < 50) and 9.4 years (95% CI, 8.5–10.2) longer for females in the high-CVH category compared with females in the low-CVH category. The corresponding estimates were 4.0 years (95% CI, 3.4–4.5) longer for males and 6.3 years (95% CI, 5.6–7.0) longer for females with moderate CVH level compared with their counterparts in the low CVH category.¹⁰¹ In a study focusing on 33 236 participants with type 2 diabetes who were 40 to 72 years of age at baseline using the same database, people with ≥ 4 ideal components in the CVH metrics enjoyed a 65% reduction (HR, 0.35 [95% CI, 0.26–0.47]) in diabetes complications and a 47% reduction (HR, 0.53 [95% CI, 0.43–0.65]) in all-cause mortality rate compared with people with no more than 1 ideal CVH metric over a median of 11.7 years of follow-up.¹⁰² Similar favorable risk reductions for risk of dying before 75 years of age were found for males and females with or without type 2 diabetes at the moderate to high CVH levels compared with low CVH among 309 789 adults from the same database.¹⁰³

- Similar associations between greater CVH in childhood using the revised metrics and more favorable health or mortality outcomes were also reported by a Finnish¹⁰⁴ study and 2 Chinese cohort^{105,106} studies. The Healthy Start Study contrasted the original Life's Simple 7 and the revised AHA's Life's Essential 8 CVH metrics in 305 children between 4 and 7 years of age and observed modest concordance between these 2 CVH metrics. The authors noted the important role that sleep health played in classifying childhood CVH levels.¹⁰⁷ Additional information on the relevance of sleep to cardiometabolic health can be found in Chapter 13 (Sleep) of this up of 9.4 years when they compared the high-CVH Statistical Update.

CVH in the United States: Mean CVH Scores (NHANES 2013–March 2020)

(See Table 2-2)

- The national estimates of the 8 CVH components for children (2–19 years of age) and adults (≥20 years of age) are displayed in Table 2-2. Multiple cycles of NHANES data were combined to provide more precise estimates on all CVH components. Dietary, PA, and BMI scores were calculated for all children who were 2 to 19 years of age; blood lipid and BP scores were calculated for children who were 6 to 19 and 8 to 19 years of age, respectively; and blood glucose and nicotine exposure scores were calculated for those who were 12 to 19 years of age in the sample. The sleep health score was available only for youths 16 to 19 years of age, so the Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.
 - For most components of CVH, mean scores were higher in US children (within corresponding age ranges of the components) than in US adults (≥20 years of age), except for the diet score and the sleep health score, for which mean scores in children were lower than in adults. Mean diet scores were the lowest among the 8 CVH components for both US children and adults.
 - Among US children, BP, blood glucose, and nicotine exposure were the CVH components scoring highest compared with the rest of the CVH components, with all mean scores in the 80s and the 90s (of 100 points as the ideal score) across race and ethnicity groups. In contrast, mean PA, lipids, and sleep health
- The corresponding mean overall CVH score was 78.4 (95% CI, 75.7–81.1) for NH Asian children, 74.1 (95% CI, 72.0–76.2) for NH White children, 72.7 (95% CI, 70.6–76.3) for Mexican American children, and 71.3 (95% CI, 68.8–73.8) for NH Black children.
- During the same period, the mean overall CVH score was 65.2 (95% CI, 64.2–66.1) for all US adults, with mean score of 69.6 (95% CI, 68.1–71.1) for NH Asian adults, 66.0 (95% CI, 64.8–67.2) for NH White adults, 63.5 (95% CI, 62.2–64.8) for Mexican American adults, and 59.7 (95% CI, 58.4–60.9) for NH Black adults (Table 2-2).
 - An article appeared online ahead of scores within the corresponding age ranges were all in the 70s across race and ethnicity categories.
 - Among US adults (Table 2-2), the lowest mean scores for CVH were observed in diet, PA, and BMI components, with mean scores ranging from the 30s to the 50s across all race and ethnicity categories. Sleep health scores were the highest among the CVH components in US adults, with mean scores in the 80s across all race and ethnicity groups except in the NH Black adult population, for whom the mean score was 75.6 (95% CI, 74.5–76.7). Mean scores for blood lipids, blood glucose, and BP among US adults were all in the 60s to the 70s range across race and ethnicity categories.
 - From 2013 to March 2020, the overall CVH score combining health scores of all 8 components was, on average, 73.6 (95% CI, 72.4–74.7) for all US children between 16 and 19 years of age (Table 2-2).

(See Charts 2-1 through 2-8)

- The overall trend for national estimates of the 8 CVH components for adults 20 to 79 years of age and trends by race and ethnicity subgroups are displayed in Charts 2-1 through 2-8 (unpublished AHA tabulation using NHANES₁₀₈). Adults who self-reported a history of CHD, MI, angina, or stroke; were pregnant; or were breastfeeding at time of examination were not included in these analyses. Dietary estimates were available only through the 2017 to 2018 NHANES data cycle at the time of this report because of the availability of the Food Patterns Equivalents Database from the US Department of Agriculture, whereas mean scores for the rest of the CVH metrics were derived through the 2017 to March 2020 combined NHANES cycle. As a result, the trends over time for the overall CVH score are not presented here. Furthermore, data for the NH Asian population are available only for CVH evaluation starting from the 2011 to 2012 NHANES data cycle.
- During this time period, CVH diet scores for US adults remained low and relatively unchanged (Chart 2-1). Adult NH Asian individuals observed slightly higher average diet scores since 2011 to 2012 compared with other race and ethnicity subgroups. The age-adjusted mean score for NH Asian adults in 2017 to 2018 was 47.8 (95% CI, 44.3–55.3). NH Black individuals had the lowest diet score on average during the past decade. In 2017 to 2018, the adjusted mean score for NH Black adults was 22.4 (95% CI, 19.1–27.7).

- Although still low overall, a mean CVH PA scores was every race and ethnicity for NH Asian adults, for ous (Chart 2-2). In the 2020, the age-adjusted from 47.9 (95% CI, 45.6– to 57.7 (95% CI, 54.0–61.4)
- Upward trends in mean scores were observed for ethnicity subgroups presented (Chart 2-3). The mean scores for the updated nicotine exposure CVH score, which now takes into account secondhand smoking exposure as well, were significantly higher in NH Asian and Hispanic individuals compared with NH White and NH Black individuals. The age-adjusted mean scores ranged between 66.8 (95% CI, 62.7–70.8) for NH Black adults and 87.0 (95% CI, 84.4–89.5) for NH Asian adults during 2017 79.4–81.5) in 2013 to 2014 (95% CI, 75.2–76.9) in
- During this time period, age-scores for US adults (Chart 2-8). NH Black mean BP score and had a nounced downward trend ric. from 65.8 (95% CI, to 57.9 (95% CI, 55.8–59.9) compared with the rest of
- to March 2020.– Upward trends were also observed across all race and ethnicity subgroups for the newest addition to the updated CVH metrics, the sleep health score, although the age-adjusted mean scores were significantly lower for NH Black individuals,

Trends in Risk Factors and Causes for YLL and YLD in the United States: 1990 to 2021

(See Tables 2-3 through 2-6)

- The leading risk factors for YLLs from 1990 to 2021 in the United States and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-3.
 - High SBP and smoking remained the first and second leading YLL risk factors in both 1990 and 2021. Age-standardized rates of YLL attributable to smoking declined by 53.9%, whereas age-standardized rates attributable to high SBP ranging from 71.5 (95% CI, 69.3–73.6) in 2007 to 2008 to 78.5 (95% CI, 76.4–80.6) in 2015 to 2016 and then to 76.6 (95% CI, 74.9–78.3) in 2017 to March 2020 compared with other race declined 47.4% and ethnicity subgroups (Chart 2-4).

– In 2021, CVH components accounted for 12 (among which 7 were related to poor diet) of the 20 leading YLL risk factors, with 6 of the 7 diet-related risk factors rising in the risk factor rank-

– Although mean CVH BMI scores were higher in NH White individuals and NH Asian individuals compared with NH Black individuals and Hispanic individuals, all race and ethnicity subgroups pre-sented here observed a steep downward trend in this CVH metric over the past decade (Chart 2-5).

In the period of 2017 to March 2020, the age-adjusted mean BMI scores ranged between 57.5 (95% CI, 54.8–60.2) for NH White adults and 50.3 (95% CI, 48.5–52.2) for NH Black adults.– Trends in age-adjusted mean scores of

ings since 1990.

the non- HDL lipids metric over the past decade improved for all race and ethnicity subgroups, except for the NH Asian population, for which the mean scores were relatively unchanged (Chart 2-6). NH Black individuals had significantly higher mean scores in this metric, ranging from 69.0 (95% CI, 67.0– 71.1) in 2007 to 2008 to 74.9 (95% CI, 72.8–

- The leading causes of YLLs from 1990 to 2021 in the United States and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-4.
 - IHD was the leading YLL cause in 1990 and second leading YLL cause in 2021, with COVID-19 ranking first. Age-standardized YLL rates attributable to IHD declined 55.5%, whereas age-standardized YLL rates resulting from tracheal, bronchus, and lung cancer declined 50.0%.
 - Type 2 diabetes also rose from the 13th to 9th leading YLL cause, whereas AD and other dementias also rose from the 10th to 6th leading YLL cause.
- The leading risk factors for YLDs from 1990 to 2021 in the United States and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-5.
 - Although they remained relatively stable through 2014, the mean CVH blood glucose scores had a steady worsening for all race and ethnicity sub-groups over the past 6 years

(Chart 2-7). The mean scores for all US individuals were 79.4 (95% CI, 78.2–80.6) in 2007 to 2008 and 80.5 (95% CI,

- High BMI, high FPG, and smoking are among the top 4 leading YLD risk factors in both 1990 and 2021, with high FPG rising in ranking and smoking dropping from the second to the fourth leading YLD risk factor during this time period. Age-standardized YLD rates attributable to smoking declined by 22.8%, and age-standardized rates

attributable to high BMI and high FPG increased by 69.3% and 123.7%, respectively, between 1990 and 2021.

- The leading causes of YLDs from 1990 to 2021 in the United States and the corresponding percent change in age-to these risk factors are presented in Table 2-6.
 - From 1990 to 2021, type 2 diabetes rose from the 10th to 3rd leading YLD cause with a 157.9% increase in the age-standardized YLD

Trends in Global Risk Factors and Causes for YLL and YLD: 1990 to 2021

(See Tables 2-7 through 2-10)

- The leading global YLL risk factors from 1990 to 2021 and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-7.
 - High SBP and smoking were the first and second leading YLL risk factors globally in 2021. Age-standardized YLL rates attributable to high SBP and smoking declined 32.3% and 42.5%, respectively, between 1990 and 2021.
 - From 1990 to 2021, high FPG rose from the 14th to 5th leading risk factor of global YLLs with a 1.6% decrease in the age-standardized YLL rates over this period.
- The leading global YLL causes from 1990 to 2021 and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-8.

age-standardized YLD rates attributable to these risk factors are presented in Table 2-10.

- From 1990 to 2021, type 2 diabetes rose from the 10th to 7th leading global cause of YLD during this

Furthering the AHA's Impact Through Continued Efforts to

(See Tables 2-3 through 2-6)

- IHD rose from the third to second leading global YLL cause between 1990 and 2021, whereas age-standardized YLL rates declined by 31.6% during this period.
- ICH and ischemic stroke rose from the seventh to fifth and from the 12th to 8th leading cause of global YLL, respectively, between 1990 and 2021.
- Type 2 diabetes also rose from the 26th to 14th leading global YLL cause, showing a 9.8% increase in age-standardized YLL rate.
- The leading global risk factors for YLDs from 1990 to 2021 and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-9.
 - High FPG and high BMI were the first and second leading YLD risk factors globally in 2021, replacing iron deficiency and smoking, which were first and second in 1990. Age-standardized YLD rates attributable to high FPG and high BMI increased 74.6% and 69.0%.
 - The leading global causes of YLDs from 1990 to

- Renewed efforts to maintain and improve CVH will be foundational to successful reductions in mortality and disability in the United States and globally. Individuals with more favorable levels of CVH have significantly lower risk for several of the leading causes of death and YLD, including IHD,²⁹ AD,¹⁰⁹ stroke,^{110,111} CKD,¹¹² diabetes,¹¹³ and breast cancer¹¹⁴ (Tables 2-4 and 2-6). In addition, 6 of the 10 leading US risk factors for YLL and 4 of the 10 leading risk factors for YLD in 2019 were components of CVH (Tables 2-3 and 2-5). Taken together, these data demonstrate the tremendous importance of continued efforts to improve CVH.
- There is increasing recognition that optimizing pre-pregnancy and maternal CVH will result in long-term benefits to the health of the birthing individual and the offspring. See Chapter 11 (Adverse Pregnancy Outcomes) for additional information.
- As the benefits of ideal CVH become increasingly evident, attention is turning to developing inter-ventions to promote CVH with a focus on imple-mentation science.¹¹⁵ An increasing number of studies are using community-based, school-based, or technology-enhanced interventions to directly improve CVH score.¹¹⁶⁻¹²⁰

Global Efforts to Improve CVH

- A recent scoping review examining our knowledge of CVH across low- and middle-income countries revealed that limited data exist on CVH in these countries, 85% are cross-sectional, and 71% came from only 10 countries.¹²¹
- Many challenges exist related to implementation of prevention and treatment programs in inter-national settings; some challenges are unique to individual countries/cultures, whereas others are universal. Partnerships and collaborations with local, national, regional, and global partners are foundational to effectively address relevant national health priorities in ways that facilitate contextualization within individual countries and 2021 and the cultures. corresponding

Table 2-1. AHA's Life's Essential 8: New and Updated Metrics for Measurement and Quantitative Assessment of CVH

Domain	CVH metric	Method of measurement	Quantitative assessment of CVH
Health behaviors	Diet	Measurement: Self-reported daily intake of a DASH-style eating pattern Example tools for measurement: DASH diet score ^{122,123} (populations); MEPA ¹²⁴ (individuals)	Quantitative assessment of diet (population) Score Points 100 (top) 75th 50 percentile 25 percentile 0 (bottom) Score Points 100 80 50
	PA	Measurement: Self-reported minutes of moderate or vigorous PA per week Example tools for measurement: NHANES PAQ-K questionnaire ¹²⁵	Metabolic moderate greater active Score Points 100 90 80 60 40 20
	Nicotine exposure	Measurement: Self-reported use of cigarettes or inhaled NDS Example tools for measurement: NHANES SMQ ¹²⁶	Metabolic use second Score Points 100 75 ≥5 y

(Continued)

Table 2-1. Continued

Domain	CVH metric	Method of measurement	Quantification of CVH metric:	Quantification of CVH metric:
	Sleep health	Measurement: Self-reported average hours of sleep per night Example tools for measurement: "On average, how many hours of sleep do you get per night?" Consider objective sleep/actigraphy data from wearable technology if available	Metric: Average hours of sleep per night Scoring: <u>PointsLevel</u> 100 7–<9 90 9–<10 70 6–<7 40 5–<6 or ≥10 20 4–<5 0 <4	Metric: Average hours of sleep per night (or per 24 h for ≤5 y of age; see notes for age-appropriate ranges) Scoring: <u>PointsLevel</u> 100 Age-appropriate optimal range 90 <1 h above optimal range 70 <1 h below
Health factors	BMI	Measurement: Body weight (kilograms) divided by height squared (meters squared) Example tools for measurement: Objective measurement of height and weight	Metric: BMI percentiles for age and sex, starting in infancy; see for suggestions for <2 y of age Scoring: <u>PointsLevel</u> 100 5th–<85th percentile 70 85th–<95th percentile 30 95th percentile–<120% of the 95th percentile	
	Blood lipids	Measurement: Plasma TC and HDL-C with calculation of non-HDL-C Example tools for measurement: Fasting or nonfasting blood sample	Metric: Non-HDL-C (mg/dL) Scoring: <u>PointsLevel</u> 100 <130 60 130–159 40 160–189 20 190–	Metric: Non-HDL-C (mg/dL), starting no later than 9–11 y of age and earlier per clinician discretion Scoring: <u>PointsLevel</u> 100 <100 60 100–119 40 120–144 20 145–189
	Blood glucose	Measurement: FBG or casual HbA1c Example tools for measurement: Fasting (FBG, HbA1c) or nonfasting (HbA1c) blood sample	Metric: FBG (mg/dL) or HbA1c (%) Scoring: <u>PointsLevel</u> 100 No history of diabetes and FBG <100 (or HbA1c <5.7) 60 No diabetes and FBG 100–125 (or HbA1c 5.7–6.4; prediabetes) 40 Diabetes with HbA1c <7.0 30 Diabetes with	Metric: FBG (mg/dL) or HbA1c (%), symptom-based screening at any age or risk-based screening starting at ≥10 y of age or onset of puberty per clinician discretion Scoring: <u>PointsLevel</u> 100 No history of diabetes and FBG <100 (or HbA1c <5.7) 60 No diabetes and FBG 100–125 (or HbA1c 5.7–6.4; prediabetes)

(Continued)

Table 2-1. Continued

Domain	CVH metric	Method of measurement	Qua CVH
	BP	Measurement: Appropriately measured SBP and DBP Example tools for measurement: Appropriately sized BP cuff	Met DBP Sco Poir 100 <12 (opt 75 129 (ele 130 (sta hyp 140 0 ≥10 Sub

AHA indicates American Heart Association; BMI, body mass index; BP, blood pressure; CVH, cardiovascular health; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HEI, Healthy Eating Index; MEPA, Mediterranean Eating Pattern for Americans; NDS, nicotine-delivery system; NHANES, National Health and Nutrition Examination Surveys; PA, physical activity; PAQ-K, Physical Activity Questionnaire K; SBP, systolic blood pressure; SMQ, smoking assessment; and TC, total cholesterol.

*Cannot meet these metrics until solid foods are being consumed.

Notes on implementation:

Diet: See . For adults and children, a score of 100 points for the CVH diet metric should be assigned for the top (95th percentile) or a score of 15 to 16 on the MEPA (for individuals) or for those in the ≥95th percentile on the DASH score or HEI-2015 (for populations). The 75th to 94th percentile should be assigned 80 points, given that improvement likely can be made even among those in this top quartile. For individuals, the MEPA points are stratified for the 100-point scoring system approximately by quantiles. In children, a modified MEPA is suggested that is based on age-appropriate foods. The writing group recognizes that the quantiles may need to be adjusted or recalibrated at intervals with population shifts in eating patterns. In children, the scoring applies only once solid foods are being consumed. For now, the reference population for quantiles of HEI or DASH score should be the NHANES sample from 2015 to 2018. The writing group acknowledges that this may need to change or be updated over time. Clinicians should use judgment in assigning points for culturally contextual healthy diets. For additional notes on scoring in children, see .

PA: Thresholds are based in part on US Physical Activity Guidelines. For adults, each minute of moderate activity should count as 1 minute and each minute of vigorous activity should count as 2 minutes toward the total for the week. For children, each minute of moderate or vigorous activity should count as 1 minute. The score for PA is not linear, given that there is a greater increase in health benefit for each minute of marginal exercise at the lower end of the range and the association tends to approach an asymptote at the higher end of the range.

If scoring is desired for children ≤5 years of age, see . For additional notes on scoring in children, see .

Nicotine exposure: The writing group recommends subtracting 20 points for children and adults exposed to indoor secondhand smoke at home, given its potential for long-term effects on cardiopulmonary health.¹²⁷ For additional notes on scoring in children, see .

Sleep health: Thresholds are based in part on sleep guidelines. Clinicians may consider subtracting 20 points from the sleep score for adults or children with untreated or undertreated sleep apnea if information is available. Note that overall scoring reflects the inverse U-shaped association of sleep duration with health outcomes such that excessive sleep duration is also considered to be suboptimal for CVH.

For children, age-appropriate optimal sleep durations are as

follows¹²⁸:

4 to 12 months of age, 12 to 16 hours per 24 hours (includes naps);

1 to 2 years of age, 11 to 14 hours per 24 hours;

3 to 5 years of age, 10 to 13 hours per 24 hours;

6 to 12 years of age, 9 to 12 hours; and

13 to 18 years of age, 8 to 10 hours.

For additional notes on scoring in children, see .

BMI: Thresholds are based in part on National Heart, Lung, and Blood Institute (NHLBI) guidelines. The writing group acknowledges that BMI is an imperfect metric for determining healthy body weight and body composition. Nonetheless, it is widely available and routinely calculated in clinical and research settings. BMI ranges may differ for individuals from diverse ancestries. For example, the World Health Organization has recommended different BMI ranges for individuals of Asian or Pacific ancestry. For individuals in these groups, point scores should be aligned as appropriate:

Points Level, kg/m²

100 18.5–22.9

75 23.0–24.9

50 25.0–29.9

25 30.0–34.9

0 ≥35.0

Clinicians may want to assign 100 points for overweight individuals (BMI, 25.0–29.9 kg/m²) who are lean with higher muscle mass. For underweight individuals (<18.5 kg/m² in adults or below the fifth percentile in children), the writing group defers to clinician judgment in assigning points on the basis of individual assessment

(Continued)

Table 2-1. Continued

as to whether the underweight BMI is healthy or unhealthy. Conditions that should be considered unhealthy include chronic catabolic illnesses (eg, cancer), eating disorders, and growth failure (for children). For additional notes on scoring in children, see .

Blood lipids: Thresholds are based in part on 2018 Cholesterol Clinical Practice Guideline.¹²⁹ The levels of non-HDL-C for adults were selected on the basis of current guideline recommendations and in concert with the observation that non-HDL-C levels are generally ≈30 mg/dL higher than low-density lipoprotein cholesterol (LDL-C) levels in normative ranges in the population. For children, thresholds for non-HDL-C were chosen on the basis of NHLBI pediatric guidelines, pediatric LDL-C thresholds for diagnosis of familial hypercholesterolemia phenotypes (+30 mg/dL), and current distributions of non-HDL-C to smooth transitions to adult point scales. The writing group recommends subtracting 20 points from the blood lipid score if the level of non-HDL-C represents a treated value, given the residual risk present in those who require treatment. There may be a modest shift in point scores for this metric as individuals age from pediatric to adult metrics. For additional notes on scoring in children, see .

Blood glucose: Thresholds are based in part on American Diabetes Association guidelines.¹³⁰ If an individual patient with prediabetes (ie, not yet diagnosed formally with diabetes) is being treated with metformin to prevent the onset of diabetes and has normoglycemic levels, the writing group recommends clinician judgment for assigning point values (ie, consider subtracting 20 points). The maximal point value for patients with well-controlled diabetes was set at 40, given the residual risk present in those with diabetes. For additional notes on scoring in children, see .

BP: Thresholds are based in part on the 2017 Hypertension Clinical Practice Guidelines and the guidelines for children.¹³¹ The writing group recommends subtracting 20 points from the BP score if the level of BP represents a treated value, given the residual risk present in those who require treatment. For additional notes on scoring in children, see .

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Table 2-2. Mean (95% CI) Score for Each Component of CVH Metrics by Race and Ethnicity Strata Among US Children 2 to 19 Years of Age and US Adults ≥20 Years of Age: NHANES 2013 to March 2020

Individual component of	NHANES years	Overall	NH Black	NH White	NH Asian	MA
Health behaviors		2–19 y of age				
Diet* score (2–19)	2013–2018	41.2 (39.0–43.5)	31.7 (28.8–34.6)	41.1 (37.6–44.5)	49.8 (43.0–56.5)	44.3 (40.8–47.8)
PA score (2–19 y)	2013–March 2020	75.2 (74.2–76.3)	74.7 (73.0–76.3)	77.5 (76.0–78.9)	72.5 (69.9–74.9)	71.0 (68.4–73.7)
Nicotine exposure	2013–March 2020	85.4 (84.1–86.7)	86.8 (84.6–88.9)	83.3 (81.0–85.5)	92.8 (90.5–95.1)	88.0 (85.7–90.3)
Sleep health score	2013–March 2020	77.8 (76.0–79.6)	72.5 (70.0–75.0)	79.8 (77.1–82.5)	77.9 (74.7–81.2)	77.7 (75.1–80.4)
Health factors						
BMI score (2–19 y)	2013–March 2020	81.4 (80.0–82.8)	78.9 (75.7–82.0)	84.3 (82.5–86.0)	89.3 (87.0–91.7)	74.9 (72.6–77.2)
Blood lipids score	2013–March 2020	73.7 (72.6–74.8)	77.3 (75.3–79.2)	73.6 (71.8–75.4)	69.9 (66.9–73.0)	73.5 (71.6–75.4)
Blood glucose score	2013–March 2020	92.5 (91.7–93.2)	89.3 (88.0–90.7)	93.3 (92.0–94.5)	93.0 (90.8–95.2)	91.7 (90.2–93.2)
BP score (8–19 y)	2013–March 2020	95.5 (95.0–96.0)	94.2 (93.3–95.0)	95.8 (95.1–96.3)	96.1 (95.1–97.0)	95.5 (94.6–96.3)
Overall score (16–)	2013–March 2020	73.6 (72.4–74.7)	71.3 (68.8–73.8)	74.1 (72.0–76.2)	78.4 (75.7–81.1)	72.7 (70.6–76.3)
Health behaviors		≥20 y of age†				
Diet* score	2013–2018	44.38 (42.6–46.1)	31.4 (28.5–34.3)	46.6 (44.4–48.8)	53.1 (49.7–56.5)	42.9 (40.9–44.9)
PA score	2013–March 2020	49.23 (47.4–51.0)	45.1 (42.7–47.6)	51.0 (48.9–53.1)	51.8 (48.3–55.3)	42.4 (39.9–44.9)
Nicotine exposure	2013–March 2020	69.3 (68.0–70.5)	64.0 (62.1–65.9)	68.1 (66.3–69.9)	85.4 (83.5–87.3)	75.7 (73.8–77.6)
Sleep health score	2013–March 2020	84.2 (83.6–84.8)	75.6 (74.5–76.7)	86.1 (85.4–86.9)	86.3 (84.9–87.7)	83.1 (81.9–84.3)
Health factors						
BMI score	2013–March 2020	57.2 (56.2–58.2)	52.0 (50.5–53.5)	58.9 (57.6–60.2)	58.5 (57.0–60.1)	50.9 (49.2–52.5)
Blood lipids score	2013–March 2020	67.7 (66.8–68.6)	73.7 (72.4–74.9)	67.0 (65.9–68.1)	66.9 (65.4–68.5)	66.2 (64.4–68.0)
Blood glucose	2013–March 2020	76.4 (75.7–77.2)	72.2 (71.3–73.2)	77.8 (76.9–78.6)	74.7 (72.9–76.5)	73.2 (71.2–75.2)
BP score	2013–March 2020	68.2 (67.3–69.0)	60.6 (59.2–62.0)	68.2 (67.1–69.4)	70.7 (68.9–72.5)	73.4 (71.8–75.0)
Overall score	2013–March 2020	65.2 (64.2–66.1)	59.7 (58.4–60.9)	66.0 (64.8–67.2)	69.6 (68.1–71.1)	63.5 (62.2–64.8)

Values are mean (95% CI). In March 2020, the COVID-19 (coronavirus disease 2019) pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹³²

BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; MA, Mexican American; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and PA, physical activity.

*Scaled to 2000 kcal/d and in the context of appropriate energy balance and a Dietary Approaches to Stop Hypertension–type eating pattern. Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

†Standardized to the age distribution of the 2000 US standard population.

Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

Table 2-3. Leading 20 Risk Factors of YLL and Death in the United States: Rank, Number, and Percent Change, 1990 and 2021

Risk factors	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate
High SBP	2	1	7928.37 (6583.97 to 9106.79)	7479.07 (6017.03 to 8807.80)	–5.67 (–12.93 to 1.70)	–47.43 (–51.55 to –43.73)
Smoking	1	2	8626.22 (7434.04 to 9816.94)	7334.37 (6040.21 to 8579.75)	–14.98 (–19.69 to –10.57)	–53.91 (–56.42 to –51.62)
High FPG	5	3	3454.63 (2926.15 to 4025.07)	6584.20 (5278.16 to 7909.75)	90.59 (77.04 to 105.54)	4.68 (–2.21 to 12.22)
High BMI	4	4	3589.44 (1572.40 to 5670.98)	6554.70 (3339.00 to 9600.13)	82.61 (65.21 to 115.16)	1.83 (–8.24 to 21.47)
Drug use	16	5	973.22 (872.92 to 1111.92)	4583.68 (4158.73 to 5055.83)	370.98 (318.34 to 429.09)	269.24 (227.75 to 316.07)
Kidney dysfunction	7	6	2409.70 (1955.84 to 2851.13)	4114.23 (3582.54 to 4589.78)	70.74 (55.81 to 91.24)	–4.94 (–13.01 to 6.29)
High alcohol use	8	7	2122.03 (1890.02 to 2425.16)	3320.01 (2961.75 to 3694.25)	56.45 (45.17 to 67.66)	0.63 (–6.11 to 7.43)
High LDL-C	3	8	4744.59 (3236.26 to 6301.13)	3156.69 (2051.13 to 4336.17)	–33.47 (–37.30 to –30.26)	–62.09 (–64.16 to –60.37)
Diet low in whole	9	9	1626.26 (875.23 to 2329.42)	1539.66 (782.75 to 2266.02)	–5.33 (–10.34 to –0.93)	–45.95 (–48.71 to –43.56)
Low temperature	12	10	1209.84 (1068.89 to 1373.00)	1458.33 (1280.92 to 1594.73)	20.54 (12.69 to 26.74)	–37.98 (–41.46 to –34.71)
Diet low in fruits	14	11	1086.82 (433.94 to 1676.50)	1411.95 (845.25 to 1908.91)	29.92 (6.78 to 102.24)	–24.50 (–37.73 to 16.37)
Diet high in processed	17	12	964.55 (248.98 to 1579.03)	1391.63 (376.25 to 2275.86)	44.28 (28.03 to 63.92)	–16.60 (–26.14 to –4.53)
Diet low in vegetables	24	13	546.30 (303.67 to 819.41)	1014.76 (695.38 to 1373.26)	85.75 (57.83 to 113.67)	6.54 (–9.35 to 22.43)
Diet high in sodium	26	14	498.76 (1.01 to 1914.47)	934.24 (28.10 to 2758.38)	87.31 (40.88 to 3168.70)	7.56 (–20.81 to 1960.94)
Diet high in red meat	19	15	943.55 (–0.74 to 1637.59)	916.28 (–0.59 to 1536.24)	–2.89 (–22.96 to 30.69)	–45.17 (–55.62 to –34.72)
Ambient particulate	6	16	2649.86 (1193.47 to 4362.26)	913.64 (464.96 to 1423.79)	–65.52 (–84.05 to –47.00)	–80.17 (–90.28 to –70.06)

(Continued)

Table 2-3. Continued

Risk factors	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
Short gestation	13	19	1171.44 (1139.96 to 1205.37)	585.43 (521.95 to 649.91)	–50.02 (–55.25 to –44.79)	–43.62 (–49.51 to –37.73)	13.03 (12.68 to 13.41)	6.51 (5.80 to 7.23)	–50.03 (–55.26 to –44.30)	–43.63 (–49.53 to –37.73)
Occupational exposure to	22	20	637.57 (464.14 to 811.00)	572.54 (424.12 to 720.96)	–10.20 (–17.73 to –2.67)	–52.08 (–56.10 to –48.06)	33.35 (24.42 to 42.28)	35.00 (25.38 to 43.70)	4.95 (–4.55 to 14.45)	–43.07 (–48.12 to –38.02)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Diseases, Injuries, and Risk Factors; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³³

Table 2-4. Leading 20 Causes of YLL and Death in the United States: Rank, Number, and Percent Change, 1990 and 2021

Diseases and	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
COVID-19		1		10 727.15 (10 522.33 to 10 952.00)				483.51 (474.40 to 494.81)		
Ischemic heart disease	1	2	10 632.67 (9910.05 to 10 975.60)	8 529.67 (7 804.26 to 8 948.11)	–19.78 (–21.84 to –17.98)	–55.54 (–56.62 to –54.56)	594.73 (534.53 to 623.66)	493.22 (432.45 to 527.14)	–17.07 (–20.15 to –14.93)	–56.11 (–57.23 to –55.00)
Tracheal, bronchus, and lung	2	3	3743.43 (3606.54 to 3843.86)	3590.39 (3354.03 to 3746.86)	–4.09 (–7.83 to –0.72)	–49.98 (–51.92 to –48.23)	158.06 (150.68 to 163.10)	175.48 (161.00 to 184.74)	11.02 (5.79 to 15.26)	–41.92 (–44.61 to –39.23)
Chronic obstructive pulmonary	4	4	1662.86 (1566.50 to 1713.10)	3343.16 (3026.32 to 3499.85)	101.05 (92.60 to 106.61)	8.68 (4.37 to 11.55)	89.78 (82.91 to 93.29)	198.04 (172.63 to 210.19)	120.57 (107.89 to 127.68)	18.15 (11.82 to 24.48)
Opioid use disorder	47	5	213.09 (199.48 to 228.20)	2629.46 (2334.46 to 2959.44)	1133.95 (977.87 to 1332.01)	929.19 (802.89 to 1089.54)	4.23 (3.96 to 4.52)	55.45 (48.82 to 62.98)	1211.24 (1039.51 to 1435.13)	942.37 (811.13 to 1073.61)
AD and other dementia	10	6	1227.53 (309.46 to 3159.50)	2340.44 (607.75 to 5840.62)	90.66 (84.53 to 99.18)	–1.96 (–4.39 to 1.20)	99.96 (25.91 to 258.21)	198.05 (53.30 to 494.05)	98.13 (90.77 to 107.74)	–1.58 (–4.27 to 1.64)
Colon and rectum cancer	6	7	1383.03 (1305.54 to 1434.65)	1577.41 (1475.16 to 1647.06)	14.05 (10.01 to 17.97)	–33.72 (–35.97 to –31.52)	67.23 (61.66 to 70.47)	75.09 (68.06 to 79.71)	11.68 (7.39 to 15.76)	–37.82 (–40.13 to –35.51)
Ischemic stroke	5	8	1391.86 (1243.72 to 1470.86)	1466.87 (1246.16 to 1581.04)	5.39 (–0.26 to 9.17)	–44.01 (–46.63 to –42.10)	99.53 (86.39 to 106.29)	115.56 (94.59 to 126.65)	16.10 (9.02 to 20.34)	–40.63 (–43.59 to –37.67)
Type 2 diabetes	13	9	964.25 (912.59 to 998.80)	1432.05 (1340.27 to 1498.94)	48.51 (43.57 to 53.73)	–16.56 (–19.29 to –13.58)	46.69 (42.89 to 48.88)	70.71 (64.16 to 75.05)	51.45 (45.86 to 56.99)	–17.34 (–20.17 to –14.51)
Other COVID-19 pandemic–		10		1342.92 (918.05 to 1816.56)				58.06 (39.51 to 79.47)		
Hypertensive HD	21	11	478.20 (449.51 to 493.05)	1292.24 (1150.28 to 1425.76)	170.23 (144.65 to 196.43)	57.01 (42.27 to 71.75)	24.00 (21.72 to 25.22)	68.69 (58.73 to 76.39)	186.19 (158.02 to 211.62)	52.98 (38.61 to 67.35)

(Continued)

Table 2-4. Continued

Diseases and	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age standardized YLL rate
Breast cancer	9	12	1271.60 (1218.46 to 1305.10)	1218.25 (1140.97 to 1274.62)	–4.20 (–8.19 to –0.80)	–45.13 (–47.36 to –43.17)
Motor vehicle road injuries	3	13	1915.28 (1889.64 to 1942.45)	1210.73 (1168.18 to 1249.15)	–36.79 (–38.96 to –34.50)	–50.65 (–52.40 to –48.84)
Pancreatic cancer	18	14	623.25 (595.67 to 640.39)	1180.47 (1112.45 to 1225.73)	89.41 (84.95 to 94.19)	3.07 (0.74 to 5.52)
Self-harm by other specified	16	15	670.45 (658.52 to 681.89)	1162.73 (1125.23 to 1201.12)	73.43 (66.99 to 79.75)	40.27 (34.83 to 45.71)
ICH	15	16	790.23 (751.02 to 815.00)	1145.77 (1059.58 to 1203.21)	44.99 (38.11 to 50.72)	–18.96 (–22.59 to –15.80)
Self-harm by	14	17	865.53 (851.41 to 879.94)	1011.87 (976.11 to 1048.33)	16.91 (12.49 to 21.56)	–11.01 (–14.44 to –7.40)
CKD due to type 2 diabetes	66	18	146.04 (119.56 to 176.35)	953.13 (850.81 to 1053.11)	552.63 (463.32 to 659.63)	249.60 (203.65 to 305.04)
Lower respiratory infections	8	19	1295.09 (1203.68 to 1347.18)	952.55 (859.94 to 1016.05)	–26.45 (–29.36 to –23.05)	–56.57 (–58.26 to –54.54)
Endocrine, metabolic,	33	20	290.31 (282.05 to 296.25)	948.30 (891.79 to 985.26)	226.65 (213.35 to 237.12)	91.90 (85.22 to 98.58)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; GBD, Global Burden of Diseases, Injuries, and Risk Factors; HD, heart disease; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³³

Table 2-5. Leading 20 Risk Factors for YLDs in the United States: Rank, Number, and Percent Change, 1990 and 2021

Risk factors	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized
High BMI	1	1	1786.71 (536.85 to 1786.71)	5088.28 (1908.99 to 5088.28)	184.78 (149.11 to 184.78)	69.25 (49.10 to 69.25)
High FPG	3	2	1083.75 (768.83 to 1083.75)	4290.44 (3092.47 to 4290.44)	295.89 (271.91 to 295.89)	123.66 (110.55 to 123.66)
Drug use	5	3	702.98 (489.37 to 702.98)	3179.31 (2246.54 to 3179.31)	352.26 (308.26 to 352.26)	280.37 (241.38 to 280.37)
Smoking	2	4	1700.48 (1112.35 to 1700.48)	2197.73 (1449.79 to 2197.73)	29.24 (20.62 to 29.24)	–22.75 (–27.48 to –18.02)
High alcohol use	4	5	1030.89 (730.38 to 1030.89)	1258.22 (896.33 to 1258.22)	22.05 (10.21 to 22.05)	–14.28 (–20.64 to –7.92)
High SBP	6	6	532.54 (374.99 to 532.54)	833.93 (569.93 to 833.93)	56.59 (42.29 to 56.59)	–11.53 (–19.55 to –3.51)
Diet high in processed meat	15	7	199.80 (46.57 to 199.80)	832.30 (198.31 to 832.30)	316.57 (289.16 to 316.57)	136.56 (121.04 to 136.56)

(Continued)

Table 2-5. Continued

Risk factors	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change (%), 1990–2021 (95%)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized
Low bone mineral density	8	8	414.14 (286.87 to	826.57 (584.32 to	99.58 (91.44 to	6.69 (2.41
Kidney dysfunction	9	9	386.30 (281.64 to	797.32 (581.45 to	106.40 (97.87 to	21.01 (16.73
Occupational ergonomic	7	10	530.40 (374.15 to	648.08 (468.77 to	22.19 (10.98 to	–12.69 (–19.85 to
Short gestation	10.5	11.5	382.40 (271.10 to	443.46 (316.41 to	15.97 (7.11 to	–4.39 (–11.84
LBW	10.5	11.5	382.40 (271.10 to	443.46 (316.41 to	15.97 (7.11 to	–4.39 (–11.84
Bullying victimization	13	13	239.14 (99.25 to	426.95 (183.69 to	78.53 (65.97 to	60.60 (49.19
Diet high in red meat	20	14	123.01 (–3.77 to	402.80 (–40.34 to	227.45 (123.06 to	85.91 (26.67
Diet high in sugar-	29	15	64.99 (29.95 to	376.26 (183.30 to	478.99 (373.33 to	233.60 (178.60 to
Low PA	24	16	86.66 (36.89 to	316.06 (134.68 to	264.72 (187.63 to	103.04 (62.35 to
Diet low in whole grains	23	17	98.51 (7.17 to	301.83 (49.97 to	206.40 (167.95 to	77.64 (54.71 to
High LDL-C	14	18	226.51 (103.43 to	292.94 (122.68 to	29.33 (16.86 to	–23.33 (–30.04 to
Ambient particulate matter	12	19	251.59 (99.28 to	287.45 (122.23 to	14.26 (–48.40 to	–35.13 (–70.65 to
Occupational noise	17	20	149.18 (102.03 to	227.03 (153.88 to	52.19 (46.11 to	–8.88 (–11.34 to

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Diseases, Injuries, and Risk Factors; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; SBP, systolic blood pressure; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³³

Table 2-6. Leading 20 Causes for YLDs in the United States: Rank, Number, and Percent Change, 1990 and 2021

Diseases and	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change (%), 1990–2021 (95%)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
Low back pain	1	1	3610.49 (2585.81 to	4940.71 (3587.05 to	36.84 (28.19 to	–7.87 (–13.00 to
Other musculoskeletal	2	2	1772.89 (1231.92 to	3749.41 (2670.48 to	111.49 (90.14 to	47.30 (32.95 to
Type 2 diabetes	10	3	732.34 (513.43 to	3362.56 (2367.85 to	359.16 (328.74 to	157.89 (140.73 to
Major depressive	5	4	1390.70 (965.05 to	3011.99 (2109.17 to	116.58 (106.42 to	74.26 (65.66 to
Anxiety disorders	4	5	1659.31 (1140.97 to	2814.41 (1928.98 to	69.61 (60.44 to	31.56 (24.87 to
Opioid use disorders	23	6	364.82 (250.25 to	2688.45 (1885.26 to	636.93 (573.49 to	531.11 (474.14 to
Age-related and other hearing	6	7	1374.55 (957.22 to	2231.33 (1567.63 to	62.33 (58.50 to	–5.63 (–7.36 to
Migraine	3	8	1704.15 (245.77 to	2129.03 (350.58 to	24.93 (18.96 to	–3.26 (–7.50

(Continued)

Table 2-6. Continued

Diseases and injuries	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)	
	1990	2021	1990	2021
Falls	7	9	953.54 (654.28 to	1689.31 (1182.88 to
Chronic obstructive	11	10	684.91 (573.21 to	1302.96 (1121.32 to
Asthma	8	11	943.69 (609.93 to	1282.33 (837.26 to
AD and other demen-tias	14	12	561.52 (382.38 to	978.20 (673.26 to
Neck pain	12	13	662.95 (438.46 to	919.64 (618.46 to
Osteoarthritis knee	18	14	457.80 (225.50 to	853.43 (420.64 to
Schizophrenia	13	15	660.74 (489.98 to	824.55 (617.70 to
Edentulism	17	16	469.54 (295.60 to	762.03 (487.56 to
Alcohol use disorders	9	17	764.87 (514.28 to	758.79 (522.53 to
Ischemic stroke	20	18	438.41 (311.56 to	711.18 (514.47 to
Autism spectrum dis-orders	15	19	495.96 (341.95 to	639.14 (443.19 to
Osteoarthritis hand	29	20	288.48 (131.02 to	558.65 (256.98 to

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; GBD, Global Burden of Diseases, Injuries, and Risk Factors; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³³

Table 2-7. Leading 20 Global Risk Factors of YLL and Death: Rank, Number, and Percent Change, 1990 and 2021

Risk factors	YLL rank (for total - number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age standardized YLL rate	1990	2021	Total No. of deaths	Age standardized death rate
High SBP	8	1	135 752.50 (113 118.36 to 156)	211 136.57 (178 644.53 to 243)	55.53 (44.97 to 67.27)	−31.21 (−35.68 to	6564.59 (5517.40 to 7510.30)	10 852.11 (9222.90 to 12 535.78)	65.31 (54.16 to 77.29)	−32.32 (−36.69 to
Smoking	9	2	122 608.46 (105 374.75 to 140)	142 365.55 (117 995.67 to 166)	16.11 (5.39 to 28.17)	−45.49 (−50.47 to	4784.43 (4087.94 to 5484.66)	6175.02 (5047.66 to 7226.38)	29.06 (16.78 to 42.63)	−42.47 (−47.81 to
LBW	1	3	246 031.65 (231 912.90 to 260)	138 557.77 (119 526.12 to 160)	−43.68 (−51.94 to −34.37)	−41.86 (−50.38 to	2735.31 (2578.32 to 2891.55)	1540.47 (1328.80 to 1784.70)	−43.68 (−51.94 to −34.37)	−41.86 (−50.38 to
Ambient particulate matter pollution	12	4	74 375.45 (52 484.13 to	108 661.22 (79 387.01 to	46.10 (16.52 to 85.31)	−17.57 (−33.63 to 1.38)	2433.56 (1750.35 to 3155.64)	4718.81 (3480.47 to 5795.95)	93.91 (56.89 to 137.15)	−13.94 (−31.09 to 5.23)
High FPG	14	5	46 610.01 (41	105 283.73 (90	125.88 (111.78 to 138.71)	1.78 (−4.30 to 7.41)	2163.06 (1895.07 to 2439.11)	5292.83 (4487.83 to 6114.99)	144.69 (130.26 to 158.94)	1.63 (−4.19 to 7.29)

(Continued)

Table 2-7. Continued

Risk factors	YLL rank (for total - number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age standardized YLL rate	1990	2021	Total No. of deaths	Age standardized death rate
Household air pollution from solid fuels	3	6	205 113.63 (147 057.37 to 257 059.06)	103 752.49 (68 848.77 to 138 258.11)	−49.42 (−61.30 to −33.03)	−64.58 (−72.21 to −54.46)	4815.87 (3773.99 to 5859.60)	3112.93 (1895.17 to 5188.70)	−35.36 (−53.84 to −6.77)	−66.27 (−75.54 to −52.18)
Short gestation	5	7	174 455.22 (162 603.72 to 187 306.72)	99 206.75 (83 123.45 to 115 290.05)	−43.13 (−51.68 to −33.48)	−41.32 (−50.15 to −32.49)	1939.80 (1807.94 to 2084.28)	1103.12 (929.21 to 1277.03)	−43.13 (−51.69 to −33.48)	−41.32 (−50.15 to −32.49)
High BMI	19	8	34 994.49 (17 488.19 to 52 500.79)	83 680.98 (41 143.49 to 126 018.47)	139.13 (124.05 to 154.30)	10.33 (3.10 to 17.33)	1459.53 (723.04 to 2287.05)	3709.06 (1847.84 to 5658.33)	154.13 (138.15 to 170.49)	8.15 (1.37 to 15.14)
High LDL-C	13	9	57 574.38 (36 342.83 to 78 805.93)	82 478.23 (52 289.74 to 112 666.72)	43.26 (34.83 to 51.70)	−34.45 (−38.05 to −30.85)	2452.01 (1431.74 to 3504.93)	3646.00 (2129.33 to 5262.17)	48.69 (40.45 to 56.94)	−38.06 (−41.08 to −35.04)
Kidney dysfunction	17	10	42 856.40 (37 744.83 to 47 967.97)	75 168.00 (66 113.41 to 84 222.59)	75.40 (64.59 to 87.08)	−18.45 (−23.62 to −13.28)	1864.83 (1596.39 to 2144.98)	3622.84 (3124.32 to 4142.44)	94.27 (81.89 to 106.64)	−20.55 (−25.84 to −15.26)
High alcohol use	18	11	42 842.70 (32 609.40 to 52 076.00)	56 110.48 (43 777.18 to 68 443.78)	30.97 (13.96 to 46.83)	−31.13 (−39.56 to −22.70)	1264.20 (951.65 to 1713.50)	1809.44 (1424.95 to 2280.48)	43.13 (24.75 to 60.45)	−30.98 (−39.43 to −22.53)
Child underweight	2	12	215 883.72 (121 721.56 to 264 045.88)	47 774.88 (18 341.48 to 77 408.28)	−77.87 (−85.35 to −70.39)	−78.82 (−86.25 to −71.39)	2506.06 (1441.43 to 3057.03)	623.82 (290.97 to 956.67)	−75.11 (−80.95 to −69.27)	−77.37 (−83.29 to −71.45)
Diet low in fruits	21	13	30 185.49 (10 345.49 to 50 025.49)	40 094.17 (16 154.17 to 64 034.17)	32.83 (22.87 to 47.33)	−36.69 (−41.47 to −31.91)	1148.88 (459.28 to 1743.21)	1683.59 (769.76 to 2397.42)	46.54 (34.92 to 65.80)	−35.30 (−40.29 to −30.31)
Unsafe sex	25	14	19 844.25 (16 711.25 to 22 977.25)	38 837.86 (36 143.86 to 41 531.86)	95.71 (66.05 to 129.84)	14.64 (−0.36 to 30.04)	452.92 (384.61 to 544.09)	900.65 (851.04 to 950.26)	98.85 (71.67 to 131.42)	8.05 (−4.97 to 21.07)
Diet high in sodium	22	15	28 119.52 (7 753.53 to 48 485.51)	38 609.26 (8606.28 to 68 552.24)	37.30 (0.04 to 56.51)	−37.32 (−53.24 to −21.40)	1221.01 (310.50 to 2716.78)	1857.70 (367.76 to 3347.64)	52.14 (9.69 to 94.59)	−34.40 (−51.16 to −17.64)
Unsafe water source	7	16	137 720.30 (80 340.30 to 214 100.30)	36 884.86 (19 464.86 to 54 304.86)	−73.22 (−78.81 to −66.81)	−77.80 (−82.47 to −73.13)	2173.55 (1265.81 to 2913.02)	802.49 (371.67 to 1233.31)	−63.08 (−72.25 to −53.88)	−76.22 (−81.34 to −71.10)
Child wasting	4	17	184 508.62 (104 314.64 to 230 702.60)	36 376.87 (20 196.87 to 52 556.87)	−80.28 (−84.06 to −76.54)	−81.08 (−84.77 to −77.39)	2148.48 (1244.60 to 2671.33)	493.99 (308.33 to 679.65)	−77.01 (−80.60 to −73.42)	−79.27 (−82.61 to −75.93)
Diet low in whole grains	23	18	24 497.82 (11 147.82 to 37 847.82)	35 969.36 (16 519.36 to 55 419.36)	46.83 (38.49 to 55.40)	−31.62 (−35.20 to −28.04)	991.50 (451.55 to 1484.97)	1546.24 (707.30 to 2385.18)	55.95 (47.41 to 64.58)	−33.45 (−36.77 to −30.13)
Second-hand smoke	15	19	44 341.85 (20 141.85 to 68 541.85)	30 755.02 (16 555.02 to 44 955.02)	−30.64 (−37.78 to −23.50)	−58.65 (−62.37 to −54.93)	1162.72 (598.58 to 1741.48)	1292.10 (683.12 to 2111.08)	11.13 (1.49 to 24.06)	−46.70 (−50.89 to −42.51)
Lead exposure	26	20	18 783.14 (−2140.6 to 40 783.14)	29 744.73 (−3602.5 to 67 744.73)	58.36 (44.90 to 74.84)	−27.30 (−33.32 to −21.28)	816.97 (−93.43 to 1711.64)	1541.91 (−184.92 to 3224.76)	88.73 (72.91 to 107.00)	−18.95 (−25.40 to −12.50)

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BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Diseases, Injuries, and Risk Factors; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLL, year of life lost because of premature mortality.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³³

Table 2-8. Leading 20 Global Causes of YLL and Death: Rank, Number, and Percentage Change, 1990 and 2021

Diseases and	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021	
	1990	2021	1990	2021	Total No. of YLLs	Age standardiz ed YLL
COVID-19		1		197 756.74 (187 900.90 to		
IHD	3	2	117 315.13 (112 735.36 to 121	184 306.89 (172 862.02 to 194	57.10 (48.40 to 65.60)	–29.24 (–32.99 to
Lower respiratory infections	1	3	203 755.78 (180 293.49 to 228	82 086.66 (72 180.87 to 92	–59.71 (–64.49 to –54.04)	–66.43 (–70.56 to
Other COVID-19 pandemic – related outcomes		4		77 380.46 (59 949.13 to 102 013.40)		
ICH	7	5	61 407.14 (57 472.81 to 65	76 770.05 (70 172.73 to 83	25.02 (12.87 to 38.20)	–39.57 (–45.32 to
Neonatal PTB	4	6	116 397.39 (107 040.98 to 125	66 505.73 (55 994.02 to 78	–42.86 (–52.63 to –32.24)	–41.09 (–51.14 to
COPD	10	7	50 060.63 (44 915.05 to 54	64 922.19 (59 331.48 to 71	29.69 (16.35 to 49.94)	–42.12 (–47.95 to
Ischemic stroke	12	8	40 721.83 (38 019.83 to 43	59 039.55 (53 954.03 to 64	44.98 (32.65 to 57.90)	–38.81 (–43.75 to
Neonatal encephalopathy due to birth asphyxia	5	9	79 422.85 (72 767.22 to 90 302.31)	54 290.95 (45 979.55 to 65 231.91)	–31.64 (–43.90 to –18.20)	–29.39 (–42.05 to –15.52)
Malaria	9	10	55 777.04 (28 085.58 to 110	52 809.22 (19 553.71 to 105	–5.32 (–31.11 to 17.30)	–16.76 (–38.67 to 3.16)
Diarrheal diseases	2	11	185 658.74 (147 478.91 to 220	51 430.25 (39 944.52 to 65	–72.30 (–77.51 to –66.04)	–77.14 (–81.35 to
Tracheal, bronchus, and lung	18	12	28 194.27 (26 730.88 to 29	45 987.99 (41 384.71 to 50	63.11 (43.96 to 83.28)	–23.03 (–32.02 to
Drug-susceptible	6	13	77 307.26 (67 711.56 to 85	38 387.69 (32 908.85 to 44	–50.34 (–57.80 to –38.39)	–69.26 (–73.88 to
Type 2 diabetes	26	14	14 978.00 (14 198.18	35 540.86 (33 217.12	137.29 (119.64 to	9.37 (1.39 to

(Continued)

Table 2-8. Continued

Diseases and	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age standardized YLL	1990	2021	Total No. of deaths	Age standardized death rate
AD and other dementias	41	17	9162.52 (2183.29 to 24)	24 750.58 (6224.34)	170.13 (154.02 to 192.84)	0.52 (−4.09 to 7.35)	663.29 (163.58 to 1764.99)	1952.68 (512.98 to 4984.74)	194.39 (176.93 to 220.09)	0.47 (−3.78 to 6.99)
Hypertensive HD	25	18	15 093.27 (11 952.15 to 16)	24 444.47 (20 447.32 to 26)	61.96 (41.16 to 100.17)	−26.94 (−35.80 to 1)	713.94 (577.53 to 1468.85)	1332.10 (1121.13 to 1468.85)	86.59 (62.76 to 126.51)	−21.99 (−31.92 to −6.74)
Colon and rectum cancer	30	19	13 970.16 (13 138.71 to 14)	23 318.79 (21 570.06 to 25)	66.92 (52.87 to 82.61)	−21.85 (−28.31 to 1)	570.32 (536.54 to 597.67)	1044.07 (950.19 to 1120.17)	83.07 (67.74 to 98.13)	−20.33 (−26.05 to 1)
Stomach cancer	23	20	22 989.38 (20 384.89 to 25)	22 460.91 (19 337.84 to 25)	−2.30 (−13.34 to 11.48)	−53.22 (−58.44 to 4)	854.18 (772.89 to 1089.58)	954.37 (821.75 to 1089.58)	11.73 (−0.71 to 26.84)	−49.11 (−54.70 to 1)

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer's Disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; GBD, Global Burden of Diseases, Injuries, and Risk Factors; HD, heart disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency virus; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; PTB, preterm birth; UI, uncertainty interval; and YLL, year of life lost to premature mortality.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³³

Table 2-9. Leading 20 Global Risk Factors for YLDs: Rank, Number, and Percentage Change, 1990 and 2021

Risk factors	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change, 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized
High FPG	3	1	13 737.13 (9554.12 to 18)	50 398.52 (35 296.76 to 67)	266.88 (256.28 to 1)	74.57 (67.58 to 1)
High BMI	4	2	13 047.62 (4145.76 to 23)	44 839.11 (16 115.14 to 77)	243.66 (222.37 to 1)	68.99 (57.21 to 1)
Iron deficiency	1	3	28 568.55 (19 474.85 to 40)	32 480.16 (21 893.33 to 46)	13.69 (9.85 to 1)	−18.26 (−21.14 to 1)
Smoking	2	4	14 926.36 (9932.27 to 20)	22 715.11 (15 531.41 to 31)	52.18 (47.94 to 1)	−25.46 (−27.24 to 1)
High alcohol use	5	5	11 756.01 (8077.93 to 16)	16 143.76 (11 228.27 to 22)	37.32 (30.03 to 1)	−20.25 (−23.20 to 1)
Occupational ergonomic	6	6	10 852.09 (7600.73 to 14)	15 569.22 (11 026.00 to 20)	43.47 (37.16 to 1)	−18.96 (−21.82 to 1)
High SBP	11	7	6671.11 (4711.79 to 1)	14 396.40 (10 133.05 to 19)	115.80 (108.04 to 1)	−2.60 (1)
Short gestation	8.5	8.5	7952.30 (5842.55 to 10)	13 829.44 (9959.54 to 17)	73.90 (61.98 to 1)	29.12 (20.25 to 1)
LBW	8.5	8.5	7952.30 (5842.55 to 10)	13 829.44 (9959.54 to 17)	73.90 (61.98 to 1)	29.12 (20.25 to 1)
Ambient particulate matter	21	10	3084.28 (2028.96 to 1)	11 343.45 (7413.96 to 15)	267.78 (204.08 to 1)	71.56 (41.76 to 1)
Kidney dysfunction	13	11	5336.42 (3868.49 to 1)	11 060.30 (8087.37 to 14)	107.26 (100.76 to 1)	−0.66 (1)
Drug use	12	12	5909.15 (4112.40 to 1)	9636.01 (6895.45 to 12)	63.07 (53.95 to 1)	9.28 (3.69 to 1)
Low bone mineral density	15	13	4353.49 (3112.57 to 1)	8426.85 (5950.12 to 11)	93.57 (89.83 to 1)	−14.39 (−15.75 to 1)

(Continued)

Table 2-9. Continued

Risk factors	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)	
	1990	2021	1990	2021
Occupational noise	18	14	3838.06 (2630.90 to	7847.44 (5313.65 to 12
Household air pollution from solid fuels	10	15	6747.06 (4385.96 to 9083.24)	7710.47 (3655.16 to 591.28)
Occupational injuries	7	16	8888.39 (6530.37 to 11	7518.69 (5280.91 to 12
Bullying victimization	19	17	3773.89 (1569.01 to	6166.23 (2690.93 to 12
High LDL-C	23	18	2625.91 (1199.83 to	5247.88 (2326.08 to 12
Unsafe sex	28	19	1716.63 (1245.92 to	5137.42 (3785.35 to 12
Unsafe water source	14	20	4657.42 (2357.80 to	4833.85 (2166.44 to 12

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BMI indicates body mass index; FPG, fasting plasma glucose; GBD, Global Burden of Diseases, Injuries, and Risk Factors; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³³

Table 2-10. Leading 20 Global Causes for YLDs: Rank, Number, and Percentage Change, 1990 and 2021

Diseases and	YLD rank (for total number)		Total No. of YLD, in thousands (95% UI)		Percent change, 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
Low back pain	1	1	43 386.23 (31 083.94 to 58	70 156.96 (50 194.20 to 94	61.70 (58.59 to 65.45)	–11.22 (–11.82 to
Major depressive disorder	4	2	23 843.69 (16 349.84 to 32	46 018.84 (31 460.39 to 62	93.00 (87.25 to 98.80)	16.07 (13.19 to
Age-related and other hearing loss	6	3	21 269.54 (14 621.10 to 29	44 449.94 (30 689.65 to 62	108.98 (104.02 to 113.15)	5.31 (4.23 to
Migraine	3	4	27 412.20 (4076.61 to 60	43 378.89 (6732.64 to 95	58.25 (53.75 to 66.10)	1.13 (–4.05 to
Other musculoskeletal	7	5	18 979.06 (13 024.02 to 26	42 988.18 (29 647.81 to 59	126.50 (120.36 to 133.29)	25.82 (23.36 to
Anxiety disorders	5	6	22 996.73 (15 814.12 to 31	42 509.65 (29 396.72 to 57	84.85 (79.23 to 91.63)	18.17 (15.57 to
Type 2 diabetes	11	7	9952.99 (6985.11 to 13	39 800.01 (28 016.29 to 54	299.88 (289.04 to 311.63)	94.66 (89.38 to
Dietary iron deficiency	2	8	28 406.13 (19 357.61 to 40	32 315.75 (21 779.58 to 46	13.76 (9.91 to 17.61)	–18.19 (–21.09 to
Falls	8	9	14 846.59 (10 450.14 to 20	24 172.95 (16 816.84 to 32	62.82 (57.38 to	–13.69 (–15.40 to
Neck pain	9	10	11 442.36 (7608.94 to 16	20 415.50 (13 638.71 to 28	78.42 (69.94 to 87.21)	0.14 (–1.52 to
Other gynecological diseases	12	11	9882.51 (6702.66 to 14	15 603.39 (10 581.11 to 22	57.89 (54.69 to 61.67)	–8.84 (–10.97 to
COPD	17	12	6796.66 (5696.89 to	14 857.50 (12 405.35 to 17	118.60 (112.82 to 123.65)	3.29 (0.94 to
Schizophrenia	13	13	8762.31 (6477.26 to 11	14 816.61 (10 926.46 to 19	69.09 (65.16 to 72.86)	0.64 (–0.48 to

(Continued)

Table 2-10. Continued

Diseases and	YLD rank (for total number)		Total No. of YLD, in thousands (95% UI)		Percent change, 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
COVID-19		14		14 252.86 (5138.71 to 33)		
Neonatal PTB	15	15	7952.30 (5842.55 to 10)	13 829.44 (9959.54 to 17)	73.90 (61.98 to 84.96)	29.12 (20.25 to
Osteoarthritis knee	23	16	5145.34 (2507.48 to	12 019.07 (5858.11 to 23)	133.59 (131.71 to 135.70)	8.22 (7.55 to
Near vision loss	32	17	4316.10 (1937.50 to	11 649.94 (5214.02 to 22)	169.92 (150.81 to 187.19)	37.92 (28.63 to
AD and other dementias	31	18	4409.78 (3029.44 to	11 582.11 (7961.94 to 15)	162.65 (156.93 to 168.08)	2.63 (1.12 to
Autism spectrum disorders	16	19	7868.39 (5351.16 to 11)	11 544.04 (7842.31 to 16)	46.71 (44.44 to 48.61)	2.10 (0.56 to
Ischemic stroke	21	20	5454.41 (3922.23 to	11 318.37 (8183.93 to 14)	107.51 (102.50 to 112.50)	−1.67 (−3.59 to

During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer's Disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; GBD, Global Burden of Diseases, Injuries, and Risk Factors; PTB, preterm birth; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³³

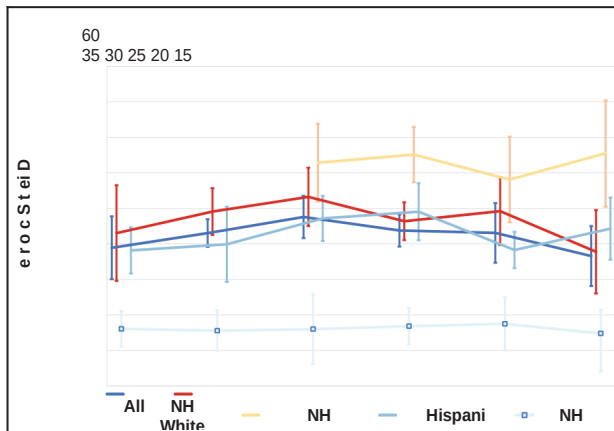
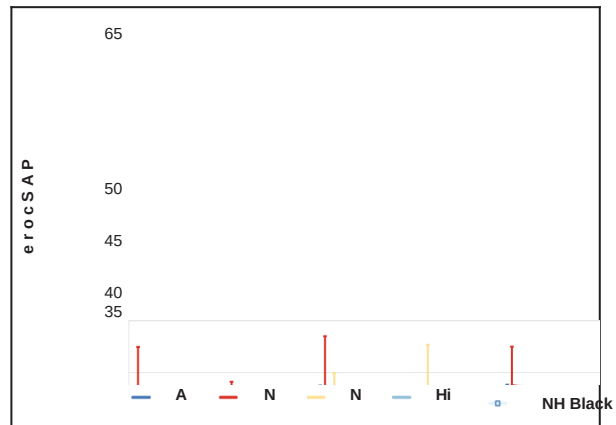


Chart 2-1. Trends in age-adjusted mean scores (95% CI) for the diet component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to 2018.



Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

Chart 2-2. Trends in age-adjusted mean scores (95% CI) for the PA component of CVH among US adults ≥ 20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and PA, physical activity.

Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

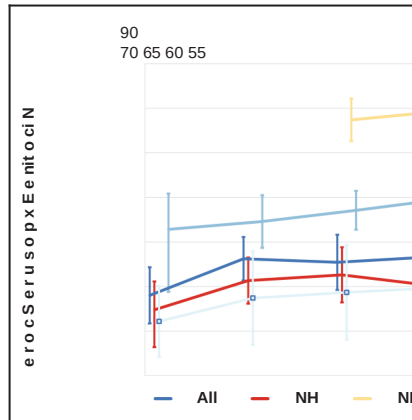
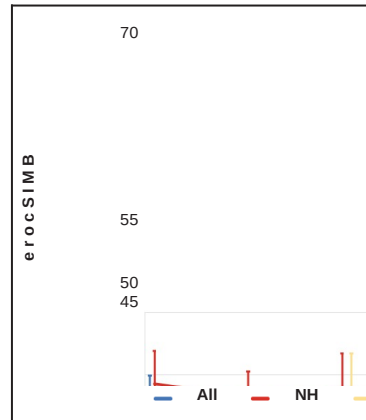


Chart 2-3. Trends in age-adjusted mean scores (95% CI) for the nicotine exposure component of CVH among US adults



≥20 years of age, NHANES 2007 to 2008 through 2017 to

Chart 2-5. Trends in age-adjusted mean scores (95% CI) for the BMI component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.

March 2020.

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

BMI indicates body mass index; CI, confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

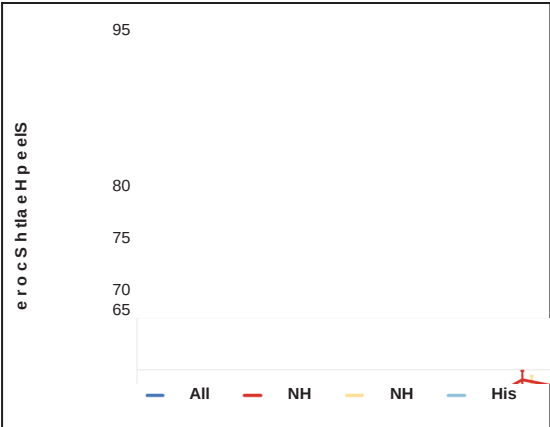
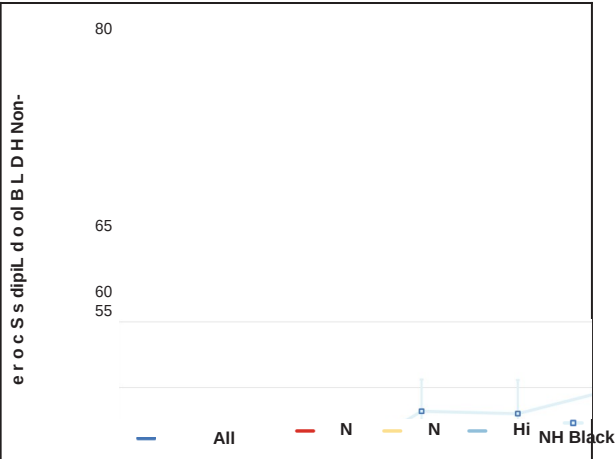


Chart 2-4. Trends in age-adjusted mean scores (95% CI) for the sleep health component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.



CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

Chart 2-6. Trends in age-adjusted mean scores (95% CI) for the non-HDL blood lipids component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.

CI indicates confidence interval; CVH, cardiovascular health; HDL, high-density lipoprotein; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

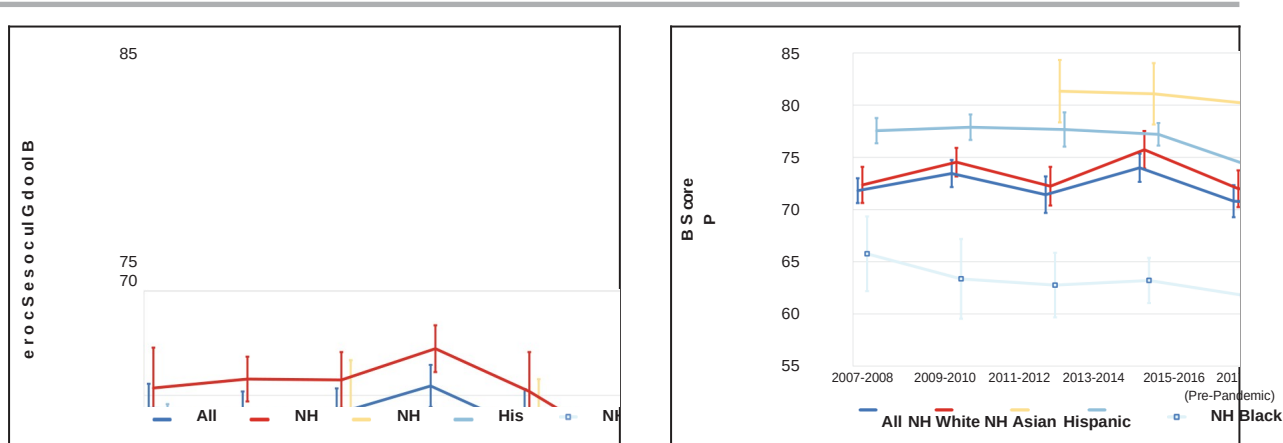


Chart 2-7. Trends in age-adjusted mean scores (95% CI) for the blood glucose component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March

Chart 2-8. Trends in age-adjusted mean scores (95% CI) for the BP component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.

2020.

BP indicates blood

pressure; CI, confidence interval; CVH,

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.¹⁰⁸

REFERENCES

1. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
2. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
3. Zheng Y, Huang T, Guasch-Ferre M, Hart J, Laden F, Chavarro J, Rimm E, Coull B, Hu H. Estimation of Life's Essential 8 score with incomplete individual metrics. *Front Cardiovasc Med*. 2023;10:1216693. doi: 10.3389/fcvm.2023.1216693
4. Herraiz-Adillo A, Ahlqvist VH, Higuera-Fresnillo S, Berglund D, Wennberg P, Lenander C, Daka B, Ekstedt M, Sundström J, Ortega FB, et al. Life's Essential 8 and carotid artery plaques: the Swedish cardiovascular pulmonary bioimage study. *Front Cardiovasc Med*. 2023;10:1173550. doi: 10.3389/fcvm.2023.1173550
5. Radovanovic M, Jankovic J, Mandic-Rajcevic S, Dumic I, Hanna RD, Nordstrom CW. Ideal cardiovascular health and risk of cardiovascular events or mortality: a systematic review and meta-analysis of prospective studies. *J Clin Med*. 2023;12:4417. doi: 10.3390/jcm12134417
6. Zhang Y, Yu C, Chen S, Tu Z, Zheng M, Lv J, Wang G, Liu Y, Yu J, Guo Y, et al. Ideal cardiovascular health and mortality: pooled results of three prospective cohorts in Chinese adults. *Chin Med J (Engl)*. 2023;136:141–149. doi: 10.1097/CM9.0000000000002379
7. Shay CM, Gooding HS, Murillo R, Foraker R. Understanding and improving cardiovascular health: an update on the American Heart Association's concept of cardiovascular health. *Prog Cardiovasc Dis*. 2015;58:41–49. doi: 10.1016/j.pcd.2015.05.001

10. Gao B, Song S, Guo J. Associations between Life's Simple 7 and incident depression among adults aged 50 years and older: a 15-year cohort study. *Psychiatry Res.* 2023;320:115046. doi: 10.1016/j.psychres.2022.115046
11. Gou R, Chang X, Li Z, Pan Y, Li G. Association of Life's Essential 8 with osteoarthritis in United States adults: mediating effects of dietary intake of live microbes. *Front Med.* 2023;10:1297482. doi: 10.3389/fmed.2023.1297482
12. Shim SY, Jung SJ, Kim SU, Kim HC. Ideal cardiovascular health metrics and the risk of nonalcoholic fatty liver disease in Korean adults. *Clin Hypertens.* 2023;29:3. doi: 2910.1186/s40885-022-00227-0
13. Van Sloten T, Valentin E, Climie RE, Deraz O, Weiderpass E, Jouven X, Goldberg M, Zins M, Empana JP. Association of midlife cardiovascular health and subsequent change in cardiovascular health with incident cancer. *JACC CardioOncol.* 2023;5:39–52. doi: 10.1016/j.jacc.2022.11.015
14. Rawal S, Johnson BR, Young HN, Gaye B, Sattler ELP. Association of Life's Simple 7 and ideal cardiovascular health in American Indians/Alaska Natives. *Open Heart.* 2023;10:e002222. doi: 10.1136/openhrt-2022-002222
15. López-Bueno R, Yang L, Calatayud J, Andersen LL, Del Pozo Cruz B. Dose-response association between cardiovascular health and mortality in cancer survivors. *Curr Probl Cardiol.* 2024;49:102176. doi: 10.1016/j.cpcardiol.2023.102176
16. Isiozor NM, Kunutsor SK, Voutilainen A, Kurl S, Kauhanen J, Laukkanen JA. Association between ideal cardiovascular health and risk of sudden cardiac death and all-cause mortality among middle-aged men in Finland. *Eur J Prev Cardiol.* 2021;28:294–300. doi: 10.1177/2047487320915338
17. Díez-Espino J, Buil-Cosiales P, Babio N, Toledo E, Corella D, Ros E, Fitó M, Gómez-Gracia E, Estruch R, Fiol M, et al. Impact of Life's Simple 7 on the incidence of major cardiovascular events in high-risk Spanish adults in the PREDIMED study cohort. *Rev Esp Cardiol (Engl Ed).* 2020;73:205–211. doi: 10.1016/j.rec.2019.05.010
18. Kim S, Chang Y, Cho J, Hong YS, Zhao D, Kang J, Jung HS, Yun KE, Guallar E, Ryu S, et al. Life's Simple 7 cardiovascular health metrics and progression of coronary artery calcium in a low-risk population. *Arterioscler Thromb Vasc Biol.* 2019;39:826–833. doi: 10.1161/ATVBAHA.118.311821
19. Brenn T. Survival to age 90 in men: the Tromsø study 1974–2018. *Int J Environ Res Public Health.* 2019;16:2028. doi: 10.3390/ijerph16112028
20. Szlejf C, Suemoto CK, Santos IS, Brunoni AR, Nunes MA, Viana MC, Barreto A. Greater adherence to Life's Simple 7 is associated with less arterial stiffness: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Hypertens.* 2019;32:769–776. doi: 10.1016/j.pcad.2015.05.003

SM, Lotufo PA, Bensenor IM. Poorer cardiovascular health is associated with psychiatric comorbidity: results from the ELSA-Brasil Study. *Int J Cardiol.* 2019;274:358–365. doi: 10.1016/j.ijcard.2018.06.037

doi: 10.1093/ajh/hpz057

9. Chen X, Sun J, Zeng C, Jin F, Ma S, Song J, Chen Z. Association between Life's Essential 8 and periodontitis: a population-based study. *BMC Oral Health.* 2024;24:1–10. doi: 10.1186/s12903-023-03816-z
21. Dong Y, Hao G, Wang Z, Wang X, Chen Z, Zhang L. Ideal cardiovascular health status and risk of cardiovascular disease or all-cause mortality in Chinese middle-aged population. *Angiology.* 2019;70:523–529. doi: 10.1177/0003319718813448

22. Uijl A, Koudstaal S, Vaartjes I, Boer JMA, YT, Asselbergs FW, Hoes AW, Sluijs I. Risk for prevention with the American Heart *Heart Fail*. 2019;7:637–647. doi:
23. Wu S, Xu Y, Zheng R, Lu J, Li M, Chen L, et al. Hypertension defined by 2017 cular health metrics, and risk of spective cohort study. *Lancet Rea Health* 10.1016/j.lanwnc.2021.100350
24. Del Brutto OH, Mera RM, Recalde BY. 7 and all-cause mortality: a population-middle-aged and older adults of Amerindian *Prev Med Rep*. 2022;25:101668. doi:
25. Wang T, Lu J, Su Q, Chen Y, Bi Y, Mu Y, Chen L, Hu R, Tang X, Yu X, et al; 4C Study Group. Ideal cardiovascular health metrics and major cardio-vascular events in patients with prediabetes and diabetes. *JAMA Cardiol*. 2019;4:874–883. doi: 10.1001/jamacardio.2019.2499
26. Ning N, Zhang Y, Liu Q, Zhou W, He Y, Liu Y, Jin L, Ma Y. American cardiovascular health with premature *Am Coll Cardiol*. 2020;76:2695–2707.
39. Rempakos A, Prescott B, Mitchell GF. tion of Life's Essential 8 with Framingham Heart Study. *J Am Heart* 10.1161/iaha.123.030764
40. Corlin L, Short ML, Vasan RS, Xanthakis ideal cardiovascular health through comes and mortality in the 2020;5:549–556. doi:
41. Gave B, Taien GS, Vasan RS, Lassale Jouven X. Association of changes in risk of subsequent cardiovascular Heart As- sociation's new "Life's Essential 8" score in association with cardiovascular disease: a national cross-sectional analysis. *Public Health*. 2023;225:336–

- 2020;9:e017458. doi: 10.1161/JAHA.120.017458
42. Yang PS, Jang E, Yu HT, Kim TH, Pak HN, Lee MH, Joung B. Changes in cardiovascular risk factors and cardiovascular events in the elderly population. *J Am Heart Assoc.* 2021;10:e019482. doi: 10.1161/JAHA.120.019482
43. Muchira JM, Gona PN, Mogos MF, Stuart-Shor E, Leveille SG, Piano MR, Hayman LL. Parental cardiovascular health predicts time to onset of cardiovascular disease in offspring. *Eur J Prev Cardiol.* 2022;29:883–891. doi: 10.1016/j.puhe.2023.10.027
44. Li Y, Gray A, Xue L, Farb MG, Ayalon N, Andersson C, Ko D, Benjamin EJ, Levy D, Vasani RS, et al. Metabolomic profiles, ideal cardiovascular health, and risk of heart failure and atrial fibrillation: insights from the Framingham Heart Study. *J Am Heart Assoc.* 2023;12:e028022. doi: 10.1161/jaha.122.028022
45. Mahemuti N, Zou J, Liu C, Xiao Z, Liang F, Yang X. Urinary albumin-to-creatinine ratio in normal range, cardiovascular health, and all-cause mortality. *JAMA Netw Open.* 2023;6:e2348333. doi: 10.1001/jamanetworkopen.2023.48333
46. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. *J Am Coll Cardiol.* 2011;57:1690–1696. doi: 10.1016/j.jacc.2010.11.041
47. Tsao CW, Aday AW, Almarazooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2023 update: a report from the American Heart Association [published corrections appear in *Circulation.* 2023;147:e622 and *Circulation.* 2023;148:e4]. *Circulation.* 2023;147:e93–e621. doi: 10.1161/CIR.0000000000001123
48. Sutton S, Sims M, Winters K, Correa A, Escoffery C, Arriola KJ. The association between cardiovascular health with internet and mobile technology use among Jackson Heart Study participants. *Telemed J E Health.* 2023;29:1035–1042. doi: 10.1089/tmj.2022.0186
49. Kulshreshtha A, Vaccarino V, Judd SE, Howard VJ, McClellan WM, Muntner

44. Perak AM, Lancki N, Kuang A, Labarthe DR, Allen NB, Shah SH, Lowe LP, Grobman WA, Lawrence JM, Lloyd-Jones DM, et al; HAPO Follow-Up Cooperative Research Group. Associations of maternal cardiovascular health in pregnancy with offspring cardiovascular health in early adolescence. *JAMA*. 2021;325:658–668. doi: 10.1001/jama.2021.0247
45. Muchira JM, Gona PN, Mogos MF, Stuart-Shor EM, Leveille SG, Piano MR, Hayman LL. Association of parental cardiovascular health with disability-adjusted life years in the offspring: results from the Framingham Heart Study. *Circ Cardiovasc Qual Outcomes*. 2023;16:e008809. doi: 10.1161/circoutcomes.121.008809
46. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA*. 2012;308:1795–1801. doi: 10.1001/jama.2012.14312
47. Wang L, Song L, Li D, Zhou Z, Chen S, Yang Y, Hu Y, Wang Y, Wu S, Tian Y. Ideal cardiovascular health metric and its change with lifetime risk of cardiovascular diseases: a prospective cohort study. *J Am Heart Assoc*. 2021;10:e022502. doi: 10.1161/JAHA.121.022502
48. Tian Q, Chen S, Zhang J, Li C, Wu S, Wang Y, Wang Y. Ideal cardiovascular health metrics and life expectancy free of cardiovascular diseases: a prospective cohort study. *EPMA J*. 2023;14:185–199. doi: 10.1007/s13167-023-00322-8
49. Xu C, Zhang P, Cao Z. Cardiovascular health and healthy longevity in people with and without cardiometabolic disease: a prospective cohort study. *EClinicalMedicine*. 2022;45:101329. doi: 10.1016/j.eclinm.2022.101329
50. Zhang N, Yang Y, Wang A, Cao Y, Li J, Yang Y, Zhang K, Zhang W, Wu S, Wang Z, et al. Association of ideal cardiovascular health metrics and cognitive functioning: the APAC study. *Eur J Neurol*. 2016;23:1447–1454. doi: 10.1111/ene.13056
- P, Hong Y, Safford MM, Goyal A, Cushman M. Life's Simple 7 and risk of incident stroke: the reasons for geographic and racial differences in stroke study. *Stroke*. 2013;44:1909–1914. doi: 10.1161/STROKEAHA.111.000352
33. Cao Z, Li S, Yang H, Xu C, Zhang Y, Yang X, Yan T, Liu T, Wang Y. As-

51. Yang M, Liu Y, Hu X, Ren D, Yang Q, Mao J, Chen J. Association of Life's Simple 7 with mild cognitive impairment in community-dwelling older adults in China: a cross-sectional study. *Front Aging Neurosci.* 2023;15:1203920. doi: 10.3389/fnagi.2023.1203920
- with risks of stroke and stroke subtypes: a prospective cohort study. *EClinicalMedicine.* 2021;33:100791. doi: 10.1016/j.eclinm.2021.100791
34. Wu S, Wu Z, Yu D, Chen S, Wang A, Wang A, Gao X. Life's Essential 8 and risk of stroke: a prospective community-based study. *Stroke.* 2023;54:2369–2379. doi: 10.1161/STROKEAHA.123.042525
35. Petermann-Rocha F, Deo S, Celis-Morales C, Ho FK, Bahuguna P, McAllister D, Sattar N, Pell JP. An opportunity for prevention: associations between the Life's Essential 8 score and cardiovascular incidence using prospective data from UK Biobank. *Curr Probl Cardiol.* 2023;48:101540. doi: 10.1016/j.cpcardiol.2022.101540
36. Nguyen ATH, Saeed A, Bambs CE, Swanson J, Emechebe N, Mansuri F, Talreja K, Reis SE, Kip KE. Usefulness of the American Heart Association's ideal cardiovascular health measure to predict long-term major adverse cardiovascular events (from the Heart SCORE Study). *Am J Cardiol.* 2021;138:20–25. doi: 10.1016/j.amjcard.2020.10.019
37. Bundy JD, Zhu Z, Ning H, Zhong VW, Paluch AE, Wilkins JT, Lloyd-Jones DM, Whelton PK, He J, Allen NB. Estimated impact of achieving optimal cardiovascular health among US adults on cardiovascular disease events. *J Am Heart Assoc.* 2021;10:e019681. doi: 10.1161/JAHA.120.019681
38. Perak AM, Ning H, Khan SS, Bundy JD, Allen NB, Lewis CE, Jacobs DR Jr, Van Horn LV, Lloyd-Jones DM. Associations of late adolescent or young adult

53. Ferreira NV, Gonçalves NG, Szlejf C, Goulart AC, de Souza Santos I, Duncan BB, Schmidt MI, Barreto SM, Caramelli P, Feter N, et al. Optimal cardio-vascular health is associated with slower cognitive decline. *Eur J Neurol*. 2024;31:e16139. doi: 10.1111/ene.16139
54. Zhou R, Chen H-W, Li F-R, Zhong Q, Huang Y-N, Wu X-B. "Life's Essential 8" cardiovascular health and dementia risk, cognition, and neuroimaging markers of brain health. *J Am Med Dir Assoc*. 2023;24:1791–1797. doi: 10.1016/j.jamda.2023.05.023
55. Peloso GM, Beiser AS, Satizabal CL, Xanthakis V, Vasan RS, Pase MP, Destefano AL, Seshadri S. Cardiovascular health, genetic risk, and risk of dementia in the Framingham Heart Study. *Neurology*. 2020;95:e1341–e1350. doi: 10.1212/WNL.0000000000010306
56. Sabia S, Fayosse A, Dumurgier J, Schnitzler A, Empana JP, Ebmeier KP, Dugravot A, Kivimaki M, Singh-Manoux A. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *BMJ*. 2019;366:l4414. doi: 10.1136/bmj.l4414
57. Liang Y, Ngandu T, Laatikainen T, Soininen H, Tuomilehto J, Kivipelto M, Qiu C. Cardiovascular health metrics from mid- to late-life and risk of dementia: a population-based cohort study in Finland. *PLoS Med*. 2020;17:e1003474. doi: 10.1371/journal.pmed.1003474

58. Wu J, Xiong Y, Xia X, Orsini N, Qiu C, Kivipelto M, Rizzuto D, Wang R. Can dementia risk be reduced by following the American Heart Association's Life's Simple 7? A systematic review and dose-response meta-analysis. *Ageing Res Rev.* 2023;83:101788. doi: 10.1016/j.arr.2022.101788
59. Climie RE, Tafflet M, van Sloten T, de Lauzon-Guillain B, Bernard JY, Dargent-Molina P, Plancoulaine S, Lioret S, Jouven X, Charles MA, et al. Cardiovascular health at age 5 years: distribution, determinants, and association with neurodevelopment. *Front Pediatr.* 2022;10:827525. doi: 10.3389/fped.2022.827525
60. Lamar M, Estrella ML, Capuano AW, Leurgans S, Fleischman DA, Barnes LL, Lande-Maia BS, Bennett DA, Marquez DX. A longitudinal study of cardiovascular health metrics and depression among U.S. adults: National Health and Nutrition Examination Survey, 2007-2014. *Ann Epidemiol.* 2019;31:49-56.e2. doi: 10.1016/j.annepidem.2018.12.005
61. Zhang Z, Jackson S, Merritt R, Gillespie C, Yang Q. Association between cardiovascular health metrics and depression among U.S. adults: National Health and Nutrition Examination Survey, 2007-2014. *Ann Epidemiol.* 2019;31:49-56.e2. doi: 10.1016/j.annepidem.2018.12.005
62. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
63. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
64. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
65. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
66. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
67. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
68. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
69. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
70. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
71. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
72. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
73. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
74. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
75. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
76. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
77. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
78. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
79. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
80. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
81. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
82. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
83. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
84. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
85. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
86. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
87. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
88. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
89. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
90. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
91. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
92. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
93. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
94. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
95. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
96. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
97. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
98. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
99. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438
100. Williams A, Nolan TS, Brock G, Garner J, Brewer LC, Sanchez EJ, Joseph JJ. Association of socioeconomic status with Life's Simple 7. *J Am Heart Assoc.* 2022;11:e023438. doi: 10.1161/JAHA.121.023438

- the Multi-Ethnic Study of Atherosclerosis. *Am J Health Educ.* 2023;54:451–80. Hawes MR, Roth KB, Wang X, Stefancic A, Weatherly C, Cabassa LJ. Ideal serious mental illness. *J Health Care Poor Underserved.* 2020;31:1669–1692. doi: 10.1080/19325037.2023.2254354
62. Brunoni AR, Szlejf C, Suemoto CK, Santos IS, Goulart AC, Viana MC, Koyanagi A, Barreto SM, Moreno AB, Carvalho AF, et al. Association between ideal cardiovascular health and depression incidence: a longitudinal analysis of ELSA-Brasil. *Acta Psychiatr Scand.* 2019;140:552–562. doi: 10.1353/hpu.2020.0126
- cardiovascular health in racially and ethnically diverse people with

81. Zheng Y, Wen X, Bian J, Zhao J, Lipkind HS, Hu H. Racial, ethnic, and geographic disparities in cardiovascular health among women of childbearing age in the United States. *J Am Heart Assoc.* 2021;10:e020138. doi: 10.1111/acps.13109

10.1161/JAHA.120.020138

82. Jankovic J, Mandic-Rajcevic S, Davidovic M, Jankovic S. Demographic and socioeconomic inequalities in ideal cardiovascular health: a systematic review and meta-analysis. *PLoS One*. 2021;16:e0255959. doi: 10.1371/journal.pone.0255959
- 2022;154:106891. doi: 10.1016/j.ypmed.2021.106891

83. Leung CW, Wolfson JA, Brandt EJ, Rimm EB. Disparities in cardiovascular health by food security status and Supplemental Nutrition Assistance Program participation using Life's Essential 8 metrics. *JAMA Netw Open*. 2023;6:e2321375– doi: 10.1002/hlth.1614
- chronic obstructive pulmonary disease with American Heart Association's Life's Simple 7 cardiovascular health metrics. *Respir Med*. 2017;131:85–93. doi: 10.1016/j.rmed.2017.08.001
66. Lee JH, Yang PS, Yu HT, Kim TH, Jang E, Uhm JS, Pak HN, Lee MH, Joung B. Association of cardiovascular health and incident atrial fibrillation in elderly population. *Heart*. 2021;107:1206–1212. doi: 10.1136/heartjnl-2020-318858
67. Osibogun O, Ogunmoroti O, Spatz ES, Fashanu OE, Michos ED. Ideal cardiovascular health and resting heart rate in the Multi-Ethnic Study of Atherosclerosis. *Prev Med*. 2020;130:105890. doi: 10.1016/j.ypmed.2019.105890
68. DeCoste LR, Wang N, Palmisano JN, Mendez J, Hoffmann U, Benjamin EJ, Long MT. Adherence to ideal cardiovascular health metrics is associated with reduced odds of hepatic steatosis. *Hepatol Commun*. 2021;5:74–82. doi: 10.1002/hep4.1614

10.1001/jamanetworkopen.2023.21375

84. Mujahid MS, Moore LV, Petito LC, Kershaw KN, Watson K, Diez Roux AV. Neighborhoods and racial/ethnic differences in ideal cardiovascular health (the Multi-Ethnic Study of Atherosclerosis). *Health Place*. 2017;44:61–69. doi: 10.1016/j.healthplace.2017.01.005
85. Hines AL, Albert MA, Blair JP, Crews DC, Cooper LA, Long DL, Carson AP. Neighborhood factors, individual stressors, and cardiovascular health among Black and White adults in the US: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *JAMA Netw Open*. 2023;6:e2336207. doi: 10.1001/jamanetworkopen.2023.36207
86. Joseph JJ, Williams A, Azap RA, Zhao S, Brock G, Kline D, Odei JB, Foraker R, Sims M, Brewer LC, et al. Role of sex in the association of socioeconomic status with cardiovascular health in Black Americans: the Jackson Heart Study. *J Am Heart Assoc*. 2023;12:e030695. doi: 10.1161/jaha.123.030695
69. De La Cruz N, Shabaneh O, Appiah D. The association of ideal cardiovascular health and ocular diseases among US adults. *Am J Med*. 2021;134:252–259.e1. doi: 10.1016/j.amjmed.2020.06.004
70. Wang Q, Zhou C, Dong C, Zhang J, Xie Z, Sun H, Fu C, Hao W, Zhu D. Midlife Life's Simple 7, psychosocial health, and physical frailty, hospital frailty, and comprehensive frailty 10 years later. *Nutrients*. 2023;15:2412.

87. Ko YA, Shen J, Kim JH, Topel M, Mujahid M, Taylor H, Quyyumi A, Sims M, Vaccarino V, Baltrus P, et al. Identifying neighbourhood and individual resilience profiles for cardiovascular health: a cross-sectional study of Blacks living in the Atlanta metropolitan area. *BMJ Open*. 2021;11:e041435. doi: 10.1136/bmjopen-2020-041435
doi: 10.3390/nu15102412
71. Palta P, Griswold M, Ranadive R, Bandeen-Roche K, Folsom AR, Petruski-Ivleva N, Burgard S, Kucharska-Newton A, Windham BG. Midlife cardiovascular health and robust versus frail late-life status: the Atherosclerosis Risk in Communities (ARIC) study. *J Gerontol A Biol Sci Med Sci*. 2022;77:1222–1229. doi: 10.1093/gerona/glab310
88. Piedra LM, Andrade FCD, Hernandez R, Perreira KM, Gallo LC, Gonzalez 2022;77:1222–1229. doi: 10.1093/gerona/glab310
72. Chen L, Li X, Lv Y, Tan X, Zhong VW, Rong S, Liu G, Liu L. Physical frailty, adherence to ideal cardiovascular health and risk of cardiovascular disease: a prospective cohort study. *Age Ageing*. 2023;52:1–9. doi:

HM, Gonzalez S, Cai J, Chen J, Castaneda SF, et al. Association of subjective social status with Life's Simple 7s cardiovascular health index among Hispanic/Latino people: results from the HCHS/SOL. *J Am Heart Assoc*. 2021;10:e012704. doi: 10.1161/JAHA.119.012704

89. Diaz CL, Shah NS, Lloyd-Jones DM, Khan SS. State of the nation's cardiovascular health and targeting health equity in the United States: a narrative review. *JAMA Cardiol*. 2021;6:963–970. doi: 10.1001/jamacardio.2021.1137
73. Das Gupta D, Kelekar U, Abram-Moyle M. Association between ideal cardiovascular health and multiple disabilities among US adults, BRFSS 2017–2019. *Public Health*. 2023;218:60–67. doi: 10.1016/j.puhe.2023.02.014
74. Caleyachetty R, Echouffo-Tcheugui JB, Muennig P, Zhu W, Muntner P, Shimbo D. Association between cumulative social risk and ideal cardiovascular health in US adults: NHANES 1999–2006. *Int J Cardiol*. 2021;328:1–10. doi: 10.1016/j.ijcard.2021.05.007
90. Lloyd-Jones DM, Elkind M, Albert MA. American Heart Association's cardiovascular health and targeting health equity in the United States: a narrative review. *JAMA Cardiol*. 2021;6:963–970. doi: 10.1001/jamacardio.2021.1137
75. Lassale C, Cene CW, Asselin A, Sims M, Jouven X, Gaye B. Sociodemographic determinants of change in cardiovascular health in middle adulthood in a bi-racial cohort. *Atherosclerosis*. 2022;346:98–108. doi: 10.1016/j.atherosclerosis.2022.01.006
76. Johnson AE, Herbert BM, Stokes N, Brooks MM, Needham BL, Lloyd-Jones DM, Elkind M, Albert MA. American Heart Association's cardiovascular health and targeting health equity in the United States: a narrative review. *JAMA Cardiol*. 2021;6:963–970. doi: 10.1001/jamacardio.2021.1137

ciation's 2024 Impact Goal: every person deserves the opportunity for a full, healthy life. *Circulation*. 2021;144:e277–e279. doi: 10.1161/CIRCULATIONAHA.121.057617

nity for a full, healthy life. *Circulation*. 2021;144:e277–e279. doi:

91. Angell SY, McConnell MV, Anderson CAM, Bibbins-Domingo K, Boyle DS, Capewell S, Ezzati M, de Ferranti S, Gaskin DJ, Goetzel RZ, et al. The American Heart Association 2030 Impact Goal: a presidential advisory from the American Heart Association. *Circulation*. 2020;141:e120–e138. doi: 10.1161/CIR.0000000000000758
92. Waagaard L, Herraiz-Adillo A, Ahlqvist VH, Higuera-Fresnillo S, Berglund D, Wennberg P, Daka B, Lenander C, Sundström J, Östgren CJ, et al. Body mass index and weight gain in pregnancy and cardiovascular health in middle age: a cohort study. *BJOG*. 2023;131:1136–1145. doi: 10.1111/1471-0528.17740
- Magnani JW. Educational attainment, race, and ethnicity as predictors

93. Nichols AR, Rifas-Shiman SL, Switkowski M-F, Chavarro JE, Oken E. History of lar health in female individuals. *JAMA Netw* e23504241. doi: 10.1016/j.amepre.2015.03.034
94. Willis BL, DeFina LF, Bachmann JM, Franzini Leonard D, Berry JD. Association of ideal long-term healthcare costs. *Am J Prev* 10.1016/j.amepre.2015.03.034
95. Osondu CU, Aneni EC, Valero-Elizondo J, Guzman H, Younus A, Ogunmoroti O. vascular health is associated with lower source utilization in a large US employee South Florida Employee Study. *Mayo Clin* 10.1016/j.mayocp.2016.12.026
96. Lloyd-Jones DM, Ning H, Labarthe D, Brewer L, Sharma G, Rosamond W, Foraker RE, Black T, Grandner MA, Allen NB, et al. Status of cardiovascular health in US adults and children using the American Heart health score and incident 2019:2:e194758. doi: 10.1161/
111. Dong C, Rundek T, Wright CB, Anwar cardiovascular health predicts lower stroke, and vascular death across Northern Manhattan Study. 10.1161/
112. Rebholz CM, Anderson CA, Grams AR, Coresh J, Appel LJ. Relationship Impact Goals (Life's Simple 7) with from the Atherosclerosis Risk in Heart Assoc. 2016;5:e003192. doi: 10.1161/
113. Joseph JJ, Bennett A, Echouffo Association's new "Life's Essential 8" metrics: prevalence estimates from the National

- Circulation*. 2022;146:822–835. doi: 10.1161/circulationaha.122.060911
97. Shetty NS, Parcha V, Patel N, Yadav I, Basetty C, Li C, Pandey A, Kalra R, Li P, Arora G, et al. AHA Life's Essential 8 and ideal cardiovascular health among young adults. *Am J Prev Cardiol*. 2023;13:100452. doi: 10.1016/j.ajpc.2022.100452
98. Ma H, Wang X, Xue Q, Li X, Liang Z, Heianza Y, Franco OH, Qi L. Cardiovascular health and life expectancy among adults in the United States. *Circulation*. 2023;147:1137–1146. doi: 10.1161/CIRCULATIONAHA.122.062457
99. Sun J, Li Y, Zhao M, Yu X, Zhang C, Magnussen CG, Xi B. Association of the American Heart Association's new "Life's Essential 8" with all-cause and cardiovascular disease-specific mortality: prospective cohort study. *BMC Med*. 2023;21:116. doi: 10.1186/s12916-023-02824-8
100. Yi J, Wang L, Guo X, Ren X. Association of Life's Essential 8 with all-cause and cardiovascular mortality among US adults: a prospective cohort study from the NHANES 2005-2014. *Nutr Metab Cardiovasc Dis*. 2023;33:1134–1143. doi: 10.1016/j.numecd.2023.01.021
101. Wang X, Ma H, Li X, Heianza Y, Manson JE, Franco OH, Qi L. Association of cardiovascular health with life expectancy free of cardiovascular dis-ease, diabetes, cancer, and dementia in UK adults. *JAMA Intern Med*. 2023;183:340–349. doi: 10.1001/jamainternmed.2023.0015
102. Zhang Y, Yang R, Hou Y, Chen Y, Li S, Wang Y, Yang H. Association of cardiovascular health with diabetic complications, all-cause mortality, and life expectancy among people with type 2 diabetes. *Diabetol Metab Syndr*. 2022;14:158. doi: 10.1186/s13098-022-00934-6
103. Sun Y, Yu Y, Zhang K, Yu B, Yu Y, Wang Y, Wang B, Tan X, Wang Y, Lu Y, et al. Association between Life's Essential 8 score and risk of premature mortality in people with and without type 2 diabetes: a prospective cohort study. *Diabetes Metab Res Rev*. 2023;39:e3636. doi: 10.1002/dmrr.3636
104. Isiozor NM, Kunutsor SK, Voutilainen A, Laukkanen JA. Life's Essential 8 and the risk of cardiovascular disease death and all-cause mor-tality in Finnish men. *Eur J Prev Cardiol*. 2023;30:658–667. doi: 10.1093/eurjpc/zwad040
105. Xing A, Tian X, Wang Y, Chen S, Xu Q, Xia X, Zhang Y, Zhang X, Wang A, Wu S. "Life's Essential 8" cardiovascular health with premature car-diovascular disease and all-cause mortality in young adults: the Kailuan prospective cohort study. *Eur J Prev Cardiol*. 2023;30:593–600. doi: 10.1093/eurjpc/zwad033
106. Jin C, Li J, Liu F, Li X, Hui Y, Chen S, Li F, Wang G, Liang F, Lu X, et al. Life's Essential 8 and 10-year and lifetime risk of atherosclerotic car-diovascular disease in China. *Am J Prev Med*. 2023;64:927–935. doi: 10.1016/j.amepre.2023.01.009
107. Perng W, Aris IM, Slopen N, Younoszai N, Swanson V, Mueller NT, Sauder KA, Dabelea D. Application of Life's Essential 8 to assess cardiovascu-lar health during early childhood. *Ann Epidemiol*. 2023;80:16–24. doi: 10.1016/j.annepidem.2023.02.004
108. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2024.

Nettleton JA, Prizment AE, Folsom AR. Ideal cardiovascular health is inversely associated with incident cancer: the Atherosclerosis Risk in Communities study. *Circulation*. 2013;127:1270–1275. doi: 10.1161/CIRCULATIONAHA.112.001183

115. Agarwala A, Patel J, Stephens J, Roberson S, Scott J, Beckie T, Jackson EA; on behalf of the American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention and Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Implementation of prevention science to eliminate health care inequities in achieving cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2023;148:1183–1193. doi: 10.1161/CIR.0000000000001171

116. Acevedo M, Varleta P, Casas-Cordero C, Berríos A, Navarrete C, Valentino G, Lopez R, Smith SC. Mobile-phone text messaging to promote ideal cardiovascular health in women. *Open Heart*. 2023;10:e002214. doi: 10.1136/openhrt-2022-002214

117. Castro M, Vijay A, Govind N, Barathan M, Medina L, Upadhyaya A, Vijayaraghavan K. evalUation of imPact of a novel immersive technol-ogy in patient engagement of LiFe simple 7 to prevent risk of hearT disease: UPLIFT clinical trial. *Postgrad Med*. 2023;135:10–11. doi: 10.1080/00325481.2023.2187148

118. Guo P, Zhou Y, Zhu Y. Effects of a school-based lifestyle intervention on ideal cardiovascular health in Chinese children and adolescents: a national, multicentre, cluster-randomised controlled trial. *Lancet Glob Health*. 2023;11(suppl 1):S14. doi: 10.1016/s2214-109x(23)00097-9

119. Hayes JF, LaRose JG, Gorin AA, Lewis CE, Bahnson J, Phelan S, Wing RR; Study of Novel Approaches to Weight Gain Prevention (SNAP) Research Group. Weight gain prevention interventions in the Study of Novel Approaches to Weight Gain Prevention (SNAP) trial promote ideal cardiovascular health in young adults. *Obesity (Silver Spring)*. 2023;31:1530–1537. doi: 10.1002/oby.23753

120. McCarthy MM, Yan J, Jared MC, Ilkowitz J, Gallagher MP, Dickson VV. Time, technology, social support, and cardiovascular health of emerging adults with type 1 diabetes. *Nurs Res*. 2023;72:185–192. doi: 10.1097/NNR.0000000000000645

121. Garegnani L, Franco JVA, Escobar Liquitay CM, Brant LCC, Lim HM, de Jesus Jessen NP, Singh K, Ware LJ, Labarthe D, Perman G. Cardiovascular health metrics in low and middle-income countries: a scoping review. *Prev Med*. 2023;172:107534. doi: 10.1016/j.ypmed.2023.107534

122. Mellen PB, Gao SK, Vitolins MZ, Goff DC Jr. Deteriorating dietary habits among adults with hypertension: DASH dietary accordance, NHANES 1988-1994 and 1999-2004. *Arch Intern Med*. 2008;168:308–314. doi: 10.1001/archinternmed.2007.119

123. Gao S. Diet and exercise: behavioral management of hypertension and diabetes [dissertation]. University of Washington; 2006.

124. Cerwinske LA, Rasmussen HE, Lipson S, Volgman AS, Tangney CC. Evaluation of a dietary screener: the Mediterranean Eating Pattern for Americans tool. *J Hum Nutr Diet*. 2017;30:596–603. doi: 10.1111/jhn.12451

109. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement*. 2015;11:718–726. doi: 10.1016/j.jalz.2015.05.016

110. Jin C, Huang S, Hu FB, et al. Association of trajectory of cardiovascular

110. Wu S, An S, Li W, Lichtenstein AH, Gao J, Kris-Etherton PM, Wu Y,

126. National Health and Nutrition Examination Survey. Smoking and tobacco use: SMQ. 2015. Accessed April 1, 2024.
127. Raghuvver G, White DA, Hayman LL, Woo JG, Villafane J, Celermajer D, Ward KD, de Ferranti SD, Zachariah J; on behalf of the American Heart Association Committee on Atherosclerosis, Hypertension, and Obesity in the Young of the Council on Cardiovascular Disease in the Young; Behavior Change for Improving Health Factors Committee of the Council on Lifestyle and Cardiometabolic Health and Council on Epidemiology and Prevention; and Stroke Council. Cardiovascular consequences of childhood secondhand tobacco smoke exposure: prevailing evidence, burden, and racial and socioeconomic disparities: a scientific statement from the American Heart Association [published correction *Circulation*. 2016;134:e366]. *Circulation*. 2016;134:e336–e359. doi: 10.1161/CIR.0000000000000443
128. American Academy of Pediatrics. Healthy sleep habits: how many hours does your child need?. 2016. Accessed April 1, 2024.
- Heart Association Task Force on Clinical Practice Guidelines [published corrections appear in *Circulation*. 2019;139:e1182–e1186 and *Circulation*. 2023;148:e5]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
130. American Diabetes Association. Practice guidelines resources. Accessed April 1, 2024.
131. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: does your child need?. 2016. Accessed April 1, 2024.
129. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al.

RS, Braun

132. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, Fryar CD, Gu S, Hales CM, Hughes JP, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Rep*. 2021;158:1–21. doi: 10.15620/cdc:106273
- 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American
133. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed July 1, 2024.

3. SMOKING/TOBACCO Prevalence

See Table 3-1 and Charts 3-1
through 3-4

Youth

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Tobacco use is one of the leading death in the United States and, among youth, the most common form of major risk factor for CVD, including identified combustible tobacco use and delivery system use (e-cigarettes and hand smoke exposure to have CVH in the AHA's Life's Essential 8. The 2025 AHA Statistical Update stated, throughout the rest of this chapter, tobacco use and smoking estimates for adolescents and from the NHIS⁴ (10 to 17 years of age) because these data are not applicable to US youths.⁵

Other forms of tobacco use are increasingly common. E-cigarette use, which is a vaporized liquid that is often flavored (vaping), has risen sharply among young adults and high school students. The variety of e-cigarette products has increased. A notable evolution in electronic cigarette technology and marketing with the advent of pod mods, small devices that deliver high levels of nicotine salts in loose-leaf tobacco.⁷ Cigars, filtered cigars, smokeless (pipe) tobacco, and nicotine increasingly common in recent years. This chapter addresses the most recent data on combustible cigarettes, electronic cigarettes, and other forms of tobacco that are available.

- Prevalence of tobacco use in middle and high school and ethnicity in 2023 is shown in Figure 3-1.
- In 2023⁸:
 - 27.9% (95% CI, 25.8%–29.9%) of students (corresponding to 14.7% (95% CI, 12.5%–16.9%) of students (corresponding to reported ever use of any tobacco)
 - 12.6% (95% CI, 11.1%–14.1%) of students (corresponding to 6.6% (95% CI, 5.1%–8.5%) of students (corresponding to current (past 30 days) use of tobacco product).
 - 1.9% (95% CI, 1.5%–2.4%; 290 000 users) of all high school students
 - 1.1% (95% CI, 0.6%–1.9%; 120 000 users) of all middle school students
 - 1.8% (95% CI, 1.4%–2.4%) of students (280 000 users) of middle school students
 - 0.7%–1.8% of middle school students used cigars in the past 30 days
 - 1.5% (95% CI, 1.1%–2.2%) of students (230 000 users) of middle school students
 - 0.5%–1.2% of middle school students used smokeless tobacco in the past 30 days
 - 1.2% (95% CI, 1.0%–1.6%) of students (180 000 users) and 1.4% of middle school students used other oral nicotine products in the past 30 days
 - 1.1% (95% CI, 0.8%–1.6%) of students (170 000 users) and 1.8% of middle school students used hookah in the past 30 days
- Of youths who smoked in the past 30 days in 2021, 18.9% (95% CI, 17.0%–20.8%) of middle and high school students (70 000 users) reported smoking in the past 30 days.⁹

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published

data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- In 2023, tobacco use within the past month for ethnicity_s:
 - The highest prevalence of tobacco product (12.6% [95% CI, 8.8%–17.7%]) compared with youths, 9.5% (95% CI, 7.7%–11.6%) in NH Black youths, and 8.0% (95% CI, 4.7%–13.2%)
- middle and high school students varied by race and use was reported among NH multiracial youths 11.7% (95% CI, 10.1%–13.4%) in Hispanic White youths, 9.3% (95% CI, 7.5%–11.3%) in NH in NH American Indian or Alaska Native youths.

-
- The prevalence of past 30-day cigarette use was comparable among NH White youths (1.6% [95% CI, 1.1%–2.3%]) and NH multiracial youths (1.6% [95% CI, 1.0%–2.8%]) compared with Hispanic youths (2.1% [95% CI, 1.5%–3.1%]). For cigar use, the prevalence among NH White youths was 1.0% (95% CI, 0.7%–1.4%) compared with 2.2% (95% CI, 1.7%–2.8%) in Hispanic youths, with a prevalence among NH White youths was 1.2% (95% CI, 0.7%–1.8%) compared with 1.6% with <12 years of education, 30.7% among those with a General Educational Development high school equivalency, 17.1% among those with a high school diploma, 16.1% among those with some college, 13.7% among those with an associate's degree, and 5.3% among those with an undergraduate degree compared (95% CI, 1.1%–2.4%) in Hispanic youths. For nicotine pouches use,

or not living with partner; and 10.4% of those married or living with a partner reported cigarette use every day or some days.

the prevalence – 15.3% of lesbian/gay/bisexual individuals

(95% CI, 0.9%–2.2%) compared with 1.9% (95% CI, 1.1%–3.3%) in Hispanic youths. For other oral nicotine products use, the prevalence among NH White youths was 1.2% (95% CI, 0.9%–1.5%) compared with 1.5% (95% CI, 1.1%–2.0%) in Hispanic youths. For hookah use, the prevalence was comparable among Hispanic youths (1.3% [95% CI, 1.0%–1.7%])

and NH multiracial youths (1.3% [95% CI, 0.7%–2.4%]) compared with NH White youths (0.7% [95% CI, 0.4%–1.1%]).

- The percentage of high school (10.0% or 1 560 000 users) and middle school (4.6% or 550 000 users) students who used e-cigarettes in the past 30 days exceeded the proportion using cigarettes in the past 30 days in 2023 (Chart 3-1).

reported current cigarette use compared with 11.4% of heterosexual/straight individuals.

- By region, the prevalence of individuals reporting current cigarette smoking was highest in the Midwest (14.0%) and South (12.4%) and lowest in the Northeast (10.4%) and West (8.9%).
- According to data from BRFSS 2022, the state with the highest age-adjusted percentage of individuals who reported current cigarette smoking was West Virginia (21.9%). The state with the lowest age-adjusted percentage of individuals who reported current cigarette smoking was Utah (6.7%; Chart 3-2).¹⁰ • In 2021, smoking prevalence was higher among adults ≥18 years of age who reported having a disability or activity limitation (18.5%) than among

those reporting no
disability or limitation

Adults

(See Charts 3-2 and 3-3)

- According to the NHIS 2021 data, among adults ≥18 years of age:
 - 11.5% (95% CI, 11.1%–12.0%) of adults reported cigarette use every day or some days.
 - 13.1% (95% CI, 12.4%–13.9%) of males and 10.1% (95% CI, 9.5%–10.7%) of females reported cigarette use every day or some days.
 - 5.3% of those 18 to 24 years of age, 12.6% of those 25 to 44 years of age, 14.9% of those 45 to 64 years of age, and 8.3% of those ≥65 years of age reported cigarette use every day or some days.
- 11.7% of NH Black adults, 5.4% of NH Asian adults, 7.7% of Hispanic adults, and 11.7% of NH White adults reported cigarette use every day or some days. Prevalence rates were statistically unreliable for NH American Indian and Alaska Native adults.
- By income-to-poverty ratio (income level), reported cigarette use every day or some days was 18.3% of people with low (0–1.99) income compared with 12.3% of those with middle (2.00–3.99) income and 6.7% of those with high (≥4.00) income.
- In adults ≥25 years of age, the percentage reporting current cigarette use was 20.1% for those

ing prevalence decreased among adults 18 to 24 years of age (19.2% [95% CI, 17.5%–20.9%] in 2011 to 4.9% [95% CI, 3.7%–6.0%] in 2022; average annual percentage change, –11.3% [95% CI, –13.2% to –9.4%]), whereas it remained stable among adults ≥65 years of age (8.7% [95% CI, 7.9%–9.5%] in 2011 to 9.4% [95% CI, 8.7%–10.2%] in 2022; average annual percentage change, –0.1% [95% CI, –0.8% to 0.7%]).¹¹ Among adults ≥65 years of age, smoking prevalence increased from 13.0% in 2011 to 15.8% in 2022 for those with income <200% FPL but remained stable with no significant change for those of higher income. • Among individuals who reported cigarette use every day or some days, 28.1% reported having serious psychological stress compared with 10.9% who reported no serious psychological distress; 19.4% were ever told by a health care professional that they had depression compared with 9.9% who had never been told that they had depression.⁴

- Among females who gave birth in 2017, 6.9% smoked cigarettes during pregnancy. Smoking prevalence during pregnancy was greatest for females 20 to 24 years of age (9.9%), followed by females 15 to 19 years of age (8.3%) and 25 to 29 years

of age (7.9%).¹² Rates were American Indian or Alaska and lowest in NH Asian to differences by education. Prevalence was highest among high school (12.2%) and with a master's degree and

- E-cigarette prevalence in 2022 is 3-3. Comparing current e-days) prevalence across the of Columbia, and territories age-adjusted prevalence was Rico (2.4%) and Maryland prevalence was observed in Alabama (6.4%).

Incidence

- According to the 2022 NSDUH¹³:
 - ≈1.35 million people ≥12 years of age had smoked cigarettes for the first time within the past 12 months (2022 NSDUH, Table 4.2B). Of those, 437 000 were 12 to 17 years of age, 475 000 were 18 to 20 years of age, 317 000 were 21 to 25 years of age, and 122 000 were ≥26 years of age when they first smoked cigarettes.
 - Overall, for underage individuals (12–20 years of age), use of tobacco products in the past month was 5.0% (1.9 million) compared with 20.1% (49.0 million) of individuals of legal age for tobacco (≥21 years of age; 2022 NSDUH, Table 2.1A and 2.1B).

Lifetime Risk

Youth

- Per NSDUH data for age, overall, the lifetime use was 8.7%, with lifetime NSDUH, Tables 2.1B).¹³
 - The lifetime use of tobacco adolescents 12 to 17 years following:
 - Sex: Lifetime use was (8.9%) than females (Table 2.13B).
 - Race and ethnicity: Prevalence was highest among NH American Native adolescents (10.0%). Hispanic adolescents (10.0%).
 - Among underage individuals (12–20 years of age), 1.2 million smoked cigarettes in the past month, of whom 200 000 reported daily smoking, compared with 39.9 million individuals of legal age for tobacco (≥21 years of age), of whom 23.9 million reported daily smoking (2022 NSDUH, Table 2.1A).
- According to nationally representative data from the PATH study between 2013 and 2016, in youths 12

(8.0%), NH Black adolescents (7.5%), and NH Asian adolescents (2.2%; 2022 NSDUH, Table 2.13B).

Adults

- According to 2022 NSDUH data, the lifetime use of tobacco products varied by demographic factors (2022 NSDUH, Table 2.13B)¹³:
 - Sex: Lifetime use was higher in males (69.9%) than females (54.5%).
 - Race and ethnicity: Lifetime use was high-est in American Indian or Alaska Native adults (70.5%) and NH White adults (69.5%), followed by Hispanic or Latino adults (51.8%), NH Black adults (50.8%), and NH Asian adults (34.9%).
- In 2022, the lifetime use of smokeless tobacco for adults ≥18 years of age was 15.0% (2022 NSDUH, Table 2.19B).¹³

to 15 years of age, use of an e-cigarette was inde-pendently associated with new

Secular Trends

tible cigarettes (OR, 4.09 [95% CI, 2.97–5.63]) and past 30-day use (OR, 2.75 [95% CI, 1.60–4.73]) at 2 years of follow-up. For youths who tried another non–e-cigarette tobacco product, a similar strength of association for cigarette use at 2 years was observed.¹⁴ Similar findings have been reported from a 2017 to 2019 prospective cohort of youths and young adults 15 to 27 years of age.¹⁵ In 2018 and compared with those who

reported never using an e-cigarette, those who reported ever e-cigarette use had significantly higher odds of ever use of combus-tible cigarettes (aOR, 7.29 [95% CI, 4.10–12.97]) and current use of combustible cigarettes (aOR, 8.26 [95% CI, 3.17–21.53]) 1 year later in 2019.

Youth

- According to data from MTF (8th, 10th, and 12th grades combined), the percentage of adolescents who reported smoking cigarettes in the past month was 2.1% in 2022 and similarly 2.1% in 2023.¹⁶ Data from NSDUH (12–17 years of age) show that the percentage of adolescents who reported smoking cigarettes in the past month was 1.7% in 2021 and 1.2% in 2022 (NSDUH, Table 2.1B).¹³

Adults

- Since the US Surgeon General's first report on the health dangers of smoking, the age-adjusted prevalence rate of smoking among adults has declined,

from 51% of males smoking in 1965 to 15.6% in 2018 and from 34% of females in 1965 to 12.0% in 2018, according to NHIS data.¹⁷ The decline in smoking, along with other factors (including improved treatment and reductions in the prevalence of risk factors such as uncontrolled hypertension and high cholesterol), is a contributing factor to secular declines in the CHD death rate.¹⁸

- On the basis of NHIS data between 2020 and 2021, e-cigarette use increased (from 3.7% to 4.5%). In 2021, 18.7% (46 million) of US adults reported currently using any commercial tobacco product, including cigarettes (11.5%), e-cigarettes (4.5%), cigars (3.5%), smokeless tobacco (2.1%), and pipes (including hookah; 0.9%).⁴
- According to 2017 to 2020 data from BRFSS, the

Among the US Black population, cigarette use is associated with elevated measures of subclinical

PAD in a dose-dependent manner whereby those who self-reported smoking ≥ 20 cigarettes/d and

higher pack-years had higher odds of subclinical PAD compared with those who self-reported smoking 1 to 19 cigarettes per day. Individuals who reported current smoking had an

prevalence of current e-cigarette use increased from 4.4% (95% CI, 4.3%–4.5%) in 2017 to 5.5% (95% CI, 5.4%–5.7%) in 2018 but decreased slightly to 5.1% (95% CI, 4.9%–5.3%) in 2020 primarily among individuals 18 to 20 years of age.¹⁹ Daily e-cigarette use increased slightly through-

individuals) demonstrated a 25% greater risk for CHD in smoking females than in smoking males (RR, 1.25 [95% CI, 1.12–1.39]).²⁴

- Cigarette smoking is a risk factor for both ischemic stroke and SAH in adjusted analyses (RR, 1.9 [95% CI, 1.7–2.2] and 2.9 [95% CI, 2.5–3.5] for individuals who smoke versus those who do not smoke, respectively) and has a synergistic effect on other stroke risk factors such as oral contraceptive use.²⁵• A meta-analysis comparing pooled data of ≈3.8 million smoking and nonsmoking individuals found a similar risk of stroke associated with current smoking in females and males (RR, 1.06 [95% CI, 0.99–1.13]).²⁶

CHD in smoking females than in smoking males (RR, 1.25 [95% CI, 1.12–1.39]).²⁴

- Cigarette smoking is a risk factor for both ischemic stroke and SAH in adjusted analyses (RR, 1.9 [95% CI, 1.7–2.2] and 2.9 [95% CI, 2.5–3.5] for individuals who smoke versus those who do not smoke, respectively) and has a synergistic effect on other stroke risk factors such as oral contraceptive use.²⁵• A meta-analysis comparing pooled data of ≈3.8 million smoking and nonsmoking individuals found a similar risk of stroke associated with current smoking in females and males (RR, 1.06 [95% CI, 0.99–1.13]).²⁶

as the number of cigarettes per day increases. Similar health risks for CHD events were reported in a systematic review of regular cigar smoking.²¹

- Smoking is an independent risk factor for CHD. It appears to have a multiplicative effect with the other major risk factors for CHD: high serum levels of lipids, untreated hypertension, and diabetes.²⁰

- In a 2022 cohort study of 551 338 adults, self-reported smoking was associated with a higher risk of all-cause mortality (HR, 2.80 [95% CI, 2.73–2.88]).²² Associations were similar for both males and females but differed by race (Hispanic race, 2.01 [95% CI, 1.84–2.18]; NH Black race, 2.19 [95% CI, 2.06–2.33]; NH White race, 3.00 [95% CI, 2.91–3.10]; and other NH race and ethnicity, 2.16 [95% CI, 1.88–2.47]).

CVH Impact

- A 2010 report by the US Surgeon General on how tobacco causes disease summarized an extensive body of literature on smoking and CVD and the mechanisms through which smoking is thought to cause CVD.²⁰ There is a sharp increase in CVD risk with low levels of exposure to cigarette smoke (even among individuals who smoke <5 cigarettes/d), including secondhand smoke, and a less rapid further increase in risk

- Those who report current smoking have a 2 to 4 times increased risk of stroke compared with those who do not smoke or those who have quit for >10 years.^{25,27} Among JHS participants without a history of stroke (N=4410), the risk of stroke was higher among individuals who reported current smoking compared with individuals who never smoked (HR, 2.48 [95% CI, 1.60–3.83]).²⁸
- A meta-analysis of 26 studies reported that compared with never smoking, current smoking (RR, 1.75 [95% CI, 1.54–1.99]) and former smoking (RR, 1.16 [95% CI, 1.08–1.24]) were associated with an increased risk of HF.²⁹ In MESA, compared with never smoking, current smoking was associated with an adjusted doubling in incident HF (HR, 2.05 [95% CI, 1.36–3.09]). The increased risk was similar for HFpEF (HR, 2.51) and HFrEF (HR, 2.58).³⁰
- A study of 32 428 pregnant females 15 to 49 years of age with data obtained from the NFHS-4 from India examined the relationship between tobacco use and hypertension.³¹ The prevalence of hypertension among pregnant tobacco users was significantly higher than that of nonusers (7.5% versus 6.1% respectively; $P=0.01$). The unadjusted odds of having hypertension was 1.17 (95% CI, 1.02–1.3) times higher among tobacco users than nonusers and increased with age ($P<0.001$) and in rural areas ($P=0.02$) after adjustment for other covariates. The association varied inversely with wealth quintile ($P=0.01$), although the association with education status was not significant.

- An analysis from the JHS tions of BP with volatile sure in nonsmokers and never-smokers and 416 age-rent smokers.³² The urinary tile organic compounds were spectrometry. Among acrolein and crotonaldehyde a 1.6–mm Hg (95% CI, 0.4–0.8–mm Hg (95% CI, 0.01–

SBP, and the styrene metabolite was associated with a 0.4–mm Hg (95% CI, 0.09–0.8; $P=0.02$) higher DBP. Current smokers, who were at higher risk of hypertension (RR, 1.2 [95% CI, 1.1–1.4]), had 2.8–mm Hg (95% CI, 0.5–5.1) higher systolic BP and had higher urinary levels

- Using the longitudinal PATH 2019), which included 17 539 of age without prior heart or high cholesterol at the association between reported hypertension.⁴⁵ exposure, lagged by 1 wave, use, exclusive established days) of electronic nicotine arettes, and dual use. The of several volatile organic compound metabolites. The associations were stronger among those who were <60 years of

of hypertension was 3.7% between waves 2 and 5. In adjusted analysis, exclusive cigarette use was associated with an increased risk of self-reported incident hypertension compared with nonuse (aHR, 1.21 [95% CI, 1.06–1.38]). However, exclusive electronic nicotine delivery systems use (aHR, 1.00 [95% CI, 0.68–1.47]) and dual use (aHR, 1.15 [95% CI, 0.87–1.52]) were not associated with self-age and male.

- Short-term exposure to hookah^{33,34} smoking is associated with a significant increase in BP and heart rate and changes in cardiac function and blood flow, similar to those associated with cigarette smoking.³⁵ The high levels of carbon monoxide mask the short-term vascular impairment associated with hookah smoking—a vasodilator molecule—released from the charcoal

reported hypertension.

briquettes used to heat the flavored tobacco product.³⁶ In a recent meta-analysis of 42 studies, compared with nonsmoking individuals, those who smoke hookah had significantly lower HDL-C (–3.39 mg/dL [95% CI, –5.13 to –1.65]; $P<0.001$) and higher LDL-C (+8.77 mg/dL [95%

- Dual use of e-cigarettes and combustible cigarettes was associated with significantly higher odds of CVD (OR, 1.36 [95% CI, 1.18–1.56]) compared with exclusive combustible cigarette use.⁴³ The association of dual use (relative to exclusive cigarette use) with CVD was 1.57 (95% CI, 1.18–2.07) for daily e-cigarette users and 1.31 (95% CI, 1.13–1.53) for occasional e-cigarette users.
- In a pooled analysis of data collected from 10 randomized trials (N=2564), those who smoke had a higher risk of death or HF hospitalization (HR, 1.49 [95% CI, 1.09–2.02]), as well as reinfarction (HR, 1.97 [95% CI, 1.17–3.33]), after primary PCI in

CI, 0.55–17.0]; $P=0.04$), triglycerides (+30.6 mg/dL [95% CI, 14.4–46.7]; $P<0.001$), and fast-ing glucose (+4.66 mg/dL [95% CI, 0.53–8.80]; $P=0.03$).³⁷ The long-term effects of hookah smoking remain unclear.

STEMI.⁴⁶ [95% CI, 1.20–2.66]), and dual use of e-cigarettes and combustible cigarettes was associated with CVD, as a composite of self-reported CHD, MI, or stroke, compared with current combustible cigarettes users who never used e-cigarette (OR, 1.36 [95% CI, 1.18–1.56]).^{42,43} Similar to e-cigarette vaping and despite the absence of tobacco combustion, flavored electronic hookah vaping has been shown to impair endothelial function, likely mediated by oxidative stress acutely.⁴⁴
- The long-term CVD risks associated with e-cigarette use are not known because of a lack of longitudinal data.^{38,39} However, e-cigarette vaping⁴⁰ has been linked to elevated levels of preclinical biomarkers associated with cardiovascular injury such as markers for sympathetic activation, oxidative stress, inflammation, thrombosis, and vascular dysfunction.⁴¹ In addition, daily e-cigarette use is independently associated with MI (OR, 1.79

- In a 2-sample mendelian randomization study that examined the causal effect of 12 lifestyle risk factors on the risk of stroke, genetically predicted life-time smoking was associated with ischemic (OR, 1.23 [95% CI, 1.10–1.39]) and large-artery (OR, 1.72 [95% CI, 1.26–2.36]) stroke.⁴⁷ In another mendelian randomization study, genetic liability to smoking was associated with increased risk of PAD (OR, 2.13 [95% CI, 1.78–2.56]; $P=3.6\times10^{-16}$), CAD (OR, 1.48 [95% CI, 1.25–1.75]; $P=4.4\times10^{-6}$), and stroke (OR, 1.40 [95% CI, 1.02–1.92]; $P=0.04$).⁴⁸

Family History and Genetics

- Genetic variation contributes to smoking initiation, smoking regularity, nicotine dependence, and smoking cessation, among other smoking traits. Twin studies have estimated heritability as large as 70% for the transition from regular smoking to nicotine dependence⁴⁹ and $\approx 50\%$ for other smoking measures.^{50,51} A much smaller fraction (8.0%) of variation in smoking initiation and other smoking phenotypes is explained by common SNPs⁵²;

these estimates are consistent across ancestral populations.

- Smoking phenotypes have a shared genetic basis, with estimates of genetic correlation showing moderate genetic overlap ($|r_g|$ –0.30 to 0.63).⁵²
- GWASs have identified loci associated with smoking initiation, heaviness of smoking, smoking regularity, smoking cessation, and age of smoking initiation. In analyses of up to smoking initiation, 33 loci for age at smoking initiation, 140 loci for cigarettes per day, and 128 loci for smoking cessation were identified.⁵² The majority of variants had consistent effect sizes across ancestral populations (African, American, East Asian, and

– A study using BRFSS 2011 to 2016 data before the federal legislation found that metro-politan and micropolitan statistical areas with local Tobacco 21 policies yielded significant reductions in smoking among youths 18 to 20 years of age.⁵⁹ Between 2009 and 2019, data from BRFSS showed that statewide adoption of Tobacco 21

European ancestries), although transportability of PRS across ancestral populations was poor. Novel loci include genes with roles in nervous system function (*NRXN1*) and neurocircuitry in addition

- Before the federal minimum age of sale increase, 19 states (Hawaii, California, New Jersey, Oregon, Maine, Massachusetts, Illinois, Virginia, Delaware, Arkansas, Texas, Vermont, Connecticut, Maryland, Ohio, New York, Washington, Pennsylvania, and Utah), Washington, DC, and at least 470 localities (including New York City, NY; Chicago, IL; San Antonio, TX; Boston, MA; Cleveland, OH; and both Kansas City, KS, and Kansas City, MO) passed legislation setting the minimum age for the purchase of tobacco to 21 years.⁶¹
- The genetic architecture of smoking shares similarities with alcohol dependence,^{52,53} CAD,^{52,54} and schizophrenia.⁵⁵

Smoking Prevention

Tobacco 21 legislation was signed into law on December 20, 2019, increasing the federal minimum age for sale of tobacco products from 18 to 21 years.⁵⁶

- Such legislation may reduce the rates of smoking during adolescence—a time during which the majority of those who smoke start smoking—by limiting access because most people who buy cigarettes for adolescents are <21 years of age.
 - For instance, investigators used repeated cross-sectional, statewide surveys of adolescents in Minnesota in 2016 and 2019 across a range of tobacco products (including

Awareness, Treatment, and

any tobacco, cigarettes, cigars, e-cigarettes, hookah, chewing tobacco, flavored tobacco, and multiple products).⁵⁷ Eighth and ninth grade students exposed to Tobacco 21 laws had significantly lower odds of tobacco use than unexposed students in using the following: any tobacco (aOR, 0.80 [95% CI, 0.74–0.87]), cigarettes (aOR, 0.81 [95% CI, 0.67–0.99]), e-cigarettes (aOR, 0.78 [95% CI, 0.71–0.85]), flavored tobacco (aOR, 0.79 [95% CI, 0.70–0.89]), and dual/polytobacco (aOR, 0.77 [95% CI, 0.65–0.92]).

- In Massachusetts, investigators examined the associations between county-level Tobacco 21 laws and adolescent cigarette and e-cigarette use. Increasing Tobacco 21 laws were significantly ($P=0.01$) associated with decreases in cigarette use only among adolescents 18 years of age.⁵⁸

Smoking Cessation

- According to NHIS 2021 data, 66.5% of adults who reported ever-smoking had stopped smoking; the quit rate has increased 11 percentage points since 2012 (55.1%).⁴
 - According to BRFSS surveys, quit attempts varied by state between 2011 and 2017. They increased in 4 states (Kansas, Louisiana, Virginia, and West Virginia), declined in 2 states (New York and Tennessee), and did not change significantly in 44 states.
 - In 2017, the quit attempts over the past year were highest in Guam (72.3%) and lowest in Wisconsin (58.6%), with a median of 65.4%.⁶²
 - According to NHIS 2021 data,⁴ among all smoking individuals, approximately two-thirds (66.5%) of adults who report ever-smoking reported having quit smoking, with rates being lower among NH Black individuals (53.7%) than NH White individuals (67.9%); individuals who are single, never married, or not living with a partner (51.6%) than married individuals or those living with a partner (71.1%); those with low income level (income-to-poverty ratio, 0–1.99; 46.1%) than those with high income level (income-to-poverty ratio ≥ 4.00 , 72.5%); lesbian, gay, or bisexual individuals (61.3%) than heterosexual or straight individuals (66.9%); and those with severe psychological stress (45.3%) than those without serious psychological stress (67.7%).
- According to cross-sectional data from the Population Survey Tobacco Use Supplement,

past-year quit smoking from 2014 to 2015 (52.9%) to (51.3%), with only 7.5% cessation.⁶³

- Data from clinical settings counseling practices related In a study based on national 3 individuals who smoke who practice received smoking

• According to cross-sectional 2006 to 2015, receiving advice to quit increased from 60.2% in 2006 to 2007 to 64.9% from 2014

smoking had a significantly within 5 years of smoking with individuals who (HR, 0.61 [95% CI, 0.49– risks remained significantly who reported former who reported never- possibly for 25 years, after

- Among 726 individuals who Wisconsin Smokers Health

tion was associated with less progression of carotid plaque (mean change, 0.093 mm [SD, 0.0094]) but to 2015. In addition, from 2014 to 2015, the use of not IMT.⁷⁰

prescription smoking cessation medicine was significantly lower among NH Black individuals (OR, 0.51 [95% CI, 0.38–0.69]), NH Asian individuals (OR, 0.31 [95% CI, 0.10–0.93]), and Hispanic individuals (OR, 0.53 [95% CI, 0.36–0.78]) compared with White individuals. Use of prescription smoking cessation medicine was also significantly lower among those without health insurance (OR, 0.58 [95% CI, 0.41–0.83]) and higher among females (OR, 1.28 [95% CI, 1.10–

1.52]).⁶⁵ From 2014 to 2015, receipt of doctor's advice to quit among US adults who smoke was significantly lower in NH Black individuals (59.7% [95% CI, 56.1%–63.1%]) and Hispanic individuals (57.9% [95% CI, 53.5%–62.2%]) compared with NH White individuals (66.6% [95% CI,

• Cessation medications (including sustained-release bupropion, varenicline, nicotine gum, lozenge, nasal spray, and patch) are effective for helping those who smoke achieve cessation.^{71,72}

• EVITA was an RCT that examined the efficacy of varenicline compared with placebo for smoking cessation among smoking individuals who were hospitalized for ACS. At 24 weeks, rates of smoking abstinence and reduction were significantly higher among patients randomized to varenicline.

The abstinence rates at 24 weeks were higher in the varenicline (47.3%) than the placebo (32.5%) group ($P=0.012$; NNT, 6.8). Continuous abstinence rates and reduction rates ($\geq 50\%$ of daily cigarette consumption) were also higher in the varenicline

64.1%–69.1%]).

group.⁷³

- Smoking cessation reduces the risk of cardiovascular morbidity and mortality for individuals who smoke with and without CHD.
 - In several studies, a dose-response relationship has been seen among those who report current smoking between the number of cigarettes smoked per day and CVD incidence.^{66,67}
 - Quitting smoking at any age significantly lowers mortality from smoking-related diseases, and the risk declines with the time since quitting smoking.¹ Cessation appears to have both

short-term (weeks to months) and long-term (years) benefits for lowering CVD risk. Compared with those who continued to smoke, those who quit had lower risks of recurrent major atherosclerotic cardiovascular events, a composite of stroke, MI, and cardiovascular mortality (aHR, 0.66 [95% CI,

- The EAGLES trial⁷⁴ demonstrated the efficacy and safety of 12 weeks of varenicline, bupropion, or a nicotine patch in motivated-to-quit patients who smoked with major depressive disorder, bipolar disorder, anxiety disorders, posttraumatic stress disorder, obsessive-compulsive disorder, social phobia, psychotic disorders including schizophrenia and schizoaffective disorders, and borderline personality disorder. Of note, these participants were all clinically stable from a psychiatric perspective and were believed not to be at high risk for self-injury.
- Extended use of a nicotine patch (24 weeks compared with 8 weeks) has been demonstrated to be safe and efficacious for abstinence (OR, 1.70 [95% CI, 1.03–2.81]; $P=0.04$) in randomized clinical trials.⁷⁵• An RCT demonstrated the effectiveness of individual- and group-oriented financial incentives for tobacco abstinence (abstinence rate range, 0.49–0.88).⁶⁸
 - Individuals who smoke and quit smoking at 25 to 34 years of age gained 10 years of life compared with those who continued to smoke. Those 35 to 44 years of age gained 9 years, those 45 to 54 years of age gained 6 years, and those 55 to 64 years of age gained 4 years of life, on average, compared with those who continued to smoke.⁶⁶– Among those with a cumulative smoking history of at least 20 pack-years, individuals who quit

9.4%–16.0% with different incentives groups versus 6.0% for usual care; $P<0.05$ for all comparisons) through at least 12 months of follow-up.⁷⁶• In addition to medications, smoke-free policies, increases in tobacco prices, cessation advice from health care professionals, quit lines, and other counseling have contributed to smoking cessation.^{77,78}• Mass-media antismoking campaigns such as the CDC's Tips campaign (Tips From Former Smokers)

have been shown to reduce smoking-attributable morbidity and mortality and are cost-effective. Investigators estimated that the Tips campaign cost about \$48 million, saved ≈179 099 QALYs, and prevented ≈17 000 premature deaths in the United States.⁷⁹

- Despite states having collected \$25.6 billion in 2012 from the 1998 Tobacco Master Settlement Agreement and tobacco taxes, <2% of those funds are spent on tobacco prevention and cessation programs.⁸⁰
- A randomized trial of e-cigarettes and behavioral support compared with nicotine-replacement therapy and behavioral support in adults attending the UK National Health Service stop-smoking services found that 1-year cigarette abstinence rates were 18% in the e-cigarette group compared with 9.9% in the nicotine-replacement therapy group (RR, 1.83 [95% CI, 1.30–2.58]; $P<0.001$). However, among participants abstinent at 1 year, in the nicotine-replacement therapy group, only 9% were still using nicotine-replacement therapy, whereas 80% of those in the e-cigarette group were still using e-cigarettes.⁸¹
- In a meta-analysis of 55 observational studies and 9 RCTs, e-cigarettes were not associated with increased smoking cessation, but e-cigarette provision was associated with increased smoking cessation.⁸²
- In a double-blind, 2×2 factorial randomized clinical trial, patients were randomized to 1 of 4 medication groups: varenicline monotherapy for 12 weeks, varenicline plus nicotine patch for 12 weeks, varenicline monotherapy for 24 weeks, or varenicline plus nicotine patch for 24 weeks.⁸³ Results demonstrated that there were no significant differences in 7-day point prevalence abstinence at 52 weeks among those treated with combined varenicline plus nicotine patch therapy compared with those receiving varenicline monotherapy or among those treated for 24 weeks compared with 12 weeks.
- An RCT comparing combined treatment with varenicline and nicotine patch with placebo and nicotine patch for smoking cessation
- In a multisite RCT of patients who were not ready to quit smoking, investigators showed that patients could be engaged in a brief abstinence game called Take a Break.⁸⁵ In this group, there

Mortality

- According to the 2020 Surgeon General's report on smoking cessation, >480 000 Americans die as a result of cigarette smoking, and >41 000 die of secondhand smoke exposure each year, ≈1 in 5 deaths annually.
- Of risk factors evaluated by the US Burden of Disease Collaborators, tobacco use was the second leading risk factor for death in the United States and the leading cause of DALYs, accounting for 11% of DALYs in 2016.⁸⁶ Overall mortality among US individuals who smoke is 3 times higher than that for individuals who never smoke.⁶⁶
- On average, according to 2016 data, smoking males die 12 years earlier than never-smoking males, and smoking females die 11 years earlier than never-smoking females.^{18,87}
- Recent analyses from multiple cycles of the Tobacco Use Supplements to the Current Population Survey (1992–1993, 1995–1996, 1998–1999, 2000, 2001–2002, 2003, 2006–2007, or 2010–2011) show individuals with current daily (HR, 2.32 [95% CI, 2.25–2.38]) and lifelong nondaily (HR, 1.82 [95% CI, 1.65–2.01]) cigarette smoking had higher all-cause mortality risks compared with never-smoking individuals.⁸⁸
- Harmonized tobacco use data from adult participants in the 1991, 1992, 1998, 2000, 2005, and 2010 NHIS show that daily smokeless tobacco use (HR, 1.41 [95% CI, 1.20–1.66]) and daily cigar smoking (HR, 1.52 [95% CI, 1.12–2.08]) were associated with a higher mortality risk compared with no tobacco use.⁸⁹
- Increased CVD mortality risks exist among those who report daily (HR, 1.47 [95% CI, 1.40–1.54]) and nondaily (HR, 1.24 [95% CI, 1.11–1.39]) cigarette smoking was a 2-fold higher rate of cessation compared with the nicotine replacement therapy group (OR, 1.92 [95% CI, 1.01–3.68]).

mortality rate was 18.4% for males and 10.9% for females.⁹²

- Since the first report on the dangers of smoking was issued by the US Surgeon General in 1964, tobacco control efforts have contributed to a reduction of 8 million premature smoking-attributable deaths.⁹³

- If current smoking trends children will die of smoking adulthood.²⁰
- A mendelian randomization study Biobank data reported that current smoking had a higher tion (OR, 1.80 [95% CI, 1.26–0.87–5.24]: 10–19 CI, 3.66–9.54]: ≥20

CI, 3.59–10.42]).⁹⁴

E-Cigarettes and Vaping Products

(See Charts 3-1 and 3-3)

- Electronic nicotine delivery systems are battery-operated devices that deliver nicotine, flavors,

of high school (3.6 million) days, 4.6% of middle school of high school (1.6 million) rent e-cigarette use (Chart 3-
– Among high school were higher among females (8.0%) and most cial students (14.2%). In current use rates among compared with 3.5% among and other chemicals to the user in an aerosol without any combustion. Although e-cigarettes, the most common form of electronic nicotine delivery systems,

- rates among Hispanic students (6.6%) and NH Black students (5.7%) compared with NH White students (3.1 %).
- Among middle and high school students who currently use e-cigarettes, 25.2% (95% CI, 19.2%–32.3%) reported daily use.
 - Among middle and high school students who currently use e-cigarettes, 34.7% (95% CI, 28.4%–41.7%; corresponding to 740 000 users) reported using e-cigarettes on 20 to 30 days of the past 30 days.
- were introduced in the United States only around 2007, there are currently >450 e-cigarette brands and vaping products on the market, with sales in the United States showing dramatic increases from 2015 (\$304 million) through 2018 (\$2 billion).^{95–97} Juul came on the market in 2015 and has rapidly become one of the most popular vaping products

- Among current e-cigarette users, 89.4% (90.3% high school users and 87.1% of middle school users) used flavored e-cigarettes, with fruit (63.4%) being the most common flavor type used compared with candy, desserts, or other sweets (35.0%); mint (27.8%); and menthol (20.1%).⁸ The popularity of Juul likely relates to several factors, including its slim and modern design, appealing flavors, and intensity of nicotine delivery, which approximates the experience of combustible cigarettes.⁹⁹ Besides e-cigarettes and Juul, electronic hookahs (ie, electronic water pipes) are a newer category of vaping devices patented by Philip Morris in 2019.^{100,101} Unlike e-cigarettes and Juul, electronic hookahs are used through traditional water pipes, allowing the flavored aerosol to pass through the water-filled

- Among both middle and high school current e-cigarette users, the most commonly used e-cigarette device type was disposables (60.7%), followed by prefilled or refillable pods or cartridges (16.1%) and tanks or mod systems (5.9%).⁸
- According to multiple annual data sets from NYTS data, the proportion among adolescent current tobacco users who reported that the first tobacco product used was e-cigarettes increased from 27.2% in 2014 to 78.3% in 2019 and remained at bowl before being inhaled.¹⁰² The popularity of electronic hookahs is driven in part by unsubstantiated claims that the presence of water “filters out toxins,” rendering electronic hookahs as healthier tobacco 77.0% in 2021.¹⁰⁶

- According to the NYTS data between 2011 and 2020, current exclusive use of e-cigarettes increased significantly at an annual percentage alternatives.^{103,104}
- E-cigarette use has become prevalent among those who reported never smoking a cigarette. In 2016, an estimated 1.9 million tobacco users exclusively used e-cigarettes in the United States. Of these exclusive e-cigarette users, 60% were <25 years change of 226.8% from 2011 to 2014 and 14.6% years

from 2014 to 2020, whereas exclusive use of any tobacco product—including cigarettes, cigars, hookahs, and smokeless tobacco—decreased significantly.¹⁰⁷ Among high school students, current exclusive e-cigarette use increased at an annual

of age.¹⁰⁵

- Current e-cigarette user prevalence (every day versus some days) for 2022 in the United States is shown in Chart 3-3.
- According to the NYTS, in 2023,⁸ e-cigarettes were the most commonly used tobacco products

percentage change of 336.6% during 2011 to in youths: Ever use of e-cigarettes was reported by 9.7% of middle school (1.2 million) and 22.6%

2014 and 15.7% during 2014 to 2020; among middle school students, use increased at an annual percentage change of 10.4% during 2014 to 2020. • Frequent use of e-cigarettes among high school students who were current e-cigarette users increased from 27.7% in 2018 to 34.2% in 2019. In middle school students, the percentage frequently

using e-cigarettes among current users increased from 16.2% in 2018 to 18.0% in 2019.^{5,9}

representative data from the PATH study (2013–2014), there was a significant reduction in urine concentrations of tobacco-specific nitrosamines including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, polycyclic aromatic hydrocarbons, and volatile organic compounds when study participants transitioned from exclusive cigarette to exclusive e-cigarette use, with a 92% decrease in 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (from 168.4 ng/mL [95% CI: 102.3–277.1] to 12.9 ng/mL).

- In 2021, the prevalence of current e-cigarette use in adults, defined as use every day or on some days, was 4.5% according to data from the NHIS. The

pg/mg [95% CI, 6.4–25.7] creatinine; $P<0.001$).¹¹⁵ However, nicotine levels have been found to be consistent across long-term cigarette and long-term prevalence of current e-cigarette use was highest among males (5.1%); individuals 18 to 24 years of age (11.0%); lesbian, gay, or bisexual individuals (13.2%); and those reporting serious psychological distress (10.4%).⁴

e-cigarette users.^{41,116}

- According to 2021 data from BRFSS, current and daily e-cigarette use in adults ≥ 18 years of age was higher in sex- and gender-

- E-cigarette use has a significant cross-sectional association with a less favorable perception of physical and mental health and with depression.¹¹⁷ In a nationally representative sample of adults from the BRFSS database, whereas former e-cigarette users had 1.60-fold (95% CI, 1.54–1.67) higher odds of reporting a history of clinical diagnosis of depression underrepresented individuals.¹¹⁰ Data show than never users

that the prevalence of current e-cigarette use among lesbian or gay adults was 10.7% (95% CI, 9.1%–12.6%), among bisexual adults was 12.2% (95% CI, 11.0%–13.7%), and among heterosexual individuals was 6.8% (95% CI, 6.6%–

7.1%). The prevalence of daily e-cigarette use was 5.7% (95% CI, 4.4%–7.5%) among lesbian or gay adults, 6.5% (95% CI, 5.4%–7.8%) among bisexual adults, and 3.2% (95% CI, 3.0%–3.3%) among heterosexual individuals.¹¹⁰

users had 2.10 (95% CI, 1.98–2.23) times higher odds. According to 2017 BRFSS data, current e-cigarette adult users reported a significantly higher prevalence of depression (32.4%) compared with former e-cigarette users (27.3%) and nonusers (16.0%).¹¹⁸ Furthermore, compared with those who do not use e-cigarettes, the odds of self-reported depression was higher among unemployed current (OR, 2.85 [95% CI, 1.63–4.97]) and unemployed former (OR, 1.89 [95% CI, 1.26–2.84]) e-cigarette

- According to data from BRFSS, most states showed significant increases in the prevalence of current e-cigarette use from 2017 and 2018.¹⁹ Between 2018 and 2020, although several states showed significant decreases (eg, Massachusetts, from 5.6% [95% CI, 4.8%–6.5%] to 4.1% [95% CI,

users.

3.1%–5.3%]; and New York, from 5.4% [95% CI, 4.9%–5.9%] to 4.1% [95% CI, 3.5%–4.7%]), others showed significant increases (eg, Guam, from 5.9% [95% CI, 4.5%–7.9%] to 11.4% [95%

- According to the BRFSS 2016 and 2017, e-cigarettes are associated with a 39% increased odds of self-reported asthma (OR, 1.39 [95% CI, 1.15–1.68]) and self-reported chronic obstructive pulmonary disease (OR, 1.75 [95% CI, 1.25–2.45]) among never users of combustible cigarette.^{119,120} There is a dose-response relationship such that higher frequency of e-cigarette use was associated with more asthma or chronic obstructive pulmonary disease.
- Limited data exist on the prevalence of other electronic nicotine delivery devices besides e-cigarettes. According to nationally representative data from the PATH study, in 2014 to 2015, 7.7% of youths 12 to 17 years of age reported ever electronic hoo-kah use.¹¹¹ Among adults >18 years of age, 4.6% reported ever electronic hookah use, and 26.8% of them reported current use.

- An outbreak of e-cigarette or vaping product use–associated lung injury peaked in September 2019 after increasing rapidly between June and August 2019. Surveillance data and product testing indicate that tetrahydrocannabinol-containing e-cigarettes or vaping products are linked to most e-cigarette– or vaping product use–associated lung injury cases. In particular, vitamin E acetate, an additive in some tetrahydrocannabinol-containing e-cigarettes or
 - E- tobacco-related contain toxic lower constituents levels of most vaping, of risk,

with traditional cigarettes,¹¹² including volatile organic compounds.^{113,114} According to nationally

vaping-related toxicants may also play a role. As of February 18, 2020, a total of 2807 hospitalized

e-cigarette or vaping product lung injury cases or deaths States.¹²¹

- Effective August 8, 2016, the prohibited sale of e-cigarettes to persons under 21 years of age.¹²²
- In January 2020, the FDA issued enforcement action against the sale of certain unauthorized tobacco products such as fruit and menthol flavors other than tobacco and menthol).¹²³ This policy, however, applies only to cartridge- or pod-based

detectable urinary cotinine significantly higher risk of cardiovascular disease compared with those with undetectable cotinine (HR, 1.45 [95% CI, 1.04–2.01]).

- A study using the Framingham Heart Study found that there was an 18% increase in the risk of cardiovascular disease for every 1-cigarette increase in parental smoking. In addition, children of parents who smoked had 1.34 (95% CI, 1.04–1.73) the odds of smoking.

nonsmoking parents.¹²⁹

- As of December 31, 2022, 17 states (California, e-cigarette Colorado, Connecticut, Delaware, Hawaii,

unit (sealed or unsealed) designed to fit within or operate as part of an electronic nicotine delivery system.”¹²⁴ Products that would be exempted from this prohibition include self-contained, customizable, or disposable products.

- According to data from the BRFSS 2016 and 2017, e-cigarette use among adults is associated with state-level regulations and policies on e-cigarettes: OR of 0.90 (95% CI, 0.83–0.98) for laws prohibiting e-cigarette use in indoor areas; OR of 0.90 (95% CI, 0.85–0.95) for

laws requiring retailers to purchase a license to sell e-cigarettes; OR of 1.04 (95% CI, 0.99–1.09) for laws prohibiting self-service displays of e-cigarettes; OR of 0.86 (95% CI, 0.74–0.99) for laws prohibiting sales of tobacco products, including e-cigarettes, to people <21 years of age; and OR of 0.89 (95% CI, 0.83–0.96) for laws applying taxes

Massachusetts, Minnesota, New Jersey, New Mexico, New York, North Dakota, Ohio, Oregon, Rhode Island, South Dakota, Utah, and Vermont), the District of Columbia, and Puerto Rico have passed comprehensive smoke-free indoor air laws that include e-cigarettes. These laws prohibit smoking and the use of e-cigarettes in indoor areas of private worksites, restaurants, and bars.¹³⁰

• Pooled data from 17 studies in North America, Europe, and Australia suggest that smoke-free legislation can reduce the incidence of acute coronary events by 10% (RR, 0.90 [95% CI, 0.86–0.94]).¹³¹ • The percentage of the US nonsmoking population with serum cotinine ≥ 0.05 ng/mL (which indicates exposure to secondhand smoke) declined from 52.5% in 1999 to 2000 to 24.7% in 2017 to 2018, with declines occurring for both children and adults. During 2017 to 2018, the percentage of nonsmoking individuals with detectable serum

developing CHD.²⁰

– Exposure to secondhand smoke increases the RR of stroke by 20% to 30% and is associated with increased mortality (adjusted mortality rate

Secondhand Smoke

- Data from the US Surgeon General on the consequences of secondhand smoke indicate the following:
 - Nonsmoking individuals who are exposed to secondhand smoke at home or at work have a 25% to 30% increased risk of

cotinine was 38.2% for those 3 to 11 years of age, 33.2% for those 12 to 19 years of age, and 21.2% for those ≥ 20 years of age. The percentage was higher for NH Black individuals (48.0%) than for NH White individuals (22.0%) and Mexican American individuals (16.6%). People living below the poverty level (44.7%) had higher rates of sec-ondhand smoke exposure than their counterparts (21.3% of those living above the poverty level; NHANES).^{132,133}

ratio, 2.11) after a stroke.¹²⁶

- A meta-analysis of 23 prospective and 17

Cost

control studies of cardiovascular risks associated with secondhand smoke exposure demonstrated an 18%, 23%, 23%, and 29% increased RR for total mortality, total CVD, CHD,

and stroke, respectively, in those exposed to secondhand

- According to the Surgeon General's 50th anniversary report on the health consequences of smoking, the estimated annual cost attributable to smoking from 2009 to 2012 was between \$289 and \$332.5 billion: Direct medical care for adults accounted for smoke.¹²⁷ \$132.5 to \$175.9 billion; lost productivity attributable to secondhand smoke evidenced by
- A study of adults 45 to 84 years of age who did not report active smoking in MESA showed that, during a median follow-up of 17.7 years, individu-

able to premature death accounted for \$151 billion (estimated from 2005–2009); and lost productivity resulting from secondhand smoke accounted for \$5.6 billion (in 2006).¹⁸

-
- In the United States, cigarette smoking was associated with 8.7% of annual aggregated health care spending from 2006 to 2010, which represented roughly \$170 billion/y, 60% of which was paid by public programs (eg, Medicare and Medicaid).¹³⁴
 - According to the CDC and Federal Trade Commission, in 2019, the tobacco industry spent \$8.2 billion on cigarette and smokeless tobacco advertising and to data from the Federal Trade Commission, manufacturers spent \$1.0 billion on total e-cigarette advertising and promotion in 2019, which declined to \$719.9 million in 2020.¹³⁶
 - GBD investigators estimated that in 2019 tobacco was the second leading risk of mortality (high SBP was number 1), and tobacco ranked third in DALYs globally.¹⁴²
 - Worldwide, ≈80% of tobacco users live in low- and middle-income countries.¹⁴³ According to data from the GBD 2019 study, although the burden of IHD attributable to
 - In 2018, 216.9 billion cigarettes were sold by major manufacturers in the United States, which represents a 5.3% decrease (12.2 billion units) from

especially among men and elderly individuals.¹⁴⁴ smoking-attributable diseases accounted for US global health expenditures.¹⁴⁵ The total economic productivity, amounted to approximately US \$1436 billion.¹³⁷

The WHO estimated that the economic cost of \$422 billion in 2012, which represented $\approx 5.7\%$ of costs, including both health expenditures and lost

billion, which was roughly equal to 1.8% of the

- Cigarette prices in the United States increased steeply between the early 1970s and 2018, in large

world's annual GDP. The WHO further estimated that 40% of the expenditures were in developing countries.

part because of excise taxes on tobacco products. The increase in cigarette prices appeared to be larger than general inflation: Per pack in 1970, The average cost was \$0.38 and tax was \$0.18, whereas in 2018, the average cost was \$6.90 and average tax was \$2.82.¹³⁸

- From 2012 through 2016, e-cigarette sales significantly increased while national e-cigarette prices significantly decreased,¹³⁸ with total e-cigarette unit sales exponentially increasing nearly 300% from 2016 through 2019.¹³⁹ Together, these trends highlight the rapidly changing landscape of the US e-cigarette marketplace.¹³⁸
- Despite the morbidity and mortality resulting from tobacco use, Dieleman et al¹⁴⁰ estimated that tobacco interventions were among the bottom third of health care expenditures of the 154 health conditions they analyzed. They estimated that in

2019 the United States spent \$1.9 billion (95% CI, \$1.5–\$2.3 billion) on tobacco interventions, the major-ity (75.6%) on individuals 20 to 64 years of age.

Almost half of the funding (48.5%) for the intervention came from public insurance.

Global Burden of Tobacco Use

(See Table 3-1 and Chart 3-4)

- Of 204 countries and territories in 2021, East Asia and Oceania had the highest mortality rates attributable to tobacco. Mortality rates were low-est for Andean Latin America. (Chart 3-4). In 2021, tobacco caused 7.25 (95% UI, 5.74–8.70) million total deaths in 2021, with 5.68 (95% UI, 4.59–6.73) million among males and 1.57 (95% UI, 1.09–2.06)

- To help combat the global problem of tobacco exposure, in 2003, the WHO adopted the Framework Convention on Tobacco Control treaty. From this emerged a set of evidence-based policies with the goal of reducing the demand for tobacco titled MPOWER. MPOWER policies outline the following strategies for nations to reduce tobacco use: (1) monitor tobacco use and prevention policies; (2) protect individuals from tobacco smoke; (3) offer to help with tobacco cessation; (4) warn about tobacco-related dangers; (5) enforce bans on tobacco advertising; (6) raise taxes on tobacco; and (7) reduce the sale of cigarettes. More than half of all nations have implemented at least 1 MPOWER policy.^{146,147} In 2018, population coverage (either partial or full) for quit interventions increased to 78% in middle-income countries and to 97% in high-income countries; 5 billion people are now covered by at least 1 MPOWER measure. However, only 23 countries offered comprehensive cessation support in the same year.¹⁴⁸
 - The CDC examined data from 28 countries in the 2008 to 2016 Global Adult Tobacco Survey and reported that the median prevalence of tobacco smoking was 22.5% with wide heterogeneity (3.9% in Nigeria–38.2% in Greece). Among those who report current smoking, quit attempts over the prior 12 months also varied, with a median of 42.5% (range, 14.4% in China–59.6% in Senegal). Knowledge that smoking causes heart attacks (median, 83.6%; range, 38.7% in China–95.5% in Turkey) and stroke (median 73.6%; range, 27.2% in China–89.2% in Romania) varied widely across million among countries.¹⁴⁹
- females (Table 3-
4\

Chart 3-1. Continued. †Black people, White people, and people of other race are non-Hispanic; Hispanic people could be of any race. Non-Hispanic people who selected >1 race were classified as multiracial.

‡In 2023, any tobacco product use was defined as use of any tobacco product (e-cigarettes, cigarettes, cigars [cigars, cigarillos, or little cigars], smokeless tobacco [chewing tobacco, snuff, or dip, snus, or dissolvable tobacco products], hookahs, pipe tobacco, nicotine pouches, bidis [small brown cigarettes wrapped in a leaf], or heated tobacco products) on ≥1 day during the past 30 days.

§Any combustible tobacco product use was defined as use of cigarettes, cigars (cigars, cigarillos, or little cigars), hookahs, pipe tobacco, or bidis on ≥1 days during the past 30 days.

|| In 2023, multiple tobacco product use was defined as use of ≥2 tobacco products (e-cigarettes, cigarettes, cigars [cigars, cigarillos, or little cigars], smokeless tobacco [chewing tobacco, snuff, or dip, snus, or dissolvable tobacco products], hookahs, pipe tobacco, nicotine pouches, bidis, or heated tobacco products) on ≥1 days during the past 30 days.

Source: Data derived from Park-Lee et al.³

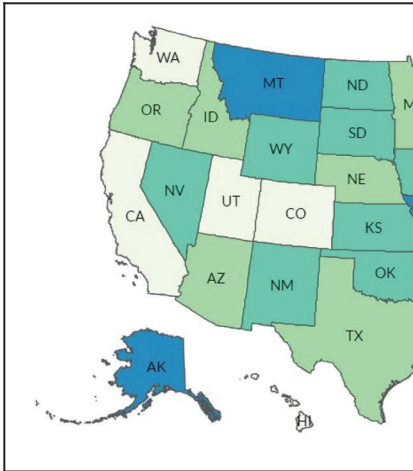


Chart 3-2. Age-adjusted prevalence (percent) of current cigarette smoking for US adults by state (BRFSS, 2022).

White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.

BRFSS indicates Behavior Risk Factor Surveillance System.

Source: BRFSS prevalence and trends data.¹⁰

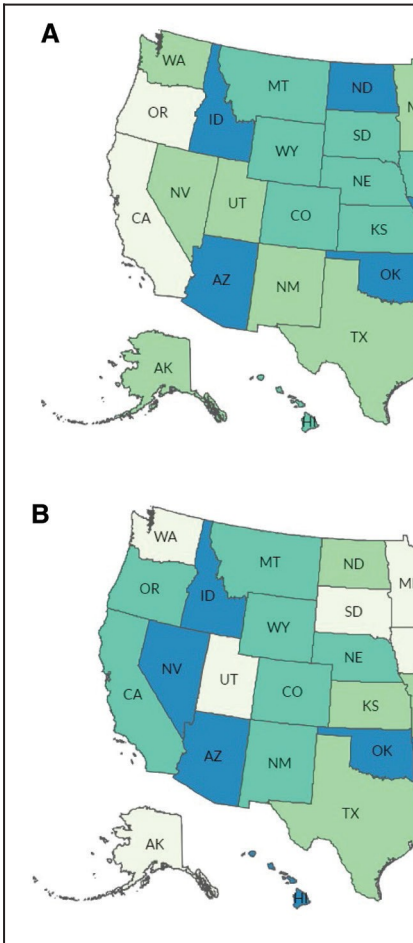


Chart 3-3. Prevalence (age-adjusted) of current electronic cigarette use (every day and some days), United States (BRFSS, 2022).

A, Everyday use. **B**, Some days use. White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been

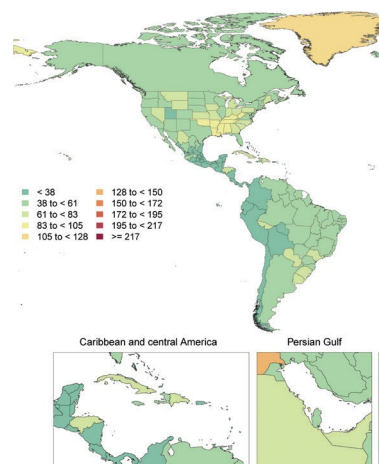


Chart 3-4. Age-standardized global mortality rates attributable to tobacco per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁴¹

REFERENCES

1. Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P, Gapstur SM. 50-Year trends in smoking-related mortality in the United States. *N Engl J Med*. 2013;368:351–364. doi: 10.1056/NEJMsa1211127
2. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
3. Park-Lee E, Ren C, Cooper M, Cornelius M, Jamal A, Cullen KA. Tobacco product use among middle and high school students—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:1429–1435. doi: 10.15585/mmwr.mm7145a1
4. Cornelius ME, Loretan CG, Jamal A, Davis Lynn BC, Mayer M, Alcantara IC, Neff L. Tobacco product use among adults—United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2023;72:475–483. doi: 10.15585/mmwr.mm7218a1
5. Gentzke AS, Creamer M, Cullen KA, Ambrose BK, Willis G, Jamal A, King BA. Vital signs: tobacco product use among middle and high school students—United States, 2011–2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:157–164. doi: 10.15585/mmwr.mm6806e1
6. Centers for Disease Control and Prevention (CDC). Electronic nicotine delivery systems key facts. 2019. Accessed March 26, 2024.
7. Barrington-Trimis JL, Leventhal AM. Adolescents' use of "pod mod" e-cigarettes: urgent concerns. *N Engl J Med*. 2018;379:1099–1102. doi: 10.1056/NEJMp1805758
8. Birdsey J, Cornelius M, Jamal A, Park-Lee E, Cooper MR, Wang J, Sawdey MD, Cullen KA, Neff L. Tobacco product use among U.S. middle and high school students: National Youth Tobacco Survey, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72:1173–1182. doi: 10.15585/mmwr.mm7244a1
9. Wang TW, Gentzke AS, Creamer MR, Cullen KA, Holder-Hayes E, Sawdey MD, Anic GM, Portnoy DB, Hu S, Homa DM, et al. Tobacco product use and associated factors among middle and high school students—United States, 2019. *MMWR Surveill Summ*. 2019;68:1–22. doi: 10.15585/mmwr.ss6812a1
10. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 7, 2024.

11. Meza R, Cao P, Jeon J, Warner KE, Levy DT. Trends in US adult smoking prevalence, 2011 to 2022. *JAMA Health Forum*. 2023;4:e234213. doi: 10.1001/jamahealthforum.2023.4213

12. Azagba S, Manzione L, Shan L, King J. Trends in smoking during pregnancy by socioeconomic characteristics in the United States, 2010-2017. *BMC Pregnancy Childbirth*. 2020;20:52. doi: 10.1186/s12884-020-2748-y

13. Center for Behavioral Statistics and Quality and Substance Abuse and Mental Health Services Administration. Results from the 2022 National Survey on Drug Use and Health: detailed tables. 2024. Accessed March 7, 2024.

14. Berry KM, Fetterman JL, Benjamin EJ, Bhatnagar A, Barrington-Trimis JL, Leventhal AM, Stokes A. Association of electronic cigarette use with subsequent initiation of tobacco cigarettes in US youths. *JAMA Netw Open*. 2019;2:e187794. doi: 10.1001/jamanetworkopen.2018.7794

15. Hair EC, Barton AA, Perks SN, Kreslake J, Xiao H, Pitzer L, Leventhal AM, Vallone DM. Association between e-cigarette use and future combustible cigarette use: evidence from a prospective cohort of youth and young adults, 2017-2019. *Addict Behav*. 2021;112:106593. doi: 10.1016/j.addbeh.2020.106593

16. Miech RA, Johnston LD, Patrick ME, O'Malley PM. Monitoring the future national survey results on drug use, 1975–2023: overview and detailed results for secondary school students. 2024. Accessed June 13, 2024.

17. Creamer MR, Wang TW, Babb S, Cullen KA, Day H, Willis G, Jamal A, Neff L. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:1013–1019. doi: 10.15585/mmwr.mm6845a2

18. US Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion, and Office on Smoking and Health. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Centers for Disease Control and Prevention; 2014.

19. Boakye E, Osuji N, Erhabor J, Obisesan O, Osei AD, Mirbolouk M, Stokes AC, Dzaye O, El Shahawy O, Hirsch GA, et al. Assessment of patterns in e-cigarette use among adults in the US, 2017-2020. *JAMA Netw Open*. 2022;5:e2223266. doi: 10.1001/jamanetworkopen.2022.23266

20. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, and Office on Smoking and Health. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Centers for Disease Control and Prevention; 2010.

21. Chang CM, Corey CG, Rostron BL, Apelberg BJ. Systematic review of cigar smoking and all cause and smoking related mortality. *BMC Public Health*. 2015;15:390. doi: 10.1186/s12889-015-1617-5

22. Thomson B, Emberson J, Lacey B, Lewington S, Peto R, Jemal A, Islami F. Association between smoking, smoking cessation, and mortality by race, ethnicity, and sex among US adults. *JAMA Netw Open*. 2022;5:e2231480. doi: 10.1001/jamanetworkopen.2022.31480
23. Clark D 3rd, Cain LR, Blaha MJ, DeFilippis AP, Mentz RJ, Kamimura D, White WB, Butler KR, Robertson RM, Bhatnagar A, et al. Cigarette smoking and subclinical peripheral arterial disease in Blacks of the Jackson Heart Study. *J Am Heart Assoc*. 2019;8:e010674. doi: 10.1161/JAHA.118.010674
24. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic S, Creager MA, Eckel RH, Elkind MS, Fornage M, et al; on behalf of the American Heart Association Stroke Council. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046
26. Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke*. 2013;44:2821–2828. doi: 10.1161/STROKEAHA.113.002342
27. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther*. 2010;8:917–932. doi: 10.1586/erc.10.56
28. Oshunbade AA, Yimer WK, Valle KA, Clark D 3rd, Kamimura D, White WB, DeFilippis AP, Blaha MJ, Benjamin EJ, O'Brien EC, et al. Cigarette smoking and incident stroke in Blacks of the Jackson Heart Study. *J Am Heart Assoc*. 2023;12:e028342. doi: 10.1161/JAHA.123.028342
39. Bhatnagar A. E-cigarettes and cardiovascular disease risk: evaluation of evidence, policy implications, and recommendations. *Curr Cardiovasc Risk Rep*. 2016;10:24. doi: 10.1007/s12170-016-0505-6
40. Bains S, Garmany R, Neves R, Giudicessi JR, Gao X, Tester DJ, Bos JM, Ackerman MJ. Temporal association between vaping and risk of cardiac events. *Mayo Clin Proc*. 2024;99:241–248. doi: 10.1016/j.mayocp.2023.09.017
41. Middlekauff HR. Cardiovascular impact of electronic-cigarette use. *Trends Cardiovasc Med*. 2020;30:133–140. doi: 10.1016/j.tcm.2019.04.006
42. Alzahrani T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction. *Am J Prev Med*. 2018;55:455–461. 2020;9:e014990. doi: 10.1161/JAHA.119.014990
29. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of heart failure: a systematic review and meta-analysis of prospective studies. *Eur J Prev Cardiol*. 2019;26:279–288. doi: 10.1177/2047487318806658
30. Watson M, Dardari Z, Kianoush S, Hall ME, DeFilippis AP, Keith RJ, Benjamin EJ, Rodriguez CJ, Bhatnagar A, Lima JA, et al. Relation between cigarette smoking and heart failure (from the Multiethnic Study of Atherosclerosis). *Am J Cardiol*. 2019;123:1972–1977. doi: 10.1016/j.amjcard.2019.03.015
31. Grover S, Anand T, Kishore J, Sinha DN, Malhotra S, Dhawan P, Goel S. Hypertension and its correlates among pregnant women consuming tobacco in India: findings from the National Family health Survey-4. *Prev Med Rep*. 2023;35:102281. doi: 10.1016/j.pmedr.2023.102281
32. McGraw KE, Konkle SL, Riggs DW, Rai SN, DeJarnett N, Xie Z, Keith RJ, Oshunbade A, Hall ME, Shimbo D, et al. Exposure to volatile organic compounds is associated with hypertension in Black adults: the Jackson Heart Study. *Environ Res*. 2023;223:115384. doi: 10.1016/j.envres.2023.115384
33. Alarabi AB, Mohsen A, Taleb ZB, Mizuguchi K, Alshbool FZ, Khasawneh

- Hall ME, DeFilippis AP, Stokes A, Bhatnagar A, et al. Association between current combustible-cigarette smokers. *Am J Med*. 2019;132:949–954.e2. doi: 10.1016/j.amjmed.2019.02.016
44. Rezk-Hanna M, Seals DR, Rossman MJ, Gupta R, Nettle CO, Means A, Dobrin D, Cheng CW, Brecht ML, Mosenifar Z, et al. Ascorbic acid prevents vascular endothelial dysfunction induced by electronic hookah (waterpipe) vaping. *J Am Heart Assoc*. 2021;10:e019271. doi: 10.1161/JAHA.120.019271
45. Cook S, Hirschtick JL, Barnes G, Arenberg D, Bondarenko I, Patel A, Jimenez Mendoza E, Jeon J, Levy D, Meza R, et al. Time-varying association between cigarette and ENDS use on incident hypertension among US adults: a prospective longitudinal study. *BMJ Open*. 2023;13:e062297. doi: 10.1136/bmjopen-2022-062297
46. Redfors B, Furer A, Selker HP, Thiele H, Patel MR, Chen S, Udelson JE, Ohman EM, Eitel I, Granger CB, et al. Effect of smoking on outcomes of primary PCI in patients with STEMI. *J Am Coll Cardiol*. 2020;75:1743–1754. doi: 10.1016/j.jacc.2020.02.045
47. Harshfield EL, Georgakis MK, Malik R, Dichgans M, Markus HS. Modifiable lifestyle factors and risk of stroke: a mendelian randomization analysis. *Stroke*. 2021;52:931–936. doi: 10.1161/STROKEAHA.120.031710
48. Levin MG, Klarin D, Assimes TL, Freiberg MS, Ingelsson E, Lynch J, Natarajan P, O'Donnell C, Rader DJ, Tsao PS, et al. Genetics of smoking and risk of atherosclerotic cardiovascular diseases: a mendelian randomization study. *JAMA Netw Open*. 2021;4:e2034461. doi: 10.1001/jamanetworkopen.2020.34461
49. Sullivan PF, Kendler KS. The genetic epidemiology of smoking. *Nicotine Tob Res*. 1999;1(suppl 2):S51–S7. doi: 10.1080/14622299050011811
50. Swan GE, Carmelli D, Rosenman RH, Fabsitz RR, Christian JC. Smoking and alcohol consumption in adult male twins: genetic heritability and shared environmental influences. *J Subst Abuse*. 1990;2:39–50. doi: 10.1016/s0899-3289(05)80044-6
- FT. Predicting thrombotic cardiovascular outcomes induced by 51. Kaprio J. waterpipe-associated chemicals using comparative toxicogenomic data-base: genes, phenotypes, and pathways. *Life Sci*. 2023;323:121694. doi: 10.1016/j.lfs.2023.121694
34. Jenssen BP, Walley SC, Boykan R, Little Caldwell A, Camenga D, Section On Nicotine and Tobacco P; Section On Nicotine and Tobacco Prevention and Treatment; Committee on Substance use and Prevention. Protecting children and adolescents from tobacco and nicotine. *Pediatrics*. 2023;151:e2023061805. doi: 10.1542/peds.2023-061805
35. Bhatnagar A, Maziak W, Eissenberg T, Ward KD, Thurston G, King BA, Sutfin EL, Cobb CO, Griffiths M, Goldstein LB, et al. Water pipe (hookah) smoking and cardiovascular disease risk: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e917–e936. doi: 10.1161/CIR.0000000000000671
36. Rezk-Hanna M, Mosenifar Z, Benowitz NL, Rader F, Rashid M, Davoren K, Moy NB, Doering L, Robbins W, Sarna L, et al. High carbon monoxide levels from charcoal combustion mask acute endothelial dysfunction induced by hookah (waterpipe) smoking in young adults. *Circulation*. 2019;139:2215–2224. doi: 10.1161/CIRCULATIONAHA.118.037375
37. Al Ali R, Vukadinović D, Maziak W, Katmeh L, Schwarz V, Mahfoud F, Laufs U, Böhm M. Cardiovascular effects of waterpipe smoking: a systematic

- dence. *COPD*. 2009;6:304–306. doi: 10.1080/15412550903049165 52. Saunders GRB, Wang X, Chen F, Jang SK, Liu M, Wang C, Gao S, Jiang Y, Khunsriraksakul C, Otto JM, et al; 23 and Me Research Team, Biobank Japan Project. Genetic diversity fuels gene discovery for tobacco and alcohol use. *Nature*. 2022;612:720–724. doi: 10.1038/s41586-022-05477-4 53. Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, Adkins AE, Aliev F, Bacanu SA, Batzler A, Bertelsen S, et al; 23 and Me Research Team. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci*. 2018;21:1656–1669. doi: 10.1038/s41593-018-0275-1
54. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47:1121–1130. doi: 10.1038/ng.3396
55. Song W, Lin GN, Yu S, Zhao M. Genome-wide identification of the shared genetic basis of cannabis and cigarette smoking and schizophrenia implicates NCAM1 and neuronal abnormality. *Psychiatry Res*. 2022;310:114453. doi: 10.1016/j.psychres.2022.114453
56. US Food and Drug Administration. Tobacco 21. Accessed March 27, 2024.
- review and meta-analysis. *Rev Cardiovasc Med*. 2020;21:453–468. doi: 10.31083/j.rcm.2020.03.135
38. Bhatnagar A, Whitset LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, Robertson RM, McAuley T, Goff D, Benowitz N; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*.
57. Wilhelm AK, Kingsbury JH, Eisenberg ME, Shyne M, Helgertz S, Borowsky IW. Local Tobacco 21 policies are associated with lower odds of tobacco use among adolescents. *Nicotine Tob Res*. 2022;24:478–483. doi: 10.1093/ntr/ntab200 2014;130:1418–1436. doi: 10.1161/CIR.000000000000107

58. Hawkins SS, Kruzik C, O'Brien M, Levine Coley R. Flavoured tobacco product restrictions in Massachusetts associated with reductions in adolescent cigarette and e-cigarette use. *Tob Control*. 2021;31:576–579. doi: 10.1136/tobaccocontrol-2020-056159

59. Friedman AS, Wu RJ. Do local Tobacco-21 18 to 20 year-olds? *Nicotine Tob Res.* 2023;92:102818. doi: 10.1093/ntr/ntz123
60. Hansen B, Sabia JJ, McNichols D, Brvan C. *Health Econ.* 2023;92:102818. doi: 10.1093/ntr/ntz123
61. Municipal Tobacco Control Technical calities that have raised the minimum legal to 21. Accessed March 27, 2024.
62. Walton K, Wang TW, Schauer GL, Hu S. State-specific prevalence of quit attempts United States, 2011-2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:15585. doi: 10.15585/mmwr.mm6828a1
63. Leventhal AM, Dai H, Higgins ST. Smoking cessation prevalence and inequalities in the United States: 2014-2019. *J Natl Cancer Inst.* 2022;114:381-390. doi: 10.1093/jnci/djab208
64. Sardana M, Tang Y, Magnani JW, Ockene IS, Allison JJ, Arnold SV, Jones PG, Maddox TM, Virani SS, McManus DD. Provider-level variation in
76. Halpern SD, French B, Small DS, Audrain-McGovern J, Loewenstein G. Randomized trial of four financial- *N Engl J Med.* 2015;372:2108-2117.
77. Babb S, Malarcher A, Schauer G. among adults—United States, 2000-2017:65:1457-1464. doi: 10.15585/mmwr.mm6828a1
78. Centers for Disease Control and adults—United States, 2001-2010. 2011;60:1513-1519.
79. Xu X, Alexander RL Jr, Simonsen SA, Davis KC, McAfee T. A cost-funded antismoking campaign. *Am J Public Health.* 2014;104:1011-1016. doi: 10.1161/ajph.2014.010011
- smoking cessation assistance provided in the cardiology clinics: insights from the NCDR PINNACLE Registry. *J Am Heart Assoc.* 2019;8:e011412. doi: 10.1161/ahajournal.2019.010011

80. Antman E, Arnett D, Jessup M, Sherwin C. The 50th anniversary of the US Surgeon General's report on tobacco: what we've accomplished and where we go from here. *J Am Heart Assoc*. 2014;3:e000740. doi: 10.1161/JAHA.113.000740
81. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, et al. a randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380:629–637. doi: 10.1161/JAHA.118.011307
65. Tibuakuu M, Okunrintemi V, Jirru E, Echouffo Tcheugui JB, Orimoloye OA, Mehta PK, DeFilippis AP, Blaha MJ, Michos ED. National trends in cessation counseling, prescription medication use, and associated costs among US adult cigarette smokers. *JAMA Netw Open*. 2019;2:e194585. doi: 10.1001/jamanetworkopen.2019.4585
66. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-Century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013;368:341–350. doi: 10.1056/NEJMSa1211128
67. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9
68. van den Berg MJ, van der Graaf Y, Deckers JW, de Kanter W, Algra A, Kappelle LJ, de Borst GJ, Cramer MM, Visseren FLJ; SMART Study Group. Smoking cessation and risk of recurrent cardiovascular events and mortality after a first manifestation of arterial disease. *Am Heart J*. 2019;213:112–122. doi: 10.1016/j.ahj.2019.03.019
69. Duncan MS, Freiberg MS, Greevy RA Jr, Kundu S, Vasani RS, Tindle HA. Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA*. 2019;322:642–650. doi: 10.1001/jama.2019.10298
70. Stein JH, Smith SS, Hansen KM, Korcarz CE, Piper ME, Fiore MC, Baker TB. Longitudinal effects of smoking cessation on ca-

82. Wang RJ, Bhadriraju S, Glantz SA. E-cigarette use and adult cigarette smoking cessation: a meta-analysis. *Am J Public Health.* 2021;111:230–246. doi: 10.2105/AJPH.2020.305999

83. Baker TB, Piper ME, Smith SS, Bolt DM, Stein JH, Fiore MC. Effects of combined varenicline with nicotine patch and of extended treatment duration on smoking cessation: a randomized clinical trial. *JAMA.* 2021;326:1485–1493. doi: 10.1001/jama.2021.15333

84. King A, Vena A, de Wit H, Grant JE, Cao D. Effect of combination treatment with varenicline and nicotine patch on smoking cessation among smokers who drink heavily: a randomized clinical trial. *JAMA Netw Open.* 2022;5:e220951. doi: 10.1001/jamanetworkopen.2022.0951

85. Houston TK, Chen J, Amante DJ, Blok AC, Nagawa CS, Wijesundara JG, Kamberi A, Allison JJ, Person SD, Flahive J, et al. Effect of technology-assisted brief abstinence game on long-term smoking cessation in individuals not yet ready to quit: a randomized clinical trial. *JAMA Intern Med.* 2022;182:303–312. doi: 10.1001/jamainternmed.2021.7866

86. Mokdad AH, Ballestros K, Echko M, Glenn S, Olsen HE, Mullany E, Lee A, Khan AR, Ahmadi A, Ferrari AJ, et al; US Burden of Disease Collaborators. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. *JAMA.* 2018;319:1444–1472. doi: 10.1001/jama.2018.0158

87. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health Interview Survey: public-use data files and documentation. Accessed March 27, 2024.

88. Inoue-Choi M, McNeel TS, Hartge P, Caporaso NE, Graubard BI, Freedman 10.1016/j.atherosclerosis.2020.11.010 public health service report. *Am J Prev Med.* 2008;35:158–176. doi: 10.1016/j.amepre.2008.04.009

71. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons and Staff. A clinical practice guide-line for treating tobacco use and dependence: 2008 update: a U.S.

ND. Non-daily cigarette smokers: mortality risks in the U.S. *Am J Prev Med*.

2019;56:27–37. doi: 10.1016/j.amepre.2018.06.025

89. Inoue-Choi M, Shiels MS, McNeel TS, Graubard BI, Hatsukami D, Freedman ND. Contemporary associations of exclusive cigarette, cigar, pipe, and smokeless tobacco use with overall and cause-specific mortality in the United States. *JNCI Cancer Spectr*. 2019;3:pkz036. doi:

72. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn 10.1093/jncics/pkz036

EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al.

2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published corrections appear in *Circulation*. 2019;140:e649–e650, *Circulation*. 2020;141:e60, and *Circulation*. 2020;141:e774].

Circulation.

2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678

73. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, et al; EVITA Investigators. Varenicline

for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation*.

2016;133:21–30. doi:

10.1161/CIRCULATIONAHA.115.019634 74. Anthenelli

RM, Benowitz NL, West R, St Aubin L, McRae T,

Lawrence D, Ascher J, Russ C, Krishen A, Evins AE.

Neuropsychiatric safety and efficacy of varenicline,

bupropion, and nicotine patch in smokers with and

90. Christensen CH, Rostron B, Cosgrove C, Altekruse SF, Hartman AM, Gibson JT, Apelberg B, Inoue-Choi M, Freedman ND. Association of cigarette, cigar, and pipe use with mortality risk in the US population. *JAMA Intern Med.* 2018;178:469–476. doi: 10.1001/jamainternmed.2017.8625
91. Mons U, Muezzinler A, Gellert C, Schottker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, et al; CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ.* 2015;350:h1551. doi: 10.1136/bmj.h1551
92. Zhang M, An Q, Yeh F, Zhang Y, Howard BV, Lee ET, Zhao J. Smoking- without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* 2016;387:2507–2520. doi: 10.1016/S0140-6736(16)30272-0
75. Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wileyto EP, Hitsman B. Long-term nicotine replacement attributable mortality in American Indians: findings from the Strong Heart Study. *Eur J Epidemiol.* 2015;30:553–561. doi: 10.1007/s10654-015-0031-8
- therapy: a randomized clinical trial. *JAMA Intern Med.* 2015;175:504–511. doi:

93. Holford TR, Meza R, Warner KE, Meernik C, Jeon J, Moolgavkar SH, Levy DT. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. *JAMA*. 2014;311:164–171. doi: 10.1001/jamainternmed.2014.8313 10.100

94. Clift AK, von Ende A, Tan PS, Sallis HM, Lindson N, Coupland CAC, Munafò MR, Aveyard P, Hippisley-Cox J, Hopewell JC. Smoking and COVID-19 outcomes: an observational and mendelian randomisation study using the UK Biobank cohort. *Thorax*. 2022;77:65–73. doi: 10.1136/thoraxjnl-2021-217080
95. Walley SC, Wilson KM, Winickoff JP, Groner J. A public health crisis: electronic cigarettes, vape, and JUUL. *Pediatrics*. 2019;143:e20182741. doi: 10.1542/peds.2018-2741
96. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, Lee M. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control*. 2014;23(suppl 3):iii3–iii9. doi: 10.1136/tobaccocontrol-2014-051670
97. Federal Trade Commission. E-cigarette report for 2015-2018. Accessed May 27, 2024.
98. Hammond D, Wackowski OA, Reid JL, O'Connor RJ. Use of JUUL e-cigarettes among youth in the United States. *Nicotine Tob Res*. 2020;22:827–832. doi: 10.1093/ntr/nty237
99. Bhatnagar A, Whitsel LP, Blaha MJ, Huffman MD, Krishan-Sarin S, Maa J, Rigotti N, Robertson RM, Warner JJ. New and emerging tobacco products and the nicotine endgame: the role of robust regulation and comprehensive tobacco control and prevention: a presidential advisory from the American Heart Association. *Circulation*. 2019;139:e937–e958. doi: 10.1161/CIR.0000000000000669
100. Jawad M, Shihadeh A, Nakkash RT. Philip Morris patents “harm reduction” electronic waterpipe. *Tob Control*. 2020;30:473–473. doi: 10.1136/tobaccocontrol-2020-055885
101. Dube SR, Pathak S, Nyman AL, Eriksen MP. Electronic cigarette and electronic hookah: a pilot study comparing two vaping products. *Prev Med Rep*. 2013;2:1–6. doi: 10.1016/j.pmedr.2013.06.001
102. Rezk-Hanna M, Benowitz NL. Cardiovascular effects of hookah smoking: potential implications for cardiovascular risk. *Nicotine Tob Res*. 2019;21:1151–1161. doi: 10.1093/ntr/nty065
103. Cornacchione J, Wagoner KG, Wiseman KD, Kelley D, Noar SM, Smith MH, Sutfin EL. Adolescent and young adult perceptions of hookah and little cigars/cigarillos: implications for risk messages. *J Health Commun*. 2016;21:818–825. doi: 10.1080/10810730.2016.1177141
104. Griffiths M, Harmon T, Gily M. Hubble bubble trouble: the need for education about and regulation of hookah smoking. *J Public Policy Marketing*. 2011;30:119–132. doi: 10.2307/23209266
105. Mirbolouk M, Charkhchi P, Orimoloye OA, Uddin SMI, Kianoush S, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP, et al. E-cigarette use without a history of combustible cigarette smoking among U.S. adults: Behavioral Risk Factor Surveillance System, 2016. *Ann Intern Med*. 2019;170:76–79. doi: 10.7326/M18-1826
106. Glantz S, Jeffers A, Winickoff JP. Nicotine addiction and intensity of exposure to toxicants associated with use and transitions between cigarettes, e-cigarettes, and no tobacco. *JAMA Netw Open*. 2015;2:953–958. doi: 10.1016/j.jpm.2015.10.012
107. Eaton DL, Kwan LY, Stratton K, eds. *Public Health Consequences of E-Cigarettes*. National Academies Press; 2018.
108. Lorkiewicz P, Riggs DW, Keith RJ, Conklin DJ, Xie Z, Sutaria S, Lynch B, Srivastava S, Bhatnagar A. Comparison of urinary biomarkers of exposure in humans using electronic cigarettes, combustible cigarettes, and smokeless tobacco. *Nicotine Tob Res*. 2019;21:1228–1238. doi: 10.1093/ntr/nty089
109. Dai H, Benowitz NL, Achutan C, Farazi PA, Degarege A, Khan AS. Exposure to toxicants associated with use and transitions between cigarettes, e-cigarettes, and no tobacco. *JAMA Netw Open*. 2015;2:953–958. doi: 10.1016/j.jpm.2015.10.012
110. Rezk-Hanna M, Benowitz NL. Cardiovascular effects of hookah smoking: potential implications for cardiovascular risk. *Nicotine Tob Res*. 2019;21:1151–1161. doi: 10.1093/ntr/nty065
111. Cornacchione J, Wagoner KG, Wiseman KD, Kelley D, Noar SM, Smith MH, Sutfin EL. Adolescent and young adult perceptions of hookah and little cigars/cigarillos: implications for risk messages. *J Health Commun*. 2016;21:818–825. doi: 10.1080/10810730.2016.1177141
112. Griffiths M, Harmon T, Gily M. Hubble bubble trouble: the need for education about and regulation of hookah smoking. *J Public Policy Marketing*. 2011;30:119–132. doi: 10.2307/23209266
113. Mirbolouk M, Charkhchi P, Orimoloye OA, Uddin SMI, Kianoush S, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP, et al. E-cigarette use without a history of combustible cigarette smoking among U.S. adults: Behavioral Risk Factor Surveillance System, 2016. *Ann Intern Med*. 2019;170:76–79. doi: 10.7326/M18-1826
114. Glantz S, Jeffers A, Winickoff JP. Nicotine addiction and intensity of exposure to toxicants associated with use and transitions between cigarettes, e-cigarettes, and no tobacco. *JAMA Netw Open*. 2015;2:953–958. doi: 10.1016/j.jpm.2015.10.012
115. Rezk-Hanna M, Benowitz NL. Cardiovascular effects of hookah smoking: potential implications for cardiovascular risk. *Nicotine Tob Res*. 2019;21:1151–1161. doi: 10.1093/ntr/nty065

117. Obisesan OH, Mirbolouk M, Osei AD, Orimoloye OA, Uddin SMI, Dzaye O, El Shahawy O, Al Rifai M, Bhatnagar A, Stokes A, et al. Association between e-cigarette use and depression in the Behavioral Risk Factor Surveillance System, 2016-2017. *JAMA Netw Open*. 2019;2:e1916800. doi: 10.1001/jamanetworkopen.2019.16800
118. Saeed OB, Chavan B, Haile ZT. Association between e-cigarette use and depression in US adults. *J Addict Med*. 2020;14:393–400. doi: 10.1097/ADM.0000000000000604
119. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Dardari ZA, DeFilippis AP, Bhatnagar A, Blaha MJ. The association between e-cigarette use and asthma among never combustible cigarette smokers: Behavioral Risk Factor Surveillance System (BRFSS) 2016 & 2017. *BMC Pulm Med*. 2019;19:180. doi: 10.1186/s12890-019-0950-3
120. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Bhatnagar A, Biswal SS, et al. Association between e-cigarette use and chronic obstructive pulmonary disease by smoking status: Behavioral Risk Factor Surveillance System 2016 and 2017. *Am J Prev Med*. 2020;58:336–342. doi: 10.1016/j.amepre.2019.10.014
121. Centers for Disease Control and Prevention, Office on Smoking and Health and National Center for Chronic Disease Prevention and Health Promotion. Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. Accessed October 25, 2024.
122. Department of Health and Human Services and Food and Drug Administration. Deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act; restrictions on the sale and distribution of tobacco products and required warning statements for tobacco products. Accessed October 25, 2024.
123. Cigarette use by adolescents in the US, 2014 to 2021. *JAMA Netw Open*. 2022;5:e2240671. doi: 10.1001/jamanetworkopen.2022.40671
107. Jebai R, Osibogun O, Li W, Gautam P, Bursac Z, Ward KD, Maziak W. Temporal trends in tobacco product use among US middle and high school students: National Youth Tobacco Survey, 2011-2020. *Public Health Rep*. 2022;138:483–492. doi: 10.1177/00333549221103812

123. US Food and Drug Administration. FDA finalizes enforcement policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint. Accessed October 25, 2025.
108. Gentzke AS, Wang TW, Cornelius M, Park-Lee E, Ren C, Sawdey MD, Cullen KA, Loretan C, Jamal A, Homa DM. Tobacco product use and associated factors among middle and high school students: National Youth Tobacco Survey, United States, 2021. *MMWR Surveill Summ.* 2022;71:1–29. doi: 10.15585/mmwr.ss7105a1

124. US Department of Health and Human Services and Food and Drug Administration. Enforcement priorities for electronic nicotine delivery systems (ENDS) and other deemed products on the market without premarket authorization (revised). Accessed March 27, 2024.
109. Collins L, Glasser AM, Abudayyeh H, Pearson JL, Villanti AC. E-cigarette marketing and communication: how e-cigarette companies market e-cigarettes and the public engages with e-cigarette information. *Nicotine Tob Res.* 2019;21:14–24. doi: 10.1093/ntr/ntx284
110. Erhabor J, Boakye E, Obisesan O, Osei AD, Tasdighi E, Mirbolouk H, DeFilippis AP, Stokes AC, Hirsch GA, Benjamin EJ, et al. E-cigarette use among US adults in the 2021 Behavioral Risk Factor Surveillance System Survey. *JAMA Netw Open.* 2023;6:e2340859. doi: 10.1001/jamanetworkopen.2023.40859
111. Rezk-Hanna M, Toyama J, Ikharo E, Brecht ML, Benowitz NL. E-hookah versus e-cigarettes: findings from wave 2 of the PATH study (2014-2015). *Am J Prev Med.* 2019;57:e163–e173. doi: 10.1016/j.amepre.2019.05.007
112. Keith RJ, Fetterman JL, Orimoloye OA, Dardari Z, Lorkiewicz PK, Hamburg NM, DeFilippis AP, Blaha MJ, Bhatnagar A. Characterization of volatile organic compound metabolites in cigarette smokers, electronic nicotine device users, dual users, and nonusers of tobacco. *Nicotine Tob Res.* 2020;22:264–272. doi: 10.1093/ntr/ntz021

125. Du Y, Liu B, Xu G, Rong S, Sun Y, Wu Y, Snetselaar LG, Wallace RB, Bao W. Association of electronic cigarette regulations with electronic cigarette use among adults in the United States. *JAMA Netw Open*. 2020;3:e1920255. doi: 10.1001/jamanetworkopen.2019.20255
126. Lin MP, Ovbiagele B, Markovic D, Towfighi A. Association of second-hand smoke with stroke outcomes. *Stroke*. 2016;47:2828–2835. doi: 10.1161/STROKEAHA.116.014099
127. Lv X, Sun J, Bi Y, Xu M, Lu J, Zhao L, Xu Y. Risk of all-cause mortality and cardiovascular disease associated with secondhand smoke exposure: a systematic review and meta-analysis. *Int J Cardiol*. 2015;199:106–115. doi: 10.1016/j.ijcard.2015.07.011
128. Lin GM, Lloyd-Jones DM, Colangelo LA, Lima JAC, Szklo M, Liu K. Association between secondhand smoke exposure and incident heart failure: the Multi-Ethnic Study of Atherosclerosis (MESA). *Eur J Heart Fail*. 2024;26:199–207. doi: 10.1002/ehf.3155

129. Groh CA, Vittinghoff E, Benjamin EJ, Dupuis
bacco smoke exposure and risk of atrial
Cardiol. 2019;74:1658–1664. doi:
130. Centers for Disease Control and Prevention
Tracking and Evaluation (STATE) System.
cluding e-cigarette. Accessed March 27.
131. Mackay DF, Irfan MO, Haw S, Pell JP.
comprehensive smoke-free legislation on
2010;96:1525–1530. doi:
132. Homa DM, Neff LJ, King BA, Caraballo RS,
BE, Sosnoff CS, Wang L: Centers for
(CDC). Vital signs: disparities in
smoke—United States, 1999–2012. *MMWR*
2015;64:103–108
133. Shastri SS, Talluri R, Shete S. Disparities in secondhand smoke expo-
sure in the United States: National Health and Nutrition Examination
Survey 2011–2018. *JAMA Intern Med*. 2021;181:134–137. doi:
10.1001/jamainternmed.2020.3975
134. Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual
flavor type—United States, 2014–2020.
2020;69:1313–1318. doi:
140. Dieleman JL, Cao J, Chai A, Chen
T, Scott KW, et al. US health care
1996–2016. *JAMA*. 2020;323:863–
141. Global Burden of Disease Study and
Evaluation. University of Washington.
142. GBD Risk Factors Collaborators.
countries and territories, 1990–2019: a
Burden of Disease Study 2019.
10.1016/S0140-6736(20)30752-2
143. WHO Media Centre. Tobacco fact
144. Zhang L, Tong Z, Han R, Guo R, Zeng
health-care spending attributable to cigarette smoking: an
update. *Am J Prev Med*.
2015;48:326–333. doi: 10.1016/j.amepre.2014.10.012
135. Centers for Disease Control and Prevention, Office on
Smoking and Health. Smoking and tobacco use.
Accessed October 24, 2024.

- regional, and national burdens of ischemic heart disease attributable to smoking from 1990 to 2019. *J Am Heart Assoc.* 2023;12:e028193. doi: 10.1161/JAHA.122.028193
145. Goodchild M, Nargis N, Tursan d'Espaignet E. Global economic cost of smoking-attributable diseases. *Tob Control.* 2018;27:58–64. doi: 10.1136/tobaccocontrol-2016-053305
 146. Mirbolouk M, Charkhchi P, Kianoush S, Uddin SMI, Orimoloye OA, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP, et al. Prevalence and distribution of e-cigarette use among U.S. adults: Behavioral Risk Factor Surveillance System, 2016. *Ann Intern Med.* 2018;169:429–438. doi: 10.7326/M17-3440
 136. Federal Trade Commission. E-Cigarette Report for 2019-2020. 2022. Accessed October 25, 2024. /f
 147. World Health Organization. WHO Framework Convention on Tobacco Control. Accessed March 27, 2024.
 137. Federal Trade Commission. Federal Trade Commission cigarette report for 2018. 2019. Accessed March 24, 2024. -
 148. World Health Organization. WHO report on the global tobacco epidemic, 2019. Accessed March 27, 2024.
 138. Centers for Disease Control and Prevention. The tax burden on tobacco, 1970-2018. Accessed March 24, 2024.
 139. Ali FRM, Diaz MC, Vallone D, Tynan MA, Cordova J, Seaman EL, Trivers KF, Schillo BA, Talley B, King BA. E-cigarette unit sales, by product and

149. Ahluwalia IB, Smith T, Arrazola RA, Palipudi KM, Garcia de Quevedo I, Prasad VM, Commar A, Schotte K, Garwood PD, Armour BS. Current to-bacco smoking, quit attempts, and knowledge about smoking risks among persons aged ≥ 15 years: Global Adult Tobacco Survey, 28 countries, 2008-2016. *MMWR Morb Mortal Wkly Rep*. 2018;67:1072–1076. doi: 10.15585/mmwr.mm6738a7

4. PHYSICAL ACTIVITY
AND SEDENTARY
BEHAVIOR

(See Table 4.1 and Charts 4.1 through 4.7)

[Click here to return to the Table of Contents](#) [Click here to return to the Abbreviations](#)

PA is defined as any body movement produced by skeletal muscles that results in energy expenditure. In 1992, the AHA first published a position statement declaring that a lack of PA was a risk factor for the development of CHD.¹ Since then, an abundance of research has firmly established a lack of PA as a major risk factor for CVD (eg, CHD, stroke, PAD, HF).²

The 2018 Physical Activity Guidelines for Americans recommend that children and adolescents accumulate at least 60 minutes of PA daily, including aerobic and muscle- and bone-strengthening activity.³ The guidelines recommend that adults accumulate at least 150 min/wk of moderate-intensity or 75 min/wk of vigorous-

2019 CVD primary prevention clinical practice guidelines⁴ support the aerobic recommendations. For most people, examples of moderate-intensity activities include walking briskly or raking the yard, and examples of vigorous-intensity activities include jogging, carrying loads upstairs, strengthening activities, or shoveling snow. Achieving the aerobic PA guideline recommendations is one of the AHA's Life's Essential 8 components of ideal CVH for both children and adults.⁵ An AHA scientific statement published in 2023 updated the substantial evidence of cardiovascular benefits from meeting resistance training guidelines among individuals with and without CVD.⁶ Globally, the 2020 WHO guidelines also recommend moderate- to vigorous-intensity aerobic PA along with muscle-strengthening activities

Sedentary behavior is defined as "any waking behavior characterized by an energy expenditure ≤ 1.5 METs while in a sitting, reclining, or lying posture."¹¹ Sedentary behavior is a distinct risk factor (low), and includes activities such as driving/riding in a vehicle, using a screen (eg, watching television, playing video

Physical Activity Guidelines for Americans that adults should "move more and sit less throughout the day."³ Globally, the WHO guidelines recommend reducing sedentary behaviors across all age groups and abilities.⁷ PA is characterized by several dimensions (eg, frequency, duration, and intensity) and domains or types (eg, occupational, domestic, transportation, and leisure). Measurement of PA in population studies can be defined by 2 broad assessment methods: (1) self-reported methods that use questionnaires, diaries, or logs and (2) device-based methods that use wearable devices (eg, pedometers,

across all age groups and abilities.⁷ Increasing moderate-intensity PA and replacing sedentary behavior with light-intensity PA can provide health benefits.^{3,7} The WHO guidelines for PA also include recommendations for those living with a disability,⁸ supporting research on wheelchair users.^{9,10}

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Prevalence and Secular Trends

Youth PA

(See Charts 4-1 and 4-2)

• According to parental report, in 2022, the nationwide percentage of youths 6 to 17 years of age who were active for ≥ 60 minutes every day of the week was 18.9% (95% CI, 18.1%–19.7%).¹² The percentage was higher for youths 6 to 11 years of age (25.2% [95% CI, 24.0%–26.6%]) compared with youths 12 to 17 years of age (12.9% [95% CI, 12.0%–13.8%]; Chart 4-1) and higher for males (22.0% [95% CI, 20.8%–23.3%]) compared with females (15.6% [95% CI, 14.6%–16.6%]). The percentage varied by race and ethnicity of the child: 13.4% (95% CI, 11.1%–16.2%) for NH Asian children, 14.5% (95% CI, 12.4%–16.8%) for NH Black children, 16.2% (95% CI, 14.4%–18.2%) for Hispanic children, 20.6% (95% CI, 18.1%–23.4%) for NH other children, and 21.8% (95% CI, 20.8%–22.8%) for NH White children. The percentage was higher among English-speaking households (19.6% [95% CI, 18.8%–20.5%]) compared with households with a primary language other than English (14.1% [95% CI, 11.8%–16.8%]). Considering the highest education in the household, the percentage was 18.2% (95% CI, 14.8%–22.3%) for those with less than a high school education, 20.7% (95% CI, 18.6%–22.9%) for those with a high school education or passing a General Educational Development

Test, 19.0% (95% CI, 17.4%–some college or technical CI, 17.4%–19.3%) for those or higher.

- The 2021 nationwide percentage students who engaged in ≥ 60 7 days of the week was 25.0%).¹³ The percentage was higher grade, from 25.6% in ninth grade to 20.8% (95%

in 12th grade. The percentage was higher in males (31.7% [95% CI, 30.2%–33.2%]) than females (15.7% [95% CI, 14.1%–17.4%]). The percentage varied by race and ethnicity: Hispanic, 18.9% (95% CI, 17.3%–20.5%); NH Asian, 19.4% (95% CI, 14.6%–25.3%); NH Black, 19.7% (95% CI, 17.5%–22.0%); Native Hawaiian or Other Pacific Islander, 23.2% (95% CI, 16.1%–32.2%); NH White, 27.7% (95% CI, 25.1%–30.4%); and American Indian/ Alaska Native, 40.0% (95% CI, 22.5%–60.3%).

- In 2021, the percentage of high school students who participated in muscle-strengthening activities (such as push-ups, sit-ups, or weight lifting) on ≥ 3 d/wk was 44.9% (95% CI, 42.5%–47.2%) nationwide and was lower in the 12th grade (40.4% [95% CI, 37.6%–43.3%]) compared with the ninth grade (48.1% [95% CI, 44.8%–51.4%]).¹³ More high school males (56.6% [95% CI, 54.4%–58.8%]) than females (32.3% [95% CI, 29.7%–35.1%]) reported participating in muscle-strengthening activities on ≥ 3 d/wk. The percentage varied by race and ethnicity: NH Black, 40.7% (95% CI, 36.1%–45.4%); NH Asian, 41.7% (95% CI, 35.2%–48.5%); Native Hawaiian or Other Pacific Islander, 43.2% (95% CI, 31.6%–55.6%); Hispanic, 44.2% (95% CI, 41.9%–46.5%); NH White, 47.0% (95% CI, 43.3%–50.6%); and

and ethnicity: Black, 10.8% Asian, 13.5% (95% CI, 7.9%–13.5% (95% CI, 10.5–17.1%); 13.5% (95% CI, 11.8%–20.4%); White, 18.6% (95% and American Indian or (95%, 15.1%–50.5%). The meeting both between 2019 and 2021.

American Indian/ Alaska Native, 54.8% (95% CI, 39.2%–69.5%).

- The percentage of high school students who were physically active for ≥ 60 minutes on all 7 d/ wk decreased over the past decade from 28.7% (95% CI, 27.1%–30.3%) in 2011 to 23.9% (95% CI, 22.8%–25.0%) in 2021. The percentage of high school students participating in muscle- strengthening activities on ≥ 3 d/wk decreased over the past decade from 55.6% (95% CI, 53.6%–57.5%) in 2011 to 44.9% (95% CI, 42.5%–47.2%) in 2021 (Chart 4-2).¹³
- The 2021 nationwide percentage of high school students who met both PA recommendations (were both physically active for ≥ 60 minutes on all 7 d/wk and participated in muscle-strengthening activities on ≥ 3 d/wk) was 16.0% (95% CI, 14.2%–17.9%).¹⁴ Males were more likely to meet both PA recommendations (22.9% [95% CI, 20.5%–25.4%]) compared with females (8.8% [95% CI, 7.3%–10.6%]). There were also significant differences across race

- Wrist-worn accelerometry data from 6030 youths 3 to 19 years of age in the NHANES National Youth Fitness Survey 2012 and NHANES 2011 to 2014 indicated that the median daily total volume of PA (measured by MIMS units) peaked at 6 years of age for both males and females.¹⁵ In contrast, the lowest median daily total volume of PA occurred at 17 years of age in males and 18 years of age in females. Generally, for both males and females, total PA volume was successively higher from 3 to 6 years of age, declined from 6 to ≈15 years of age, and then plateaued through 19 years of age.

Youth Physical Education Classes

- In 2021, 19.0% (95% CI, 15.7%–22.7%) of high school students attended physical education classes in school daily (males, 21.1% [95% CI, 20.6%–21.6%]).¹³ Daily physical education class attendance was higher in the ninth grade (29.0% [95% CI, 23.5%–35.2%]) than in the 12th grade (11.8% [95% CI, 8.6%–15.9%]). Daily physical education varied by race and ethnicity: Asian, 9.6% (95% CI, 5.7%–15.6%); Native Hawaiian or Other Pacific Islander, 15.9% (95% CI, 8.4%–28.2%); White, 19.0% (95% CI, 15.0%–23.6%); Black, 19.6% (95% CI, 17.4%–25.2%); and American Indian/Alaska Native, 23.0% (95% CI, 14.7%–34.2%).
- Nationwide, over the past decade, the percentage of high school students who reported attending physical education classes at least once per week (on an average week while in school) was stable at 51.8% (95% CI, 46.0%–57.6%) in 2011 and 46.8% (95% CI, 39.7%–54.0%) in 2022.¹³ However, the percentage of high school students who reported attending physical education classes on all 5 days of the week decreased from 31.5% (95% CI, 26.1%–37.4%) in 2011 to 19.0% (95% CI, 15.7%–22.7%) in 2021 (Chart 4-2).

Youth Organized Sports

- According to parental report, in 2022, the nationwide percentage of youths 6 to 17 years of age participating in a sports team or sports lessons after school or on weekends was 53.8% (95% CI, 52.8%–54.9%).¹² The percentage was higher for youths 6

to 11 years of age (55.7% [95% CI, 54.2%–57.3%]) compared with youths 12 to 17 years of age (52.1% [95% CI, 50.5%–53.6%]) and higher for males (58.1% [95% CI, 56.6%–59.6%]) compared with females (49.4% [95% CI, 47.9%–50.9%]). The percentage varied by race and ethnicity of the child: 42.1% (95% CI, 39.6%–44.7%) for Hispanic children, 45.0% (95% CI, 41.6%–48.5%) for NH Black children, 50.1% (95% CI, 45.8%–54.4%) for NH Asian NH other children, and 62.2% (95% CI, 61.0%–63.3%) for NH White children. The percentage was higher among English-speaking households (57.4% [95% CI, 56.4%–58.5%]) compared with households with a primary language other than English (32.5% [95% CI, 29.5%–35.7%]). Considering the highest education in the household, the percentage of youths participating on a sports team was 25.9% (95% CI, 21.7%–30.6%) from households with less than high

cell phone, or other electronic device watching programs, playing games, accessing the internet, or using social media (not including schoolwork) on most weekdays was 22.0% (95% CI, 21.5%–22.9%).¹² The percentage was higher for increasing age groups: 0 to 5 years of age, 7.9% (95% CI, 7.1%–8.8%); 6 to 11 years of age, 18.3% (95% CI, 17.1%–19.6%); and 12 to 17 school education, 36.4% (95% CI, 33.9%–39.0%) from households with high school or passing a General Educational Development Test, 47.1% (95% CI, 44.9%–49.4%) from households with some college or technical school, and 68.0% (95% CI, 66.7%–69.1%) from households with a college degree or higher.

- In 2021, about half (49.1% [95% CI, 46.3%–51.8%]) of high school students played on at least 1 school or community sports team in the previous year (46.4% [95% CI, 43.4%–49.4%]) of females

and 21.4% (95% CI, 20.4%–22.4%) for females. The percentage varied by race and ethnicity of the child: 18.5% (95% CI, 17.8%–19.3%) for NH White children, 21.2% (95% CI, 19.2%–23.3%) for NH other children, 21.5% (95% CI, 18.4%–25.0%) for NH Asian children, 24.5% (95% CI, 22.8%–26.4%) for Hispanic children, and 32.4% (95% CI, 29.8%–35.2%) for NH Black children (Chart 4-3). The percentage was similar among English-speaking households (22.1% [95% CI, 21.4%–22.9%]) compared with households with a primary language other than English (22.4% [95% CI, 20.0%–25.0%]). Considering the highest education in the household, the percentage was 26.0% (95% CI, 22.2%–30.2%) with less than high school education, 26.2% (95% CI, 24.3%–28.2%) with high school or passing a General Educational Development Test, 26.5% (95% CI, 24.8%–28.3%) with some college or technical school, and 18.6% (95% CI, 17.8%–19.4%) with a college degree or

and 52.0% [95% CI, 49.1%–55.0%] of males); this

number was lower in the 12th grade (43.7% [95% CI, 40.0%–47.4%]) compared with the ninth grade (53.2% [95% CI, 49.4%–57.0%]).¹³

The percentage varied by race and ethnicity:

Hispanic, 39.4% (95% CI, 36.7%–42.1%); Asian, 45.0% (95% CI, 33.7%–56.8%); Black, 47.2% (95% CI, 43.1%–51.3%); Native Hawaiian or Other Pacific Islander, 50.6% (95% CI, 32.6%–68.4%); American Indian/Alaska Native, 52.8% (95% CI, 41.8%–63.6%); and White, 55.3% (95% CI, 51.4%–59.2%).

higher.

- The percentage of high school students playing on ≥1 team sport in the past year decreased over the past decade, from 58.4% (95% CI, 56.0%–60.7%) in 2011 to 49.1% (95% CI, 46.3%–51.8%) in 2021 (Chart 4-2).¹³
- From the 2018 to 2019 National Survey of Children's Health, sports participation was higher among youths 12 to 17 years living in metropolitan areas compared with those in nonmetropolitan areas.¹⁶

Youth Sedentary Behavior

Neighborhood Environment Among Youth

(See Chart 4-4)

• According to parental report, in 2022, 36.5% (95% CI, 35.7%–37.3%) of children 0 to 17 years of age lived in neighborhoods containing all 4 activity-promoting features (parks, recreation centers, sidewalks, and libraries).¹² Chart 4-4 displays the percentages of children living in neighborhoods with 1, 2, 3, or 4 neighborhood activity-promoting features. The percentage of children having all 4 neighborhood activity-promoting amenities did not vary substantially by age group (36.6% [95% CI, 35.3%–38.1%] for 0–5 years, 36.4% [95% CI, 34.9%–37.8%] for 6–11 years, and 36.6% [95% CI, 35.2%–38.0%] for 12–17 years) or sex (36.1% [95% CI, 34.9%–37.2%] for males and 37.0% [95% CI, 35.9%–38.2%] for females). The percentage varied by race and ethnicity of the child: 33.5% (95% CI, 32.6%–34.3%) for NH White children, 36.8% (95% CI, 34.9%–38.8%) for Hispanic children, 37.2% (95% CI, 34.8%–39.6%) for NH other

(See Chart 4-3)

- According to parental report, in 2022, the nationwide percentage of youths 0 to 17 years of age spending ≥4 h/d in front of a television, computer,

children, 41.4% (95% CI, 38.4%–44.4%) for NH Black children, and 52.3% (95% CI, 48.9%–55.8%) for NH Asian children. The percentage was similar

among English-speaking
CI, 36.0%–37.6%) and
many language other than
CI, 31.9%–37.3%). With
in highest level of education in
percentage of youths living in
all 4 neighborhood activity-
ied, with 23.5% (95% CI,
holds with less than high
(95% CI, 26.7%–30.6%) in

school degree or passing a General Educational
Development Test, 32.5% (95% CI, 30.8%–
34.4%) in households with some college or
technical school, and 42.7% (95% CI, 41.7%–
43.7%) in households with a college degree or
higher.

- According to parental report, in 2022, 3.9% (95%
CI, 3.9%–4.6%) of youths 0 to 17 years of age
nationwide lived in a neighborhood with litter or

to 64 years of age, and 10.8%
The percentage varied by
(23.5% for Hispanic, 29.7%
NH Asian, 30.5% for NH
for Hispanic, 16.5% for NH
Asian, 24.3% for NH White).
in both guidelines was
among men (16.1% at <100%
100%–199% of the FPL, and
the FPL) and women (9.9% at

garbage on the street or
sidewalk, poorly kept or rundown
housing, and vandalism such as
broken windows and graffiti,
whereas 76.5% (95% CI, 75.8%–
77.3%) lived in a neighborhood
with none of these detracting
elements (Chart 4-4).¹²

13.6% at 100%–199% of the FPL, and 25.9% at ≥200% of the FPL). The percentage was higher with higher urbanicity: 16.1% nonmetropolitan, 22.3% medium/small metropolitan, 26.9% large fringe met-ropolitan, and 27.8% large central metropolitan.¹⁹ From BRFSS 2022, across all US states, the District of Columbia, and territories, the median percentage of physical inactivity (defined as self-report of not participating in any PA in the past month) was 23.5%. This age-adjusted prevalence of inactiv-ity varied by state or territory of residence, ranging from the lowest in the District of Columbia (15.6%), Colorado (16.5%), and Utah (17.0) to the highest in

Adult PA

Arkansas (30.0%),
Mississippi (30.7%), and

(See Charts 4-5 and 4-6)

• According to NHIS, the percentage of adults meeting the aerobic and muscle-strengthening Physical Activity Guidelines for Americans has changed little from 2020 to 2022 (Chart 4-5).¹⁷ The percentage reporting engaging in ≥150 min/wk of moderate-intensity aerobic activity, 75 min/wk of vigorous-intensity aerobic activity, or an equivalent combination was 47.9% in 2020 and 48.1% in 2022. The percentage reporting engaging in muscle-strengthening activities of at least moderate intensity and including all major muscle groups ≥2 d/wk was 31.9% in 2020 and 31.5% in 2022. The percentage of adults meeting both aerobic PA and muscle-strengthening guidelines was 25.2% in 2020 and 25.3% in 2022. It is important to note that each of these population prevalence estimates remains below the goals set by Healthy People 2030, which are

52.9% of adults meeting aerobic PA guidelines, 36.6% of adults meeting muscle-strengthening guidelines, and 29.7% of adults meeting both guidelines.

• According to NHIS 2020, the percentage of adults reporting meeting both the aerobic PA and muscle-strengthening guidelines was lower with older age for both men and women.¹⁸ For males, the percent-age meeting both guidelines was 41.3% for 18 to 34 years of age, 29.4% for 35 to 49 years of age, 21.6% for 50 to 64 years of age, and 15.3% for ≥65 years of age; for women, the percentage meet-ing both guidelines was 28.7% for 18 to 34 years of

- In the PROPASS Consortium, an international research collaboration including 6 studies from Europe and Australia, 15 253 adults spent, on average, 1.3 h/d in moderate- to vigorous-intensity PA, 1.5 h/d in light-intensity PA, and 3.1 h/d standing, as measured by thigh-worn accelerometry.²¹
- According to 1 week of wrist-worn accelerometry data from 8675 participants ≥20 years of age in NHANES 2011 to 2014, the median daily total volume of PA (measured by MIMS units) peaked at 20 years of age for males and 36 years of age for females.¹⁵ For both males and females, total volume of PA was the lowest at 80 years of age.
- From a systematic review of 20 studies applying an intervention to increase PA, ≈70% of all studies found evidence for a positive association between the PA-promoting attributes of the built environment (walkability, density, green space) and PA.²²• A 2023 AHA scientific statement²³ highlighted strong, consistent evidence that adults with obesity, hypertension, and diabetes and of older age were less active than their counterparts without these conditions or of younger age, respectively. Other factors associated with lower PA levels in at least 1 large observational study included female sex, Black race, lower SES, having a mobility disability, living in the South or Midwest regions, living in rural communities, less walkable infrastructure, and air pollution/extreme weather. The statement concluded that promoting PA in these groups could help to reduce age, 22.7% for 35 to 49 years of age, 17.6% for 50 CVH inequities.

Adult Sedentary Behavior

- According to NHANES, self-reported mean sitting time increased by 19 min/d from 2007 to 2008 (332 min/d) to 2017 to 2018 (351 min/d).²⁴• In the PROPASS Consortium (N=15 253) including 6 studies from Europe and Australia,²¹ adults spent an average of 10.4 h/d (equating to 43.2% of the 24-hour day) in sedentary behavior as measured by thigh-worn accelerometry, which is the best practice method¹¹ for assessing time. Sedentary behavior encompassed the greatest proportion of the 24-hour day in adults, followed

vigorous-intensity PA, leisure screen time, or sedentary behavior at work.³⁰

Prevention

PA, Sedentary Behavior, and Cardiovascular Prevention Among Youth and Adults

- A meta-analysis based on 19 prospective cohort studies estimated that high compared with low sedentary by sleep (31.9%), standing (13.0%), light-intensity PA (6.4%), and moderate- to vigorous-intensity PA

study) was associated with an increased risk of fatal CVD (pooled RR, 1.27 [95% CI, 1.19–1.36]) and nonfatal CVD (RR, 1.30 [95% CI, 1.18–1.43]).³¹ Among 4 of these studies, the pooled effect of isotemporally increasing light-intensity PA and decreasing sedentary behavior by 1 hour was estimated to be 5.5%.

Genetics and Family History

- Genetic factors have been shown to contribute to the propensity to exercise.²⁵
- A systematic review of GWASs for PA and seden-

tary behavior revealed that variants in 9 candidate genes (*ACE*, *CASR*, *CYP19A*, *FTO*, *DRD2*, *CNR1*, *LEPR*, *MC4R*, and *NPC1*) were associated with PA or sedentary behavior in greater than a single

mated to reduce the risk of nonfatal CVD by 16% (RR, 0.84 [95% CI, 0.73–0.97]).

- A meta-analysis of 15 studies characterized a beneficial, inverse dose-response association between PA and incidence of AF among 1.8 million females. A nonlinear association was identified in which a greater risk reduction was observed up to 20 MET-h/wk and a less steep slope from 20 to 50 MET-h/wk ($P<0.0001$). The estimated RR of AF was study.²⁶

reduced by 16% (RR, 0.84 [95% CI, 0.80–0.88])

- A GWAS of 91 105 individuals with device-measured PA and sedentary behavior in the UK Biobank identified 7 significant loci, including 3 for overall activity (*SKIDA1*, *KANSL1-AS1*, and

SYT4) and 4 for sedentary time (*MEF2C-AS2*, *EFNA5*, *LOC105377146*, and *CALN1*).²⁷ Together, these loci accounted for 0.06% of the activity duration

at 50 MET-h/wk compared with 0 MET-h/wk.³² The dose-response relationship above 50 MET-h/wk could not be determined because of low sample size. • A meta-analysis of 15 studies found that engaging in a PA program during pregnancy reduced the incidence of HDP (RR, 0.44 [95% CI, 0.30–0.66]) but not the incidence of preeclampsia (RR, 0.81 [95% variation in the sample.

- A follow-up study in the UK Biobank identified an additional 3 novel loci (*SEC13*, *RN7SKP16*, and *PDXDC2P*) in a GWAS evaluating associations with device-measured PA metrics in 88 411 individuals.²⁸ The novel loci were associated with active to sedentary transition probability,

CI, 0.59–1.11]).³³

- moderate- to vigorous-intensity PA involving the central nervous system, and total log acceleration (6–8 am) involving the blood/immune and digestive systems.
- A GWAS of self-reported sedentary behaviors in 422 218 individuals of European ancestry from the UK Biobank yielded 145, 36, and 4 loci associated

- A systematic review of 28 studies in children and adolescents concluded that reallocation of sedentary behavior to moderate- to vigorous-intensity PA was consistently associated with lower adiposity (12 of 14 studies), greater cardiorespiratory fitness (5 of 6 studies), and more favorable cardiometabolic biomarkers (3 of 5 studies) in cross-sectional studies.³⁴ Reallocation of sedentary behavior to light-intensity PA was not consistently associated with CVH outcomes in cross-sectional studies. Few studies were prospective or evaluated reallocation of sedentary behavior bouts, limiting conclusions.
- Mendelian randomization analysis established the causal role of television watching in the risk of CAD in which each 1.5-hour increase in television watching was associated with greater odds of CAD (OR, 1.44 [95% CI, 1.25–1.66]).²⁹
- A meta-analysis of 51 studies consisting of 703 901 multiancestry individuals identified 99 significant loci associated with self-reported moderate- to

- A systematic review including 26 studies and 89 405 participants investigated the relationship between PA and CAC. The review found widely varied results: 4 studies with a positive association, 6 studies with a negative association, 2 studies with a U-shaped association, and 9 studies with null or varied subgroup findings.³⁵ Although the adverse relationship between high PA and incidence of CAC was more frequently observed in large studies and

studies of athletes, the nature between PA and CAC

- A meta-analysis including 7 studies in adults found that PA (defined within individual associated with a reduced risk impairment (HR, 0.68 [95% CI, 0.53–0.89]).⁴¹ Yet, a further indicated a J-shaped risk dence of CVD and mortality 60 min/wk of resistance above baseline beyond 130 to tance training. Based on this
- In the PROPASS Consortium.

a cross-sectional compositional data analysis esti-mated that replacing less intense activities such as sedentary time, standing, and light-intensity PA with 4 to 12 min/d of moderate-to vigorous-intensity PA was associated with cardiometabolic health benefits.²¹ For example, the minimum reallocation associated with a statistically significant reduction in BMI was replacing 7 min/d of sedentary behavior with moderate- to vigorous-intensity PA. In addition, replacing 4 min/d of light-intensity PA with moderate- to vigorous-intensity PA was associated with a sta-tistically significantly lower HbA1c.

Primary Prevention Using Self-Reported PA and Sedentary Behavior

- A meta-analysis including 94 cohorts and >30 mil- lion participants found that higher leisure-time PA or combinations of nonoccupational PA were asso- ciated with a lower risk of all- cause mortality (RR, 0.69 [95% CI, 0.65–0.73]) and CVD mortality (RR, 0.71 [95% CI, 0.66–0.77]) at 8.75 marginal MET-h/ wk.³⁷
- In contrast, a systematic review and meta- analysis of 31 articles indicated that

- A meta-analysis of 7 studies tance training was associated mortality (0.85 [95% CI, 0.79–0.93]), and 0.77–0.89]).⁴¹ Yet, a further indicated a J-shaped risk dence of CVD and mortality 60 min/wk of resistance above baseline beyond 130 to tance training. Based on this occupational activity was generally not associated with CVD mortality for both males and females.³⁸ There are multiple possi- ble explanations for the apparent paradox between leisure-time (beneficial) and occupational (not ben- eficial) activity and CVD and mortality, including that occupational PA may be of lower intensity but lon- ger duration, may have static and constrained pos- tures/activities, and may have insufficient recovery compared with leisure-time PA.³⁹
- A cohort study of 481 688 adults from Taiwan found that, compared with mostly not sitting while at work, those who mostly sat at work had a 16% (95% CI, 11%–20%) higher risk of mortality and a 34% (95% CI, 22%–46%) higher risk of CVD over 12.85 years of follow-up.⁴⁰ In a further joint analysis with leisure PA, high occupational sitting remained

- A study from Korea of 5075 adults, with an average 8-year follow-up period during which 50.1% of the population developed hypertension, found that meeting guidelines for aerobic PA was associated with a lower hazard of incident hypertension (HR, 0.68 [95% CI, 0.62–0.74]).⁴³ Adding resistance training was not associated with a lower hazard among those not meeting aerobic PA guidelines (HR, 1.29 [95% CI, 0.85–1.97]), but individuals meeting both aerobic PA and resistance training guidelines had the lowest hazard of incident hypertension (HR, 0.61 [95% CI, 0.51–0.74]).

• In 86 657 adults 40 to 79 years of age who were followed up over 6 years, those with an accelerometer-relative PA was accumulated in the late morning (HR, 0.84 [95% CI, 0.77–0.92]), stroke (HR, 0.79 [95% CI, 0.64–0.97]) compared with pattern in which PA peaked from 11 am to 5 pm.⁴⁴ A pattern in the early morning (peaking from about 7–9 am) was also associated with lower hazard of CAD (HR, 0.89 [95% CI, 0.80–0.99]) compared with the average pattern. No pattern of PA was associated with stroke.

- Also from the UK Biobank cohort study, in 81 717 adults 42 to 78 years of age, greater accelerometer- measured PA was associated with reduced rela-tive hazard of hospitalization for 9 of the 25 most common reasons.⁴⁵ Among 6 cardiometabolic

conditions included, 1-SD higher PA was associated with a decreased risk of hospitalization for VTE (HR, 0.82 [95% CI, 0.75–0.90]), ischemic stroke (HR, 0.85, [95% CI, 0.76–0.95]), and diabetes (HR, 0.79 [95% CI, 0.74–0.84]) but not IHD (HR, 0.95 [95% CI, 0.90–1.00]) or AF (HR, 1.00 [95% CI, 0.92–1.07]).

- Among 16 031 WHS participants ≥ 62 years of age, those in the highest quartile for (95% CI, 18%–54%) lower hazard for CVD compared with those in the lowest quartile (≤ 60 min/d).⁴⁶ Those in the lowest quartile for sedentary behavior (< 7.4 h/d) had a 33% (95% CI, 11%–49%) lower hazard of CVD compared with those in the highest quartile (≥ 9.5 h/d).
- In the WHI/OPACH study, every 1-h/d increase in accelerometer-assessed light-intensity PA was associated with a lower risk of CHD (HR, 0.86 [95% CI, 0.73–1.00]) and lower risk of CVD (HR, 0.92 [95% CI, 0.85–0.99]).⁴⁷ For every 1 hour of daily life movement (eg, standing and moving in a confined space), the HR for CVD was 0.86 (95% CI, 0.80–0.92).⁴⁸ Those who spent more time standing (quartile 4 versus 1: HR, 0.63 [95% CI, 0.49–0.81]) and more time standing with ambulation (quartile 4 versus 1: HR, 0.50 [95% CI, 0.35–0.71]) had a lower risk of all-cause mortality.⁴⁹

Primary Prevention Using Device-Measured Steps

- Step counting is recommended as an effective method for translating PA guidelines and monitoring PA levels because of its simplicity and the

with the lowest quartile of average steps per day): quartile 2 HR, 0.80 (95% CI, 0.69–0.93); quartile 3 HR, 0.62 (95% CI, 0.52–0.74); and quartile 4 HR, 0.51 (95% CI, 0.41–0.63).⁵⁴ For those < 60 years of age, quartile of steps was not associated with CVD events: compared with the lowest quartile of average steps per day, quartile 2 HR, 0.79 (95% CI,

increased availability of step-counting devices.^{50,51}

A meta-analysis of 17 cohort studies and including 226 889 adults found a linear, inverse relationship between steps per day and all-cause mortality (HR, 0.85 [95% CI, 0.81–0.91] per 1000-step increment) and CVD mortality (HR, 0.93 [95% CI, 0.91–0.95] per 500-step increment).⁵² Stratified analyses

revealed that benefits were similar by sex and climate groups (ie, temperate, subtropical, subpolar, and mixed zone) but also found that older adults needed fewer steps to achieve similar risk reductions compared with younger adults.

- In a harmonized meta-analysis of 15 international cohort studies that included 47 471 adults and 3013 deaths, the HR for all-cause mortality was as follows (compared with the lowest quartile of average steps per day): quartile 2 HR, 0.60 (95% CI, 0.51–0.71); quartile 3 HR, 0.55 (95% CI, 0.49–0.62); and quartile 4 HR, 0.47 (95% CI, 0.39–0.57).⁵³

- In a harmonized meta-analysis of 8 international cohort studies that included 20 152 adults and 1523 CVD events (CHD, stroke, HF), the HR for those ≥ 60 years of age was as follows (compared

Secondary Prevention by PA and Sedentary Behavior

- In a population-based study of 20 653 post-MI patients in China, moderate PA (3000–4500 MET-min/wk) and high PA (>4500 MET-min/wk) were associated with lower all-cause mortality in the year after the event (moderate PA HR, 0.59 [95% CI, 0.43–0.88]) compared with insufficient PA <3000 MET-min/wk.⁵⁵ Beyond 1 year after MI, moderate PA was no longer protective (HR, 0.83 [95% CI, 0.66–1.05]), although high PA remained associated with reduced all-cause mortality (HR 0.69 [95% CI, 0.56–0.86]).
- In the HAPIEE cohort study, adults 45 to 72 years of age with preexisting IHD had a reduced risk of IHD mortality over a mean 10.55 years of follow-up if they engaged in moderate (middle tertile: HR, 0.54 [95% CI, 0.37–0.81]) or high (highest tertile: HR, 0.48 [95% CI, 0.31–0.74]) levels of PA compared with low PA (lowest tertile).⁵⁶
- An AHA scientific statement on supervised exercise training for chronic HFpEF concluded that these patients have similar or better improvement in symptoms and exercise capacity compared with patients with HFrEF.⁵⁷ The statement called for more research on optimal implementation of supervised exercise training in patients with HFpEF.

Estimated Population-Level Benefits of Increasing PA

- According to accelerometry data from NHANES 2003 to 2006, if US adults ≥40 years of age increased their moderate- to vigorous-intensity PA by ≈10 min/d, an estimated 110 000 deaths per year could be prevented.⁵⁸
- Increasing population levels of PA could increase productivity, particularly through presenteeism, and lead to substantial economic gains.⁵⁹ Engaging in at least 150 minutes of moderate-intensity PA per week, as per the lower limit of the range recommended by the 2020 WHO guidelines, would lead to an increase in global GDP of 0.15%/y to 0.24%/y by 2050, worth up to US \$314 to \$446 billion per

year and US \$6.0 to \$8.6
the 30-year projection horizon
results vary by country
baseline levels of PA and

Global Burden

(See Table 4-1 and Chart 4-7)

- The Global Matrix 4.0 on PA for years of age compiles PA around the world and provides letter grades from A (best) to F (worst).⁶⁰ The 2022 report summarized across 57 countries and ranked global PA with a grade D, school with a grade C+, community/environment with a grade C+, active transportation with a grade C-, and sedentary behavior with a grade D+.
- A 2023 report of the Global Matrix of Para Report Cards on Physical Activity for Children and Adolescents With Disabilities included 14 countries or jurisdictions and evaluated 10 indicators (over-all PA, organized sport, active play, active transport, physical fitness, sedentary behavior, family and peers, schools, community and environment, and government) to produce Para Report Cards. The highest average ranking

that 88.2% of the world's
tries where PA capacity could

- In an analysis including 168
lence of inactivity was found
income countries (36.8%
followed by middle-income
CI, 22.6%–31.8%]) and then
(16.2% [95% CI, 14.2%–
associated with inactivity for
was 9.3%, 6.8%, and 4.3% in
was for government with a grade of
C+ and the lowest average rankings
were for overall PA, organized sport
and PA, and sedentary behavior
with grades of D-.⁶¹ Greater
participation in Para Report Cards
on PA by more countries in future
reports is strongly encouraged.
- The Global Observatory for Physical
Activity monitors trends in PA
surveillance, policy, and research in
164 countries.⁶² Compared with
2015, progress by 2020 in all 3
areas was modest. It was estimated

income countries, respectively, with similar estimates for CVD mortality. The PAR for cardiovascular events such as CHD and stroke ranged from 3.0% in low-income countries to 6.5% in high-income countries.⁶³ An analysis of global trends from 1990 to 2019 found that the estimated age-standardized CVD mortality rate attributable to low PA has decreased at a rate of 1.44% per year (95% CI, –1.50% to –1.38%). Yet, age-standardized mortality rates from CVD were consistently higher than the global average in Northern Africa and the Middle East.⁶⁴ Furthermore, trends over time indicated that rates of age-standardized mortality from CVD and type 2 diabetes attributable to low PA were increasing more quickly among younger adults 25 to 44 years of age in higher-income countries.

- In 2021, based on 204 countries and territories, mortality rates attributable to low PA among regions were highest for southern sub-Saharan Africa, North Africa and the Middle East, and Oceania. Mortality rates were lowest for high-income Asia Pacific and southern Latin America (Chart 4-7). Low PA caused an estimated 0.66 (95% UI, 0.28–1.06) million total deaths in 2021, an increase of 91.86% (95% UI, 73.49%–112.26%) since 1990 (Table 4-1).⁶⁵

Table 4-1. Deaths Caused by Low PA Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total number (millions), 2021	0.66 (0.28 to 1.06)	0.25 (0.11 to 0.40)	0.41 (0.17 to 0.68)
Percent change (%) in total number, 1990–2021	91.86 (73.49 to 112.26)	112.24 (79.78 to 149.62)	81.31 (60.35 to 107.50)
Percent change (%) in total number, 2000–2021	30.74 (21.64 to 40.52)	36.22 (21.73 to 53.42)	27.63 (18.11 to 39.87)
Rate per 100 000, age-standardized	7.99 (3.38 to 12.98)	6.96 (3.05 to 11.47)	8.74 (3.63 to 14.46)
Percent change (%) in rate, age-standardized, 1990–2021	–23.06 (–31.33 to –11.40)	–15.46 (–28.57 to 0.61)	–25.38 (–34.33 to –13.29)
Percent change (%) in rate, age-standardized, 2000–2021	–7.49 (–13.92 to –0.34)	–4.50 (–15.26 to 8.42)	–8.67 (–15.42 to 0.25)
PAF (%), all ages, 2021	0.97 (0.40 to 1.54)	0.66 (0.28 to 1.05)	1.36 (0.56 to 2.18)
Percent change (%) in PAF, all ages, 1990–2021	30.28 (18.46 to 44.98)	39.68 (21.30 to 63.74)	27.82 (13.76 to 45.40)
Percent change (%) in PAF, all ages, 2000–2021	2.20 (–4.06 to 8.82)	4.96 (–5.12 to 16.57)	1.54 (–5.02 to 9.31)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; PA, physical activity; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁶⁵

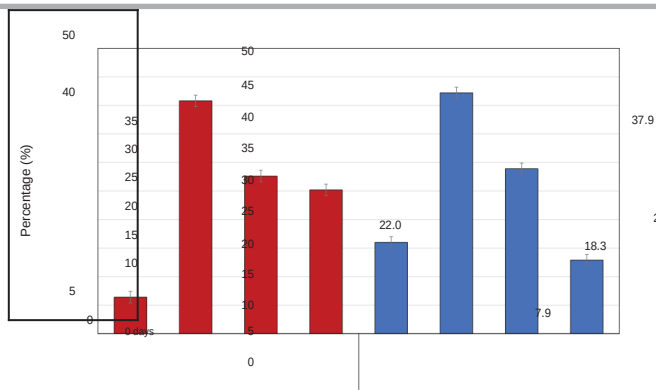
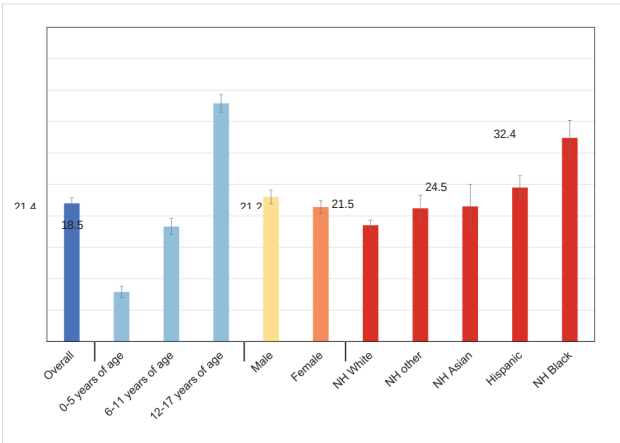


Chart 4-1. Percentage of US youths 6 to 11 and 12 to 17 years of age who were physically active for at least 60 minutes from 0 to 7 d/wk, 2022.



Error bars represent 95% CIs.
From the 2018 Physical Activity Guidelines for Americans, the aerobic guidelines recommend that youths 6 to 17 years of age should engage in at least 60 minutes of physical activity each day (7 d/wk).
Source: Data derived from National Survey of Children's Health.¹²

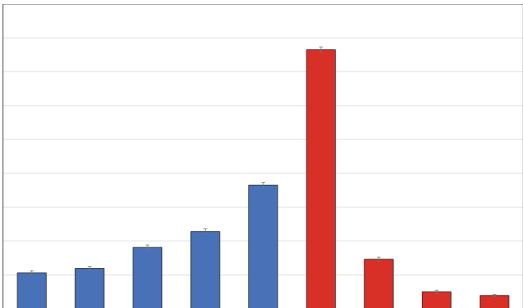
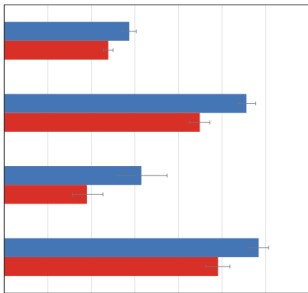


Chart 4-3. Percentage of US children 0 to 17 years of age who spent ≥4 h/d in front of a television, computer, cell phone, or other electronic device on most weekdays (not including schoolwork), overall and by age group, sex, and race and ethnicity, 2022.

Error bars represent 95% CIs.
NH indicates non-Hispanic.

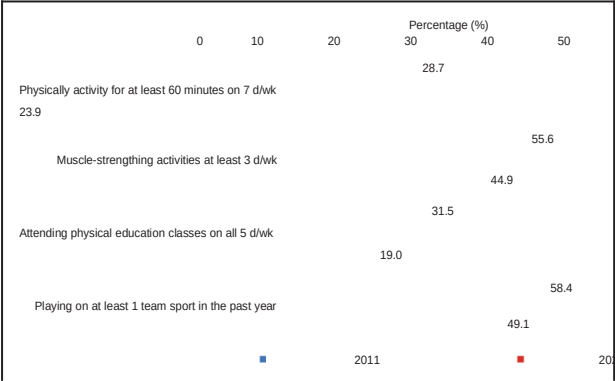
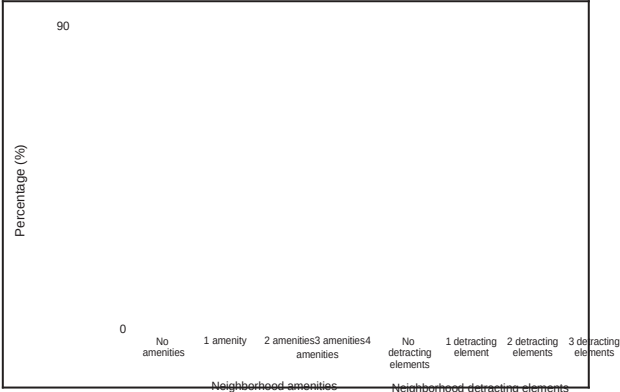


Chart 4-2. Ten-year changes in the percentage of US youths in grades 9 through 12 who met aerobic PA and muscle-strengthening recommendations, attended

education classes 5 d/wk, and played on a sports team (2011–2021).

Source: Data derived from National Survey of Children's Health.¹²



PA indicates physical activity.
From the 2018 Physical Activity Guidelines for Americans, the guidelines recommend that youths aged 6-17 years should engage in at least 60 min/d of PA and muscle-strengthening activities on 3 or more d/wk.
Source: Data derived from Youth Risk Behavior Survey.¹³

Chart 4-4. Percentage of US youths 0 to 17 years of age living in neighborhoods with health-promoting amenities and detracting elements, 2022.

Health-promoting amenities included parks, recreation centers, sidewalks, and libraries. Health-detracting elements included litter or garbage on the street or sidewalk, poorly kept or rundown housing, and vandalism such as broken windows or graffiti. Error bars represent 95% CIs.

Source: Data derived from National Survey of Children's Health.¹²

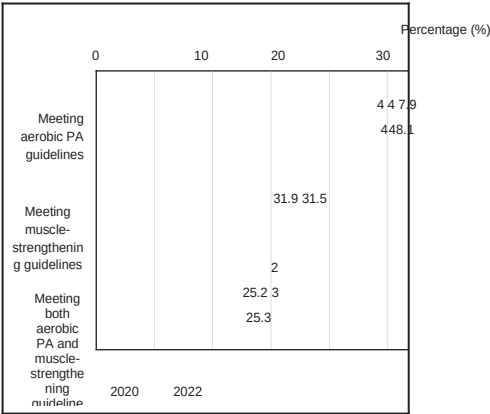


Chart 4-5. Percentage meeting guidelines for aerobic PA, muscle strengthening, or both among US adults ≥18 years of age in 2020 and 2022.

From the 2018 Physical Activity Guidelines for Americans, the aerobic guidelines recommend engaging in moderate leisure-time PA for ≥150 min/wk, vigorous activity for ≥75 min/wk, or an equivalent combination. The muscle-strengthening guidelines recommend activities of moderate or greater intensity involving all major muscle groups on ≥2 d/wk. The updated prevalence reflects the best, up-to-date estimate from the Centers for Disease Control and Prevention's ongoing PA surveillance efforts for Healthy People 2030. PA indicates physical activity. Source: Data derived from Healthy People 2030.¹⁷

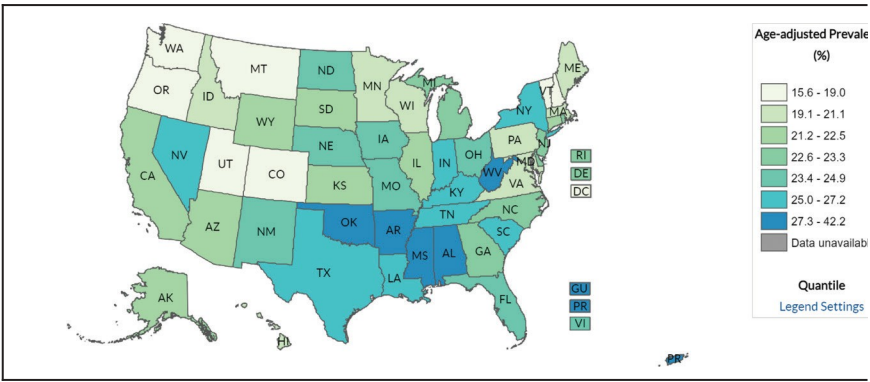


Chart 4-6. Percentage of self-reported physical inactivity among US adults ≥18 years of age, by state and territory, 2022.

Age-adjusted prevalence

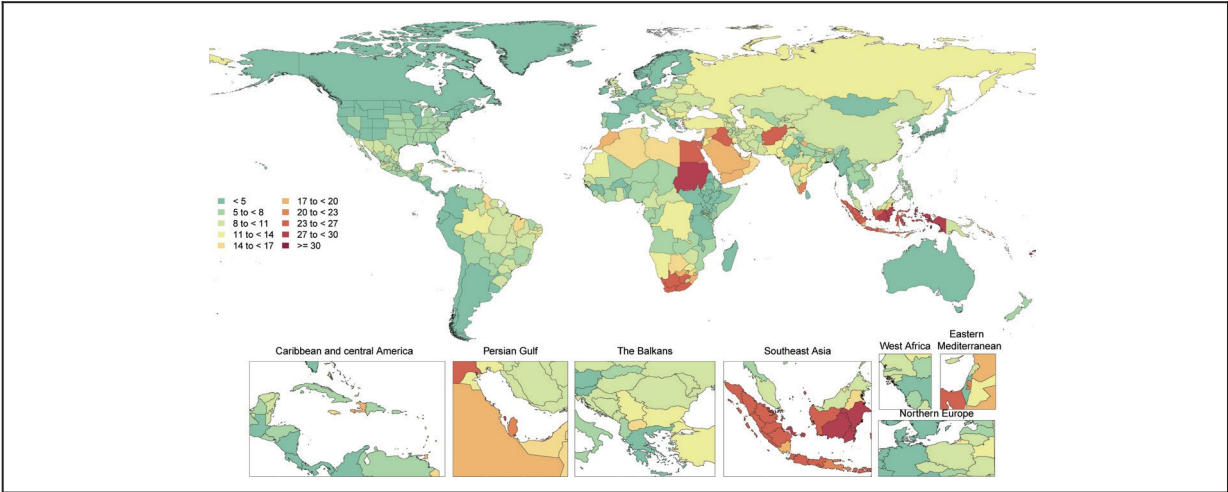


Chart 4-7. Age-standardized global mortality rates attributable to low PA per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and PA, physical activity. Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁶⁵

REFERENCES

1. Fletcher GF, Blair SN, Blumenthal J, Caspersen C, Chaitman B, Epstein S, Falls H, Froelicher ES, Froelicher VF, Pina IL. Statement on exercise: benefits and recommendations for physical activity programs for all Americans: a statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 1992;86:340–344. doi: 10.1161/01.cir.86.1.340

2. Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, Troiano RP, Sprow K, Torres A, Piercy KL; 2018 Physical Activity Guidelines Advisory Committee. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. *Med Sci Sports Exerc*. 2019;51:1270–1281. doi: 10.1249/MSS.0000000000001939

3. US Department of Health and Human Services. Physical Activity Guidelines for Americans. 2nd ed. 2018. Accessed April 7, 2024.

4. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published corrections appear in *Circulation*. 2019;140:e649–e650, *Circulation*. 2020;141:e60, and *Circulation*. 2020;141:e774]. *Circulation*. 2019;140:e596–e646. 10.1161/CIR.0000000000000678.

5. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078

6. Paluch AE, Boyer WR, Franklin BA, Laddu D, Lobelo F, Lee DC, McDermott MM, Swift DL, Weibel AR, Lane A; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; and Council on Peripheral Vascular Disease. Resistance exercise training in individuals with and without cardiovascular disease: 2023 update: a scientific statement from the American Heart Association. *Circulation*. 2024;149:e217–e231. doi: 10.1161/CIR.0000000000001189

7. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54:1451–1462. doi: 10.1136/bjsports-2020-102955

8. Carty C, van der Ploeg HP, Biddle SJH, Bull F, Willumsen J, Lee L, Kamenov K, Milton K. The first global physical activity and sedentary behavior guidelines for people living with disability. *J Phys Act Health*. 2021;18:86–93. doi: 10.1123/jpah.2020-0629
9. Selph SS, Skelly AC, Wasson N, Dettori JR, Brodt ED, Ensrud E, Elliot D, Dissinger KM, McDonagh M. Physical activity and the health of wheelchair users: a systematic review in multiple sclerosis, cerebral palsy, and spinal cord injury. *Arch Phys Med Rehabil*. 2021;102:2464–2481.e33. doi: 10.1016/j.apmr.2021.10.002
10. Gurwitz JH, Carlozzi NE, Davison KK, Evenson KR, Gaskin DJ, Lushniak B. National Institutes of Health Pathways to Prevention Workshop: physical activity and health for wheelchair users. *Arch Rehabil Res Clin Transl*. 2021;3:100163. doi: 10.1016/j.arrct.2021.100163
11. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, Chastin SFM, Altenburg TM, Chinapaw MJM; SBRN Terminology Consensus Project Participants. Sedentary Behavior Research Network (SBRN): Terminology Consensus Project process and outcome. *Int J Behav Nutr Phys Act*. 2017;14:75. doi: 10.1186/s12966-017-0525-8
12. National Center for Health Statistics and Data Resource Center for Child & Adolescent Health. National Survey of Children's Health (2016-present), interactive data query (2022). 2023. Accessed March 6, 2024.
13. Centers for Disease Control and Prevention. 1991-2021 High School Youth Risk Behavior Survey data. Accessed May 9, 2024.
14. Michael SL, Jones SE, Merlo CL, Sliwa SA, Lee SM, Cornett K, Brener ND, Chen TJ, Ashley CL, Park S. Dietary and physical activity behaviors in 2021 and changes from 2019 to 2021 among high school students—Youth Risk Behavior Survey, United States, 2021. *MMWR Suppl*. 2023;72:75–83. doi: 10.15585/mmwr.su7201a9
15. Belcher BR, Wolff-Hughes DL, Dooley EE, Staudenmayer J, Berrigan D, Eberhardt MS, Troiano RP. U.S. population-referenced percentiles for wrist-worn accelerometer-derived activity. *Med Sci Sports Exerc*. 2021;53:2455–2464. doi: 10.1249/mss.0000000000002726
16. Johnson AM, Bocarro JN, Saelens BE. Youth sport participation by metropolitan status: 2018-2019 National Survey of Children's Health (NSCH). *Res Q Exerc Sport*. 2022;94:895–904. doi: 10.1080/02701367.2022.2069662
17. US Department of Health and Human Services. Healthy People 2030: physical activity. Accessed April 14, 2024.
18. Elgaddal N, Kramarow E, Reuben C. Physical activity among adults aged 18 and over: United States, 2020. *NCHS Data Brief*. 2022;443:1–8.
19. Abildso CG, Daily SM, Umstattd Meyer MR, Perry CK, Eyster A. Prevalence of meeting aerobic, muscle-strengthening, and combined physical

- activity guidelines during leisure time among adults, by rural-urban classification and region—United States. 2020. *MMWR Morb Mortal Wkly Rep*. 2023;72:85–89. doi: 10.15585/mmwr.mm7204a1
20. Centers for Disease Control and Prevention and Behavioral Risk Factor Surveillance System. Map: overall physical inactivity. 2022. Accessed March 14, 2024.
21. Blodgett JM, Ahmadi MN, Atkin AJ, Chastin S, Chan HW, Suorsa K, Bakker EA, Hettiarachchi P, Johansson PJ, Sherar LB, et al. Device-measured physical activity and cardiometabolic health: the Prospective Physical Activity, Sitting, and Sleep (ProPASS) Consortium. *Eur Heart J*. 2024;45:458–471. doi: 10.1093/eurheartj/ehad717
22. McCormack GR, Patterson M, Fröhlich I, Lorenzetti DI. The association between the built environment and intervention-facilitated physical activity: a narrative systematic review. *Int J Behav Nutr Phys Act*. 2022;19:1–21. doi: 10.1186/s12966-022-01326-9
23. Jerome GJ, Boyer WR, Bustamante EE, Kariuki J, Lopez-Jimenez F, Paluch AE, Swift DL, Webber-Ritchey KJ, Barone Gibbs B; on behalf of the American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Peripheral Vascular Disease. Increasing equity of physical activity promotion for optimal cardiovascular health in adults: a scientific statement from the American Heart Association. *Circulation*. 2023;147:1951–1962. doi: 10.1161/CIR.0000000000001148
24. Ussery EN, Whitfield GP, Fulton JE, Galuska DA, Matthews CE, Katzmarzyk PT, Carlson SA. Trends in self-reported sitting time by physical activity levels among US adults, NHANES 2007/2008–2017/2018. *J Phys Act Health*. 2021;18:S74–S83. doi: 10.1123/jpah.2021-0221
25. Young DR, Hivert MF, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, et al; on behalf of the Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Stroke Council. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. *Circulation*. 2016;134:e262–e279. doi: 10.1161/CIR.0000000000000440
26. Aasdahl L, Nilsen TIL, Meisingset I, Nordstoga AL, Evensen KAI, Paulsen J, Mork PJ, Skarpsno ES. Genetic variants related to physical activity or sedentary behaviour: a systematic review. *Int J Behav Nutr Phys Act*. 2021;18:18. doi: 10.1186/s12966-020-01077-5
27. Doherty A, Smith-Byrne K, Ferreira T, Holmes MV, Holmes C, Pulit SL, Lindgren CM. GWAS identifies 14 loci for device-measured physical activity and sleep duration. *Nat Commun*. 2018;9:5257. doi: 10.1038/s41467-018-07743-4
28. Qi G, Dutta D, Leroux A, Ray D, Muschelli J, Crainiceanu C, Chatterjee N. Genome-wide association studies of 27 accelerometry-derived physical activity measurements identified novel loci and genetic mechanisms: a systematic
- 10.1123/inah.2022-
35. Masson W. Physical activity monitoring: a
- doi:
36. Vitor J, Melita C. A. Physical activity with meta-analysis. 10.1016/
37. Garcia L, Pearce M. Golubic R, Kelly P. Cardiovascular
- Genet Epidemiol*. 2022;46:122–138. doi: 10.1002/gepi.22441
29. van de Vegte YJ, Said MA, Rienstra M, van der Harst P, Verweij N. Genome-wide association studies and mendelian randomization analyses for leisure sedentary behaviours. *Nat Commun*. 2020;11:1770. doi: 10.1038/s41467-020-15553-w
30. Wang Z, Emmerich A, Pilon NJ, Moore T, Hemerich D, Cornelis MC, Mazzaferro E, Broos S, Ahluwalia TS, Bartz TM, et al. Genome-wide association analyses of physical activity and sedentary behavior provide insights into underlying mechanisms and roles in disease prevention. *Nat Genet*. 2022;54:1332–1344. doi: 10.1038/s41588-022-01165-1
31. Onagbiye S, Guddemi A, Baruwala OJ, Alberti F, Odome A, Ricci H, Gaeta M, Schmid D, Ricci C. Association of sedentary time with risk of cardiovascular diseases and cardiovascular mortality: a systematic review and meta-analysis of prospective cohort studies. *Prev Med*. 2024;179:107812. doi: 10.1016/j.ypmed.2023.107812
32. Anagnostopoulos I, Kousta M, Kossyvakis C, Lakka E, Vrachatis D, Deftereos S, Vassilikos VP, Giannopoulos G. Weekly physical activity and incident atrial fibrillation in females: a dose-response meta-analysis. *Int J Cardiol*. 2023;370:191–196. doi: 10.1016/j.ijcard.2022.11.007
33. Barakat R, Silva-Jose C, Zhang D, Sánchez-Polán M, Refoyo I, Montejo R. Influence of physical activity during pregnancy on maternal hypertensive disorders: a systematic review and meta-analysis of randomized controlled trials. *J Pers Med*. 2024;14:10. doi: 10.3390/jpm14010010
34. Volpato LA, Costa JC, Lopes WA, Sasaki JE, Romanzini CLP, Ronque ERV, Romanzini M. Time reallocations from sedentary behavior to physical activity and cardiovascular risk factors in children and adolescents:

analysis of large prospective studies. *Br J Sports Med.* 2023;57:979–989. doi: 10.1136/bjsports-2022-105669

38. Cillekens B, Huysmans MA, Holtermann A, van Mechelen W, Straker L, enhancing: a systematic review with meta-analysis on the association covering 23 studies with 655 892 participants. *Scand J Work Environ Health.* 2022;48:86–98. doi: 10.5271/sjweh.3993

39. Cuthbertson CC, Moore CC, Evenson KR. Paradox of occupational and leisure-time physical activity associations with cardiovascular disease. *Heart.* 2023;109:656–658. doi: 10.1136/heartjnl-2022-321856

40. Gao W, Sanna M, Chen Y-H, Tsai M-K, Wen C-P. Occupational sitting time, leisure physical activity, and all-cause and cardiovascular disease mortality. *JAMA Netw Open.* 2024;7:e2350680. doi: 10.1001/jamanetworkopen.2023.50680

41. Momma H, Kawakami R, Honda T, Sawada SS. Muscle-strengthening activities are associated with lower risk and mortality in major non-communicable diseases: a systematic review and meta-analysis of cohort studies. *Br J Sports Med.* 2022;56:755–763. doi: 10.1136/bjsports-2021-105061

42. Lee DC, Lee IM. Optimum dose of resistance exercise for cardiovascular health and longevity: is more better? *Curr Cardiol Rep.* 2023;25:1573–1580. doi: 10.1007/s11886-023-01976-6

43. Park JH, Lim NK, Park HY. Association of leisure-time physical activity and resistance training with risk of incident hypertension: the Ansan and Ansong study of the Korean Genome and Epidemiology Study (KoGES). *Front Cardiovasc Med.* 2023;10:1068852. doi: 10.3389/fcvm.2023.1068852

44. Albalak G, Stijntjes M, van Bodegom D, Jukema JW, Atsma DE, van Heemst D, Noordam R. Setting your clock: associations between timing of objective physical activity and cardiovascular disease risk in the general population. *Eur J Prev Cardiol.* 2023;30:232–240. doi: 10.1093/eurjpc/zwac239

45. Watts EL, Saint-Maurice PF, Doherty A, Fensom GK, Freeman JR, Gorzelitz JS, Jin D, McClain KM, Papier K, Patel S, et al. Association of accelerometer-measured physical activity level with risks of hospitalization for 25 common conditions in UK Adults. *JAMA Netw Open.* 2023;6:e2256186. doi: 10.1001/jamanetworkopen.2022.56186

46. Peter-Marske K, Evenson K, Moore C, Cuthbertson C, Howard A, Shiroma E, Buring J, Lee I. Association of accelerometer-measured physical activity and sedentary behavior with incident cardiovascular disease, myocardial infarction, and ischemic stroke: the Women's Health Study. *J Am Heart Assoc.* 2023;12:e028180. doi: 10.1161/JAHA.122.028180

47. LaCroix AZ, Bellettiere J, Rillamas-Sun E, Di C, Evenson KR, Lewis CE, Buchner DM, Stefanick ML, Lee IM, Rosenberg DE, et al; Women's Health Initiative (WHI). Association of light physical activity measured by accelerometry and incidence of coronary heart disease and cardiovascular disease in older women. *JAMA Netw Open.* 2019;2:e190419. doi: 10.1001/jamanetworkopen.2019.0419

48. Nguyen S, Bellettiere J, Wang G, Di C, Natarajan L, LaMonte MJ, LaCroix AZ. Accelerometer-derived daily life movement classified by machine learning and incidence of cardiovascular disease in older women: the OPACH study. *J Am Heart Assoc.* 2022;11:e023433. doi: 10.1161/JAHA.121.023433

49. Jain P, Bellettiere J, Glass N, LaMonte MJ, Di C, Wild RA, Evenson KR, LaCroix AZ. The relationship of accelerometer-assessed standing time with and without ambulation and mortality: the WHI OPACH study. *J Gerontol A Biol Sci Med Sci.* 2021;76:77–84. doi: 10.1093/gerona/glaa227

50. Kraus WE, Janz KF, Powell KE, Campbell WW, Jakicic JM, Troiano RP, Sprow K, Torres A, Piercy KL; 2018 Physical Activity Guidelines Advisory Committee. Daily step counts for measuring physical activity exposure and its relation to health. *Med Sci Sports Exerc.* 2019;51:1206–1212. doi: 10.1249/MSS.0000000000001932

51. 2018 Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. US Department of Health and Human Services; 2018.
52. Banach M, Lewek J, Surma S, Penson PE, Sahebkar A, Martin SS, Bajraktari G, Henein MY, Reiner Z, Bielecka-Dąbrowa A, et al. The association between daily step count and all-cause and cardiovascular mortality: a meta-analysis. *Eur J Prev Cardiol*. 2023;30:1975–1985. doi: 10.1093/eurjpc/zwad229
53. Paluch AE, Bajpai S, Bassett DR, Carnethon MR, Ekelund U, Evenson KR, Galuska DA, Jefferis BJ, Kraus WE, Lee IM, et al; Steps for Health Collaborative. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. *Lancet Public Health*. 2022;7:e219–e228. doi: 10.1016/S2468-2667(22)00050-0
54. Chernofsky A, Dooley EE, Ekelund U, Evenson KR, et al; Steps for Health Collaborative. Prospective association of daily steps with cardiovascular disease: a harmonized meta-analysis. *Circulation*. 2022;147:122–131. doi: 10.1161/CIRCULATIONAHA.122.061288
55. Li T, Zhang X, Wang X, Song J, Tian A, Wu C, Zhang X, Yang Y, Cui J, Xu W, et al. Time-varying effect of physical activity on mortality among myocardial infarction survivors: a nationwide population-based cohort study. *Rev Cardio-vasc Med*. 2023;24:67. doi: 10.31083/j.rcm2403067
56. Saint-Maurice PF, Graubard BI, Troiano RP, Berrigan D, Galuska DA, Fulton JE, Matthews CE. Estimated number of deaths prevented through increased physical activity among US adults. *JAMA Intern Med*. 2022;182:349. doi: 10.1001/jamainternmed.2021.7755
57. Hafner M, Yerushalmi E, Stepanek M, Phillips W, Pollard J, Deshpande A, Whitmore M, Millard F, Subel S, van Stolk C. Estimating the global economic benefits of physically active populations over 30 years (2020-2050). *Br J Sports Med*. 2020;54:1482–1487. doi: 10.1136/bjsports-2020-102590
58. Aubert S, Barnes JD, Demchenko I, Hawthorne M, Abdeta C, Abi Nader P, Adsuar Sala JC, Aguilar-Farias N, Aznar S, Bakalar P, et al. Global Matrix 4.0 physical activity report card grades for children
59. Luksiene D, Jasiukaitiene V, Radisauskas R, Tamosiunas A, Bobak M. Prognostic implications of physical activity on mortality from ischaemic heart disease: longitudinal cohort study data. *J Clin Med*. 2023;12:4218. doi: 10.3390/jcm12134218
60. Sachdev V, Sharma K, Keteyian SJ, Alcin CF, Desvigne-Nickens P, Fleg JL, Florea VG, Franklin BA, Guglin M, Halle M, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; and American College of Cardiology. Super-

61. Ng K, Sit C, Arbour-Nicitopoulos K, Aubert S, Stanish H, Hutzler Y, Santos Silva DA, Kang MG, Lopez-Gil JF, Lee EY, et al. Global Matrix of Para Report Cards on physical activity of children and adolescents with disabilities. *Adapt Phys Activ Q*. 2023;40:409–430. doi: 10.1123/apaq.2022-0111
 62. Ramirez Varela A, Hallal PC, Mejia Grueso J, Pedisic Z, Salvo D, Nguyen A, Klepac B, Bauman A, Siefken K, Hinckson E, et al. Status and trends of physical activity surveillance, policy, and research in 164 countries: findings from the Global Observatory for Physical Activity–GoPA! 2015 and 2020 Surveys. *J Phys Act Health*. 2023;20:112–128. doi: 10.1123/jpah.2022-0464
 63. Katzmarzyk PT, Friedenreich C, Shiroma EJ, Lee IM. Physical inactivity and non-communicable disease burden in low-income, middle-income and high-income countries. *Br J Sports Med*. 2022;56:101–106. doi: 10.1136/bjsports-2020-103640
 64. Zhang J, Yuan Z, Mo C, Kang Y, Wang F, Wei X, Huang S, Qin F, Jiang J, Liang H, et al. The global burden of cardiovascular diseases and type 2 diabetes attributable to low physical activity, 1990–2019: an analysis from the Global Burden of Disease Study. *Front Cardiovasc Med*. 2023;10:10. doi: 10.3389/fcvm.2023.1247705
 65. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed July 1, 2024.
- vised exercise training for chronic heart failure with preserved ejection fraction: a scientific statement from the American Heart Association and American College of Cardiology. *Circulation*. 2023;147:e699–e715. doi: 10.1161/CIR.0000000000001122

5. NUTRITION

*See Tables 5-1 through 5-5 and
Chart 5-1*

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This chapter highlights national data with a focus on key foods, food systems, and other dietary factors affecting public health. It examines current changes in intakes, and estimated support and further stimulate efforts to improve dietary habits in

sustainable outcomes at every level of the food system.²

The first study to use the AHA's

8 to quantify the CVH levels of the United States included data from individuals 2 through 79 years of age

(9888 children) participating in the 2011-2018 adults, and 74 435

This cross-sectional analysis of the NHANES 2013 to 2018 survey included 5 people in the United States representative of optimal heart health and across age and sociodemographic system for the AHA's Life's

scores for each of the 8 metrics (0 is lowest, 100 is high-

Prevalence and Trends in the AHA's Life's Essential 8's Healthy Diet Metrics

(See Tables 5-1 through 5-3)

On June 29, 2022, the AHA debuted Life's Essential 8 in a presidential advisory, an updated algorithm for quantifying CVH.¹ This update was in response to extensive evidence giving insights into the strengths and limitations of the original approach to quantifying CVH (Life's Simple 7). In AHA's Life's Essential 8, diet was 1 of the 4 items updated to reflect new evidence and to provide a guide to assess diet quality for adults and children at the population level (Table 5-1) and individual level (Table 5-2). At the population level, diet is assessed on the basis of DASH-style eating patterns. At the individual level, the Mediterranean Eating Pattern for Americans is used to assess and

monitor CVH. A DASH-style pattern emphasizes vegetables, fruits, nuts and legumes, whole grains, and low-fat dairy and is reduced in sodium, red and processed meats, and sweetened beverages (Table 5-2). The items included in the Mediterranean Eating Pattern for Americans are shown in Table 5-3.¹ The 2022 presidential advisory to the AHA acknowledges disparities by personal and environmental factors and the need for innovation in systems and structures to correct current deleterious impacts on health.¹ A call for action focused on the food systems is made in the AHA science advisory covering favorable innovations to create healthy and

est). The scores on the 8 metrics are used to generate a composite CVH score (the unweighted average of all components) that ranges from 0 to 100 points.

The mean overall CVH scores from this analysis revealed significant differences by age (range of mean values, 62.2–68.7), sex (females, 67.0; males, 62.5), and racial and ethnic group (range, 59.7–68.5).³ Diet was among the 4 metrics with the lowest scores; ranging from 23.8 to 47.7 for adults depending on the demo-graphic group. Among children 2 to 5 years of age, a mean diet score of 61.1 was observed. The score for children 12 to 19 years of age was 28.5.

Dietary Habits in the United States: Current Intakes of Foods and Nutrients

The 2020 US Dietary Guidelines Advisory Committee summarized the evidence for benefits of healthful diet patterns on a range of cardiometabolic and other disease outcomes.⁴ They concluded that the core elements of a healthy dietary pattern are (1) vegetables of all types; (2) fruits, especially whole fruits; (3) grains, of which at least half are whole grains; (4) dairy, including fat-free or low-fat milk, yogurt, and cheese or lactose-free versions and fortified soy beverages and yogurt as alternatives; (5) protein foods, including lean meats, poultry and eggs, seafood, beans, peas, lentils, nuts, seeds, and soy prod-ucts; and (6) oils, including vegetable oils and oils in food such as seafood and nuts. A healthy dietary pattern is also limited in foods and beverages high in added sugars, saturated fat, sodium, and alcoholic beverages.

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity

Adults
(See Table 5-4)

Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statisti-cal Update. We strive to use terms from the original data sources or

published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

The average dietary consumption by US adults of select-ed foods and nutrients related to cardiometabolic health based on data from NHANES 2017 to 2018 is detailed below by sex and race and ethnicity (Table 5-4):

- Consumption of whole grains was low with sex and racial variations and ranged from 0.6 (Mexican American males) to 0.9 (NH White males) serving/d.

For each of these groups, <10% of adults met guidelines of ≥ 3 servings/d.

- Whole-fruit consumption similarly showed a sex and racial difference and ranged from 1.1 (NH Black males) to 1.7 (Mexican American females) servings/d. For each of those groups except Mexican American females, <10% of adults met guidelines of ≥ 2 cups/d. When 100% fruit juices were included, the number of servings increased, and the proportions of adults consuming ≥ 2
- Nonstarchy vegetable consumption ranged from 1.5 (NH Black males) to 2.3 (NH White females) servings/d. The proportion of adults meeting guidelines of ≥ 2.5 cups/d was <10%.
- Consumption of fish and shellfish ranged from 1.0 (NH White individuals) to 1.9 (NH Black females) servings/wk. The proportions of adults meeting guidelines of ≥ 2 servings/wk were $\approx 18\%$ of NH White adults, $\approx 28\%$ of NH Black adults, and $\approx 19\%$ of Mexican American adults.
- Weekly consumption of nuts and seeds was ≈ 6 servings among NH White adults, ≈ 3 servings among NH Black adults, and ≈ 4 servings among Mexican American adults. Approximately 1 in 3

one-half to two-thirds consumed <300 mg dietary cholesterol/d.

- The ratio of (PUFAs+monounsaturated fatty acids)/SFAs ranged from 1.8 in NH White males and Mexican American males to 2.6 in NH Black females. The proportion with a ratio ≥ 2.5 ranged from 11.2% in NH White males to 40.6% in NH Black females.
 - White adults, 1 in 5 NH Black adults, and 1 in 4 Mexican American adults met guidelines of ≥ 4 servings/wk.
- Consumption of processed meats was lowest among Mexican American females (1.0 servings/wk) and highest among NH White males (≈ 2.5 servings/wk). Between 59% (NH White males) and 87% (Mexican American females) of adults consumed ≤ 2 servings/wk.
- Consumption of SSBs was lowest among NH White females (6.4 servings/wk) and highest among NH Black individuals and Mexican American males (≈ 10 servings/wk). The proportions of adults meeting guidelines of <36 oz/wk were $\approx 61\%$ for NH White adults, 48% for Mexican American adults, and 41% for NH Black adults.
- Consumption of sweets and bakery desserts ranged from 4.5 servings/wk among Mexican American males to 3.3 servings/wk among NH

- The average daily sodium consumption for Americans ≥ 1 year of age is >3400 mg, and the top 10 food categories accounted for 40% of sodium consumed.⁵ These top 10 categories included pre-pared foods with added sodium such as deli meat sandwiches, pizza, burritos, and tacos. During 2015 to 2016, the percentage of adults in the United States with sodium intake above the chronic disease risk reduction intake level was 86.7%.⁶ This is note-worthy because the chronic disease risk reduction intake for sodium was established from evidence of the beneficial effect of reducing sodium intake on CVD risk, hypertension risk, SBP, and DBP. In apparently healthy populations, when reductions in intake of sodium exceed the chronic disease risk reduction, it is expected that there will be reductions in chronic disease risk.

Children and Teenagers

According to NHANES 2015 to 2016 data, the average dietary consumption by US children and teenagers of selected foods and nutrients related to cardiometabolic health is detailed below:⁷

- Whole grain consumption was low with an estimated average intake of 0.95 serving/d (95% CI, 0.88–1.03) among US youths 2 to 19 years of age. Youth with higher parental education had higher intake.
- Whole fruit consumption was low with an estimated average intake of 0.68 serving/d (95% CI, 0.58–0.77). The consumption pattern decreased with age. NH Asian youths and those of other races, including multiracial youths, had the highest intake of whole fruit, followed by NH White youths, other Hispanic Black males.
- The proportion of total energy intake from added sugars ranged from 11.8% for NH White males to 20.4% for NH Black females. Between 16.6% of NH Black females and 38.3% of Mexican American males consumed $\leq 6.5\%$ of total energy intake from

youths, Mexican American youths, and NH Black youths. The average intake of 100% fruit juice was 0.46 serving/d (95% CI, 0.39–0.53). The consumption pattern also decreased with age. NH White youths had the lowest intake of fruit juice, followed

added sugars.

- Consumption of EPA and DHA ranged from 0.079 to 0.124 g/d in each sex and racial or ethnic sub-

by NH Asian youths and youths of other races, group. Fewer than 9% of US adults met the guideline of ≥ 0.250 g/d.

- Two-fifths to one-third of adults consumed $<10\%$ of

including multiracial youths, Mexican American youths, other Hispanic youths, and NH Black youths. •
Nonstarchy vegetable consumption was low with an estimated average intake of 0.57 serving/d (95%
CI, 0.53–0.62). The consumption pattern increased
total calories from with age.
saturated fat, and

- Consumption of fish and shellfish estimated average intake of CI, 0.04–0.07). The with age. Hispanic youths had fish and shellfish, followed by youths of other races. NH Black youths. Mexican NH White youths.
- Consumption of nuts and seeds estimated average intake of CI, 0.33–0.47). NH White intake of nuts and seeds, followed by NH Asian youths and youths of other races, including multiracial youths, other Hispanic youths, NH and Mexican American youths. The consumption pattern of nuts and seeds increased with higher
- Consumption of dietary fiber 15.1–16.0) on average among significant heterogeneity ethnicity, parental education.
- Consumption of sodium was 3.28–3.37) on average among consumption pattern youths and those of other youths. had the highest intake by NH Black youths. Mexican NH White youths.

Secular Trends

The Dietary Guidelines for Americans are published every 5 years, and adherence to them is measured with parental education and parental income. the HEI.⁴

- Consumption of unprocessed red meats was 0.31 serving/d (95% CI, 0.27–0.34) with intakes inversely related to parental educational attainment.
- Consumption of processed meats was 0.27 serving/d (95% CI, 0.24–0.29) on average with higher intake among males and lower intake among females. NH White youths had the highest intake of processed meat, followed by NH Black youths, Mexican American youths, NH Asian youths, and those of other races, including multiracial youths and other Hispanic youths.
- Consumption of SSBs was 1.0 serving/d (95% CI, 0.89–1.11) on average among US youths.

The consumption pattern of SSBs increased with age.

NH Black youths had the highest intake of SSBs, followed by Mexican American youths, NH White youths, other Hispanic youths, NH Asian youths, and those of other races, including multiracial youths.

- Consumption of sweets and bakery desserts contributed to an average of 6.07% of calories (95% CI, 5.55%–6.60%) among US youths with no significant heterogeneity across age, sex, race and ethnicity, parental education, and household

Between 1999 and 2016, the average HEI-2015 score of US adults improved from 55.7 to 57.7 (difference, 2.01 [95% CI, 0.86–3.16]; $P_{\text{trend}} < 0.001$).⁸ This was related to improvements in the macronutrient composition, including decreases in low-quality carbohydrates (primarily added sugar) and increases in high-quality carbohydrates (primarily whole grains), plant protein (primarily whole grains and nuts), and polyunsaturated fat. However, intake of low-quality carbohydrates and saturated fat remained high. The HEI-2015 score increased more in younger compared with older adults and in those with a higher compared with a lower level of income.

Trends in diet quality among youths in the United States were characterized in a study using 9 NHANES data cycles.⁷ The primary outcomes were the survey-weighted, energy-adjusted mean consumption of dietary components and proportion meeting targets of the AHA 2020 continuous diet score (range, 0–50; based on total fruits and vegetables, whole grains, fish and shellfish, SSBs, and sodium). Other outcomes were the AHA secondary score (range, 0–80; adding nuts, seeds, and legumes; processed meat; and saturated fat) and HEI-2015 score (range, 0–100). Between 1999 and 2016,

income.

- Consumption of EPA and DHA was low with an estimated average intake of 0.04 g/d (95% CI, 0.03–0.05). The consumption pattern of EPA and DHA increased with age. NH Asian youths and those of other races, including multiracial youths, had the highest intake of EPA and DHA, followed by other Hispanic youths, Mexican American youths, NH White youths, and NH Black youths.

the mean HEI-2015 score in US children and adoles-

- Consumption of SFAs was ≈12.1% of calories (95% CI, 11.8%–12.4%) among US youths. Consumption of dietary cholesterol was 254 mg/d (95% CI, 244–264) with NH White youths having the lowest intake (238 mg/d [95% CI, 226–250]) and Mexican American youths having the highest intake (292 mg/d [95% CI, 275–309]).

cents 2 to 19 years of age improved from 44.6 (95% CI, 43.5–45.8) to 49.6 (95% CI, 48.5–50.8; 11.2% improvement).⁷

The mean AHA primary diet score increased from 14.8 (95% CI, 14.1–15.4) to 18.8 (95% CI, 18.1–19.6; 27.0% improvement), and the mean AHA secondary score improved from 29.2 (95% CI, 28.1–30.4) to 33.0 (95% CI, 32.0–33.9; 13.0% improvement). Based on the AHA primary score, the estimated proportion of US children with poor dietary quality significantly decreased from 76.8% (95% CI, 72.9%–80.2%) to 56.1% (95% CI, 51.4%–60.7%); the estimated proportion with inter-mediate quality significantly increased from 23.2% (95% CI, 19.8%–26.9%) to 43.7% (95% CI, 39.1%–48.3%). The estimated proportion with an ideal diet significantly improved but remained low (from 0.07% to 0.25%).

Based on the AHA secondary score, the estimated proportion of US children with poor dietary quality significantly decreased from 61.0% (95% CI, 56.5%–65.2%) to 49.1% (95% CI, 45.0%–53.3%); the estimated proportion with intermediate quality significantly increased from 39.0% (95% CI, 34.7%–43.4%) to 50.4% (95% CI, 46.3%–54.4%).

The estimated proportion with an ideal diet significantly improved from 0.04% to 0.50%. The overall dietary quality improvement among US consumption of fruits/vegetables (especially whole fruits) and whole grains, with additional increases in total dairy, total protein foods, seafood, and plant proteins and decreased consumption of SSBs and added sugar. Persistent dietary variations were identified across multiple sociodemographic groups. The mean HEI-2015 score in 2015 to 2016 was 55.0 (95% CI, 53.7–56.4) for youths 2 to 5 years of age, 49.2 (95% CI, 47.9–50.6) for youths 6 to 11 years of age, and 47.4 (95% CI, 46.0–48.8) for youths 12 to 19 years of age.

Patterns and trends in diet quality of foods from major sources, including grocery stores, restaurants, schools, and worksites, were examined in a study including children 5 to 19 years of age and adults ≥20 years of age in a serial, cross-sectional survey of data from 8 NHANES cycles from 2003 to 2018.⁹ Relative to the other food sources, schools provided the best mean diet quality. More specifically, schools had the largest improvement in diet quality, with the percentage of the population having poor diet quality decreasing from 55.6% to 24.4% ($P_{\text{trend}} < 0.001$).

with duration of participation in WIC.¹¹ Longer duration of participation in WIC was associated with lower odds of household food insecurity (OR, 0.69 [95% CI, 0.51–0.95]), higher total dietary quality as measured by the HEI-2015 (β , 0.73 [95% CI, 0.21–1.25]), and higher obesity odds (OR, 1.20 [95% CI, 1.05–1.37]) in multivariable-adjusted regression

Trends in Dietary Supplement Intake

Use of dietary supplements is common in the United States among both adults and children. Data from NHANES 2007 to 2018 revealed that dietary supplement use increased from 50% in 2007 to 56% in 2018 in individuals ≥1 year of age.¹⁰ The use of micronutrient-containing supplements increased from 46% in 2007 to 49% in 2018; use of single-nutrient supplements also increased ($P < 0.001$). In children 1 to 18 years of age, the use of dietary supplements in any form remained stable (38%) over this time frame. However, use of micronutrient-containing supplements increased in children who experience food insecurity, from 24% to 31% ($P = 0.03$). In adults, use of dietary supplements in any form increased (54% to 61%), and use of micronutrient-containing supplements increased (49% to 54%). Dietary supplement use increased, especially in those who identify as male, NH Black, Hispanic, and low income.

Social Determinants of Dietary Intake/Health Equity

- Household food insecurity, child diet quality, and child weight status at 5 years of age are associated

supermarkets), convenience stores, and fast-food restaurants are not consistently associated with diet quality or adiposity and could be linked to social determinants of CVH.¹²

- An analysis of the 4 major outlets where food is obtained (stores, quick-serve restaurants, full-service restaurants, and schools) using 24-hour dietary recall data from 8 cycles of NHANES showed that Americans are not consuming foods that align with the Dietary Guidelines for Americans.¹³ The HEI-2015 score for schools (65/100 points) and stores (62/100 points) was significantly higher than those for full-service (51/100 points) and quick-service (39/100 points) restaurants ($P<0.0001$).

Genetics/Family History

- Genetic factors may contribute to food preferences and liking and modulate the association between dietary components and adverse CVH outcomes.^{14–16} Nutrigenetics may also contribute to variation in the metabolism of specific dietary components such as carbohydrates, amino acids, and fatty acids across individuals or ethnic and racial groups.¹⁷ Nutritional epigenomics stipulates that epigenetic alterations induced by environmental exposures such as diet and bioactive compounds may mediate the impact of diet on CVH outcomes.^{18,19}
- Ancillary studies from the POUNDS Lost trial, a 2-year randomized clinical trial including 811 overweight or obese adults examining the role of dietary interventions in weight loss, demonstrated that the weight loss and changes in BP, cholesterol, and blood glucose in response to dietary interventions were modified by DNA methylation levels at *NFATC2IP*, *CPT1A*, *TXNIP*, and *LINC00319*.²⁰
- However, a randomized trial of 609 participants with overweight/obesity and without diabetes demonstrated that, compared with the effects of healthy low-fat and healthy low-carbohydrate weight-loss diets, neither genotype pattern (3-SNP multilocus genotype responsiveness pattern) nor insulin secretion (30 minutes after a glucose challenge) modified the effects of diet on weight loss.²¹
- A comprehensive GWAS of 85 single-food intake and 85 dietary patterns derived from food

frequency questionnaires
viduals identified 814 loci
food intake and 136 loci
patterns.²² Furthermore,
assessed in the GWAS were
cantly heritable.²²

- A recent GWAS identified 26 loci
dietary carbohydrate, fat, and
study noted an enrichment of
expression in specific neurons
mineraic, and glutamateraic).

mechanisms contributing to dietary patterns.

- The interactions between a GRS composed of 97
BMI-associated variants and 3 diet-quality
scores were examined in a pooled analysis of 30
904 participants from the Nurses' Health Study,
the HPFS, and the Women's Genome Health
Study.

Higher diet quality was found to attenuate the
association between GRS and BMI (P for
interaction terms <0.005 for AHEI-2010 score,
Alternative Mediterranean Diet score, and DASH
diet score).²³ A 10-unit increase in the GRS was
associated with a 0.84-unit (95% CI, 0.72–0.96)
increase in BMI for those in the highest tertile of
AHEI score compared with a 1.14-unit (95% CI,
0.99–1.29) increase in BMI in those in the lowest
tertile of AHEI score.

- In a study of ≈ 9000 females from the WHI, a GRS
for LDL-C, composed of 1760 LDL-associated
vari-ants, explained 3.7% (95% CI, 0.09%–
11.9%) of the variance in 1-year LDL-C changes
in a dietary fat intervention arm but was not
associated with changes in the control arm.²⁴

Impact on Mortality

- Nationally representative data from 37 233 US
adults were analyzed to examine the association

[95% CI, 0.86–0.95]), and
tality (HR, 0.65 [95% CI,

- NHANES III (1988–1994) data
(20–90 years of age) with
(BMI ≥ 25 kg/m²) were
relationship between the DII
DII scores of metabolically
als with obesity/overweight
increased mortality risk
(HR_{tertile 3 versus tertile 1}, 1.44 [95%
CI, 1.11–1.86]; $P_{\text{trend}}=0.008$:

between low-carbohydrate and low-
fat diets and mortality. Neither
low-carbohydrate nor low-fat

diets were associated with total
mortality; however, healthy
low-carbohydrate (HR, 0.91 [95% CI,
0.87–0.95]; $P<0.001$) and low-fat
(HR, 0.89 [95% CI, 0.85–0.93];
 $P<0.001$) diets were associated with
lower mortality, and unhealthy low-
carbohydrate (HR, 1.07 [95% CI,
1.02–1.11]; $P=0.01$) and low-fat
(HR, 1.06 [95% CI, 1.01–1.12];
 $P=0.04$) diets were linked to
higher mortality.²⁵

- Higher intakes of fruit and vegetables
are associ-ated with lower
mortality. Specifically, data from 66
719 females from the Nurses' Health
Study (1984–2014) and 42 016
males from the HPFS (1986–
2014) showed that daily intake of 5
serv-ings of fruit and vegetables
(versus 2 servings/d) was
associated with lower total mortality
(HR, 0.87 [95% CI, 0.85–0.90]), CVD
mortality (HR, 0.88 [95% CI,
0.83–0.94]), cancer mortality (HR, 0.90

CVD-related mortality ($HR_{T3 \text{ versus } T1}, 3.29 [95\% \text{ CI}, 2.01\text{--}5.37]; P_{\text{trend}} < 0.001; HR_{1\text{-SD increase}}, 1.40 [95\% \text{ CI}, 1.18\text{--}1.66]$). These associations were not observed among adults with metabolically healthy obesity, and no cancer mortality risk was observed for either metabolically unhealthy individuals with obesity/overweight or metabolically healthy individuals with obesity. The SUN study, which began in 1999 ($N=18\,566$), and the PREDIMED study, which began in 2003 in Spain ($N=6790$), similarly analyzed the DII score in relation to mortality.

Significant associations were found in differences between the highest and lowest quartiles of the DII score and mortality in both SUN ($HR, 1.85 [95\% \text{ CI}, 1.15\text{--}2.98]; P_{\text{trend}}=0.004$) and PREDIMED ($HR, 1.42 [95\% \text{ CI}, 1.00\text{--}2.02]; P_{\text{trend}}=0.009$).²⁸

- Several studies examined the relationship between sugar intake and all-cause and cause-specific mortality. A 6-year cohort study of 13 440 US adults (mean, 63.6 years of age) found that higher consumption (each additional 12-oz serving/d) of sugary beverages ($HR, 1.11 [95\% \text{ CI}, 1.03\text{--}1.19]$) and 100% fruit juices ($HR, 1.24 [95\% \text{ CI}, 1.09\text{--}1.42]$) was associated with higher all-cause (but not CHD-specific) mortality.²⁹ In 2 Swedish studies (MDCS, $N=24\,272$; and NSHDS, $N=24\,475$), both higher consumption ($>20\%$ energy intake: $HR, 1.30 [95\% \text{ CI}, 1.12\text{--}1.51]$) and lower consumption ($<5\%$ energy intake: $HR, 1.23 [95\% \text{ CI}, 1.11\text{--}1.35]$) were associated with higher mortality risk.³⁰

- A systematic review of 18 cohort studies ($N=251\,497$) examined the relationship of glycemic index and glycemic load with risk of all-cause mortality and CVD and found no associations. However, a positive association was found with all-cause mortality among females with the highest (versus lowest) glycemic index ($RR, 1.17 [95\% \text{ CI}, 1.02\text{--}1.35]$).³¹ Using data from 137 851 participants between 35 and 70 years of age living in high-, middle-, and low-income countries across 5 continents with a median follow-up of 9.5 years, the international PURE study reported that a high glycemic index was associated with an increased risk of a major cardiovascular event or death among participants with ($HR, 1.51 [95\% \text{ CI}, 1.25\text{--}1.82]$) and

without (HR, 1.21 [95% CI, 1.11–1.34])
preexisting CVD at baseline.³²

- In an assessment of the relationship between dairy intake and mortality, data from 3 large prospective cohort studies with 217 755 US adults showed a dose-response relationship in which 2 daily servings of dairy were associated with the lowest CVD mortality and higher intake was linked to higher mortality, especially cancer cheese, yogurt, ice cream/sherbet), whole milk (and additional 0.5 serving/d) was associated with higher risks of cancer mortality (HR, 1.11 [95% CI, 1.06–1.17]), CVD mortality (HR, 1.09 [95% CI, 1.03–1.15]), and total mortality (HR, 1.11 [95% CI, 1.09–1.14]). A similar large cohort study of 45 009 Italian participants found no dose-response relationship between dairy (eg, milk, cheese, yogurt, butter) consumption and mortality, and no differences were present between full-fat and reduced-fat milk. However, there was a significant reduction of 25% in risk of all-cause mortality among those

15.8 g/d) in females and 30.9 g/d (SD, 23.1 g/d) in males, and no association was found between the highest and lowest quartiles of egg consumption and all-cause mortality (HR, 1.01 [95% CI, 0.91–1.11]; $P=0.96$) or cancer and CVD mortality. However, egg consumption appears to be inversely associated with deaths resulting from other causes

consuming 160 to 200 g/d (HR, 0.75 [95% CI, 0.61–0.91]) milk compared with nonconsumers.

- A European study examined the relationship between dietary protein and protein sources and mortality among 2641 Finnish males. Higher meat intake (HR, 1.23 [95% CI, 1.04–1.47]) and higher ratio of animal to plant protein (HR, 1.23 [95% CI,

- The association between dietary choline and overall- and cause-specific mortality was examined in a large, nationally representative study of 20 325 US adults (mean, 47.4 years of age). Higher choline consumption was found to be associated with worse lipid profiles, poorer glycemic control, and lower CRP levels (all comparisons, $P < 0.001$). Those with the highest compared with lowest consumption had increased risk of total (RR, 1.23 [95% CI, 1.09–1.38]), stroke (RR, 1.30 [95% CI, 1.02–1.66]), and CVD (RR, 1.33 [95% CI, 1.19–1.48]) mortality (all comparisons $P < 0.001$).⁴¹ A subsequent meta-analysis confirmed these results and found choline to be linked to higher mortality risk (RR, 1.12 [95% CI, 1.08–1.17]; $I^2 = 2.9$) and CVD mortality risk (RR, 1.28 [95% CI, 1.17–1.39]; $I^2 = 9.6$).⁴¹ Major contributors of choline to the American diet are meat, poultry, dairy foods, pasta, rice, and egg-based dishes.⁴²

1.02–1.49]) were associated with higher mortality. This relationship was more pronounced among those with a history of CVD, cancer, and type 2

CVH Impact of Diet Dietary Patterns

betes.^{33–35} In addition, several meta-analyses of prospective cohort studies have consistently reported that higher plant protein intake is inversely associated with total and CVD mortality, lending support for dietary recommendations to replace foods high in animal protein with plant protein sources.^{36–38}• The

association between nut and peanut butter consumption and mortality has also been assessed.

In a large prospective cohort study of 566 398 US adults (50–71 years of age at baseline) with a median follow-up of 15.5 years, nut consumption was inversely related to mortality (HR, 0.78 [95% CI, 0.76–0.81]; $P \leq 0.001$) and was associated with reductions in cancer, CVD, and infectious, respiratory, and liver and renal disease mortality (but not

- The observational findings for benefits of the Mediterranean diet have been confirmed in a large primary prevention trial in Spain among patients with CVD risk factors.⁴³ The PREDIMED trial demonstrated an ≈30% relative reduction in the risk of stroke, MI, and death attributable to cardiovascular causes in those patients randomized to unrestricted-calorie Mediterranean-style diets supplemented with extravirgin olive oil or mixed nuts,⁴³ without changes in body weight.⁴⁴ In a subgroup analysis of 3541 patients without diabetes in the PREDIMED trial, HRs for incident diabetes were 0.60 (95% CI, 0.43–0.85) for the Mediterranean diet with olive oil group and 0.82 (95% CI, 0.61–1.10) for the Mediterranean diet with nuts group compared with the control group.
- AD- or diabetes-related mortality). No significant cause-specific⁴⁰ mortality were investigated in a large cohort of 40 621 adults (29–69 years of age) in the EPIC-Spain prospective cohort study across 18 years.
- relationships were found between peanut butter and cause-specific or all-cause mortality (HR, 1.00 [95% CI, 0.98–1.04]; $P=0.001$).³⁹
- Moderate egg consumption and all-cause and Mean egg consumption was 22 g/d (SD,

- In a systematic review and meta-analysis of 29 observational studies, the RR for the highest versus lowest category of the Mediterranean diet was 0.81 (95% CI, 0.74–0.88) for CVD, 0.70 (95% CI, 0.62–0.80) for CHD/AMI, 0.73 (95% CI, 0.59–0.91) for unspecified stroke (ischemic/hemorrhagic), 0.82 (95% CI, 0.73–0.92) for ischemic stroke, and 1.01 (95% CI, 0.74–1.37) for hemorrhagic stroke.⁴⁵

- In a meta-analysis of 20 studies, the RR for each 4-point Mediterranean diet score was 0.81–0.88) for unspecified 0.81–0.91) for ischemic 0.74–0.93) for hemorrhagic
- In another systematic review, a of 3 RCTs showed a Mediterranean diet on total 0.62 [95% CI, 0.50–0.78] and (RR, 0.65 [95% CI, 0.49–0.88]).⁴⁷
- Another meta-analysis of 38 prospective cohort studies showed that the RR for the highest versus the lowest categories of Mediterranean diet adherence was 0.79 (95% CI, 0.77–0.82) for total CVD mortality, 0.73 (95% CI, 0.62–0.86) for CHD incidence, 0.83 (95% CI, 0.75–0.92) for CHD mortality, 0.80 (95% CI, 0.71–0.90) for stroke incidence, 0.87 (95% CI, 0.80–0.96) for stroke mortality, and 0.73 (95% CI, 0.61–0.88) for MI to –3.0) for every 100–mmol/d sodium excretion.
- A secondary analysis of the White participants showed patterns (vegan, lacto-ovo) at baseline were prevalence of hypertension at 1 to 3 compared with the was 0.46 (95% CI, 0.25–0.83) (95% CI, 0.45–0.73) for lacto-incidence.⁴⁷
- In an umbrella review of systematic reviews, a meta-analysis of 33 controlled trials showed that the DASH diet was associated with decreased SBP (mean difference, –5.2 mm Hg [95% CI, –7.0 to –3.4]), DBP (–2.60 mm Hg [95% CI, –3.50 to –1.70]), TC

0.62 (95% CI, 0.42–0.91) for pescatarians. This association remained after adjustment for BMI among the lacto-ovo vegetarians.⁵¹

- In a systematic review and meta-analysis of 9 prospective cohort studies, higher adherence to a plant-based dietary pattern was significantly associated with lower risk of type 2 diabetes (RR, 0.77 [95% CI, 0.71–0.84]).⁵²
- In an RCT of 48 835 postmenopausal females, a low-fat dietary pattern (lower fat and higher carbohydrates, vegetables, and fruit) intervention led to significant reductions in breast cancer followed by death (HR, 0.84 [95% CI, 0.74–0.96]) and in diabetes requiring insulin (HR, 0.87 [95% CI, 0.77–0.98]) over a median follow-up of 19.6 years compared

(–0.20 mmol/L [95% CI, –0.31 to –0.10]), LDL-C (–0.10 mmol/L [95% CI, –0.20 to –0.01]), HbA1c (–0.53% [95% CI, –0.62 to –0.43]), fasting blood insulin (–0.15 μ U/mL [95% CI, –0.22 to –0.08]), and body weight (–1.42 kg [95% CI, –2.03 to

with usual diet.⁵³

–0.82]).⁴⁸ A meta-analysis of 15 prospective cohort studies showed that the DASH diet was associ-

- In a prospective cohort study of 105 159 adults followed up for a median of 5.2 years, for a 10% increment in the percentage of ultraprocessed foods in the diet, the HR was 1.12 (95% CI, 1.05–1.20) for overall CVD, 1.13 (95% CI, 1.02–1.24) for CHD, and 1.11 (95% CI, 1.01–1.21) for cerebrovascular disease.⁵⁴
 - ated with decreased incident CVD (RR, 0.80 [95% CI, 0.76–0.85]), CHD (0.79 [95% CI, 0.71–0.88]), stroke (0.81 [95% CI, 0.72–0.92]), and diabetes (0.82 [95% CI, 0.74–0.92]).⁴⁸ In another systematic review and meta-analysis of 7 prospective cohort studies, the RR for each 4-point increment of DASH diet score was 0.95 (95% CI, 0.94–0.97) for CAD.⁴⁹ Support for BP effects of a healthy pattern with reduced sodium was seen in a dose-response meta-analysis of experimental studies including 85 clinical trials in participants with hypertension, without hypertension, or a combination. Analyses showed a linear relationship between sodium intake and reduction in SBP and DBP across the entire range of dietary sodium exposure (0.4–7.6 g/d).⁵⁰ The difference in 24-hour sodium excretion that was achieved between the intervention and control groups was equivalent to 0.1 to 7.1 g sodium/d with a median difference of 1.8 g sodium/d.⁵⁰ Over the range of sodium exposure, the overall BP difference was >15 mm Hg for SPB and ≈10 mm Hg for DBP. Linear regression analyses resulted in a lower mean SBP of 5.6 mm Hg (95% CI, –4.52 to –6.6) and a lower mean DBP of 2.3 mm Hg (95% CI, –1.7

- An umbrella review of 16 meta-analyses of 116 primary prospective cohort studies with 4.8 million participants reported moderate-quality evidence for the inverse association of healthy dietary patterns with the risk of type 2 diabetes (RR, 0.81 [95% CI, 0.76–0.86]) and for a positive association between unhealthy dietary patterns and the risk of type 2 diabetes (RR, 1.44 [95% CI, 1.33–1.56]) and MetS (RR, 1.29 [95% CI, 1.09–1.52]).⁵⁵

Fats and Carbohydrates

- In a randomized trial of 609 participants without diabetes with a BMI of 28 to 40 kg/m² that compared the effects of healthy low-fat and healthy low-carbohydrate weight loss diets, weight loss at 12 months did not differ between groups.²¹ A meta-analysis of 12 randomized studies confirmed the benefit of consuming low-carbohydrate healthy diets for multiple CVD risk factors, although the effects appear modest in general and the sustainability is uncertain.⁵⁶ For body weight, the change was –1.58 kg (95% CI, –1.58 to –0.75); for <6 months of intervention, this change was –1.14 kg

diabetes with a BMI of 28 to 40 kg/m² that compared the effects of healthy low-fat and healthy low-carbohydrate weight loss diets, weight loss at 12 months did not differ between groups.²¹ A meta-analysis of 12 randomized studies confirmed the benefit of consuming low-carbohydrate healthy diets for multiple CVD risk factors, although the effects appear modest in general and the sustainability is uncertain.⁵⁶ For body weight, the change was –1.58 kg (95% CI, –1.58 to –0.75); for <6 months of intervention, this change was –1.14 kg

(95% CI, -1.65 to -0.63); and for 6 to 11 months of intervention, the change was -1.73 kg (95% CI, -2.7 to -0.76). For triglycerides, the change was -0.15 mmol/L (95% CI, -0.23 to -0.07). However, interventions that lasted <6 months were associated with a decrease of -0.23 mmol/L (95% CI, -0.32 to -0.15), whereas those low-carbohydrate interventions that lasted 12 to 23 months were associated with a decrease of -0.17 mmol/L (95% CI, -0.26 to -0.08); in plasma LDL-C of 0.11 mmol/L (95% CI, 0.02–0.19); SBP changed -1.41 mm Hg (95% CI, -2.26 to -0.56); and DBP changed -1.71 mm Hg (95% CI, -2.36 to -1.06). The change in plasma HDL-C levels was 0.1 mm Hg (95% CI, 0.08–0.12); and the change in serum TC was 0.13 mmol/L (95% CI, 0.08–0.19). There was a nonsignificant change in fasting blood glucose level of 0.03 mmol/L (95% CI, -0.05 to 0.12).

- A study of NHANES 1999 to 2010 data from 24 144 participants comparing those in the fourth and first quartiles of consumption of dietary fats

0.98 [95% CI, 0.88–1.09]), stroke (RR, 1.02 [95% CI, 0.90–1.15]), or total CVD (RR, 0.98 [95% CI, 0.92–1.05]) over a mean follow-up of 8.1 years.⁶⁰ In a matched case-control study of 2428 postmeno-pausal females nested in the WHI Observational Study, higher plasma phospholipid long-chain SFAs (OR, 1.18 [95% CI, 1.09–1.28]) and lower PUFA n-3 (OR, 0.93 [95% CI,

by type found an inverse association between total fat (HR, 0.90 [95% CI, 0.82–0.99]) and PUFAs (0.81 [95% CI, 0.78–0.84]) but an increased association between SFAs (1.08 [95% CI, 1.04–1.11]) and all-cause mortality. In the same study, a meta-analysis of 29 prospective cohorts (N=1 164 029) was also conducted and corroborated the findings for the inverse association between total fat and PUFAs and all-cause mortality. In addition, the meta-analysis showed an inverse association between monounsaturated fatty acid intake (HR, 0.94 [95% CI, 0.89–0.99]) and all-cause mortality and between

amount of PUFA n-3 was associated with 10% lower CHD risk (OR, 0.90 [95% CI, 0.84–0.96]).⁶¹ In a study using NHANES 2007 to 2014 data (N=18 434 participants), ORs for newly diagnosed hypertension comparing dietary intakes from the highest and lowest tertiles were 0.60 (95% CI, 0.50–0.73) for n-3 fatty acids, 0.52 (95% CI, 0.43–0.62) for dietary n-6 fatty acids, and 0.95 (95% CI, 0.79–1.14) for n-6/n-3 ratio.⁶²

- In a prospective study of 3042 CVD-free adults followed up for a mean of 8.4 years, the consumption of olive oil exclusively (no other fats/oils) was inversely associated with the risk of developing CVD (RR, 0.07 [95% CI, 0.01–0.66]) compared with no olive oil consumption.⁶³

- In a meta-analysis of 40 prospective cohort studies in the United States, Asia, and Europe, total dietary fiber (HR, 0.92 [95% CI, 0.88–0.96]) and cereal fiber (HR, 0.83 [95% CI, 0.77–0.90]) were shown to be associated with decreased risk of developing type 2 diabetes among adults with overweight or obesity in US-based studies.⁶⁴ The same meta-analysis also reported increased risk of type 2 diabetes with higher glycemic index or glycemic load in monounsaturated fatty acid (0.80 [95% CI, 0.67–0.96]) and PUFA (0.84 [95% CI, 0.80–0.90]) intake and stroke mortality. A positive association between SFA (HR, 1.10 [95% CI, 1.01–1.21]) intake and CHD mortality was observed.⁵⁷ However, another meta-analysis reported a protective association between dietary SFA intake and risk for stroke (RR, 0.87 [95% CI, 0.78–0.96]), and there was a linear relationship in that every 10-g/d increase in SFA intake was associated with a 6% lower RR of stroke (RR, 0.94 [95% CI, 0.89–0.98]).⁵⁸

A recent review underscores the controversy surrounding SFA intake as a risk or protective factor for CVD and total mortality and recommends against arbitrary population-wide upper limits on SFA intake without regard to the types of SFA, the food sources, the overall micronutrient distributions, and the health outcomes of interest.⁵⁹

US and Asian studies.

A recent review underscores the controversy surrounding SFA intake as a risk or protective factor for CVD and total mortality and recommends against arbitrary population-wide upper limits on SFA intake without regard to the types of SFA, the food sources, the overall micronutrient distributions, and the health outcomes of interest.⁵⁹

- In the WHI RCT (N=48 835), a reduction of total fat consumption from 37.8% energy (baseline) to 24.3% energy (at 1 year) and 28.8% energy (at 6 years) had no effect on the incidence of CHD (RR,

- Gut microbiota is associated with the risk of obesity, type 2 diabetes, and many other cardiometabolic diseases. In a 6-month randomized controlled feed-ing trial of 217 healthy young adults with BMI <28 kg/m², the high-fat diet (fat, 40% energy) had over-all unfavorable effects on gut microbiota: increased *Alistipes* (*P*=0.04) and *Bacteroides* (*P*<0.001) and decreased *Faecalibacterium* (*P*=0.04). The low-fat diet (fat, 20% energy) appeared to have beneficial effects on gut microbiota: increased α-diversity assessed by the Shannon index (*P*=0.03) and increased abundance of *Blautia* (*P*=0.007) and *Faecalibacterium* (*P*=0.04).⁶⁵

Foods and Beverages

- In a systematic review and dose-response meta-analysis of 123 prospective studies, the risk of CHD, stroke, and HF was inversely associated with consumption of whole grain (RR_{CHD}, 0.95 [95% CI, 0.92–0.98]; RR_{HF}, 0.96 [95% CI, 0.95–0.97]), vegetables and fruits (RR_{CHD}, 0.97 [95% CI, 0.96–0.99])

- and 0.94 [95% CI, 0.90–0.97]; RR_{stroke} , 0.92 [95% CI, (RR_{CHD}, 0.67 [95% CI, 0.43–1.05]), and fish (RR_{CHD}, 0.88 [95% CI, 0.79–0.99]; RR_{stroke} , 0.86 associated with consumption of egg (RR_{HF}, 1.16 [95% CI, 1.03–1.31]), red meat (RR_{CHD}, 1.15 [95% CI, 1.08–1.23]; RR_{stroke} , 1.12 [95% CI, 1.06–1.17]; RR_{HF}, 1.08 [95% CI, 1.02–1.14]), processed meat (RR_{CHD}, 1.27 [95% CI, 1.09–1.49]:
- In a dose-response meta-analysis of prospective cohort studies in adults, each 250-mL/d increase in SSB and ASB intake was associated with an increased risk of obesity (RR, 1.12 [95% CI, 1.05–1.19] for SSB; 1.21 [95% CI, 1.09–1.35] for ASB), type 2 diabetes (1.19 [95% CI, 1.13–1.25] for Higher intake of processed CI, 1.02–1.05]) and 1.03 [95% CI, 1.01–1.05]), but was significantly associated of all-cause mortality.
 - In a network meta-analysis of tachios, hazelnuts, cashews, lipid profiles, the pistachio-with other nut-enriched diets LDL-C, and TC.⁷³
 - An umbrella review of 41 unique health outcomes sumption was more beneficial example, in dose-response of 200 mL ($\approx$ 1 cup) milk intake SSB; 1.15 [95% CI, 1.05–1.26] for ASB), hypertension (1.10 [95% CI, 1.06–1.14] for SSB; 1.08 [95% CI, 1.06–1.10] for ASB), and total mortality (1.04 [95% CI, 1.01–1.07] for SSB; 1.06, [95% CI, 1.02–1.10]

ated with a lower risk of common cardiometabolic diseases such as CVD, stroke, hypertension, type 2 diabetes, MetS, and obesity.⁷⁴ A meta-analysis of 10 cohort studies also showed that fermented dairy foods intake was associated with reduced CVD risk (OR, 0.83 [95% CI, 0.76–0.91]), in particular cheese (OR, 0.87 [95% CI, 0.80–0.94]) and yogurt (OR, 0.78 [95% CI, 0.67–0.89]).⁷⁵

- In a crossover RCT (N=25 individuals with normo-cholesterolemia and 27 with moderate hypercholesterolemia), 8-week consumption of moderate fiber (10 g/day) reduced LDL-C (SMD, -0.33 [95% CI, -0.61 to -0.04]) and CRP (SMD, -0.22 [95% CI, -0.44 to -0.00]).⁶⁹ In another meta-analysis of 8 cohort or case-control studies, whole grain or cereal fiber intake was inversely associated with type 2 diabetes (RR, 0.68 [95% CI, 0.64–0.73]).⁷⁰
- A meta-analysis reported a beneficial association of higher fish intake with CHD incidence (RR, 0.91 [95% CI, 0.84–0.97]) and mortality (0.85 [95% CI, 0.76–0.94]).⁷¹
- A network meta-analysis of isocaloric substitution interventions in 38 RCTs involving 1383 participants suggested beneficial effects of replacing sucrose and fructose with starch for LDL-C and replacing fructose with glucose for insulin resistance and uric acid; however, the evidence was judged to be of low to moderate certainty and warrants replication.⁶⁸
- In a meta-analysis of 22 RCTs, whole grain oats improved TC (SMD, 0.54 [95% CI, -0.95 to -0.12]) and LDL-C (SMD, 0.57 [95% CI, -0.84 to -0.31]), whole grain rice improved triglycerides (SMD, 0.22 [95% CI, -0.44 to -0.01]), and whole grains of all types improved HbA1c (SMD, 0.18 [95% CI, 0.01 to 0.35]).⁷²

amounts of a soluble green/roasted (35:65) coffee blend significantly reduced TC, LDL-C, very-low-density lipoprotein cholesterol, triglycerides, SBP, DBP, heart rate, and body weight among participants with moderate hypercholesterolemia. The beneficial influence on SBP, DBP, heart rate, and body weight was also observed in healthy participants.⁷⁶

- In a cross-sectional study of 12 285 adults, for males, consumption of >30 g/d alcohol was significantly associated with a higher risk of MetS (OR, 1.73 [95% CI, 1.25–2.39]), HBP (OR, 2.76 [95% CI, 1.64–4.65]), elevated blood glucose (OR, 1.70 [95% CI, 1.24–2.32]), and abdominal obesity (OR, 1.77 [95% CI, 1.07–2.92]) compared with nondrinking.⁷⁷ In males, drinkers at all levels had a lower risk of coronary disease than nondrinkers, whereas alcohol consumption was not associated with the risk of hypertension or stroke.⁷⁸ In females, consumption of 10.1 to 15.0 g/d alcohol was associated only with a higher risk of elevated blood glucose (OR, 1.65 [95% CI, 1.14–2.38]) compared with nondrinking.⁷⁷

0.77–0.94]).⁷¹
to

Compared with nondrinkers, consumption of 0.1

- An analysis of data from 6 prospective cohort studies in the United States in which baseline data were collected from 1985 to 2002 showed that higher intake of processed meat (aHR, 1.07 [95% CI, 1.04–1.11]), unprocessed red meat

(aHR, 1.03 [95% CI, 1.01–1.06]), and poultry (aHR, 1.04 [95% CI, 1.01–1.06]), but not fish, was significantly associated with an increased risk of incident CVD.⁷²

10.0 g/d alcohol was associated with a lower risk of coronary disease and stroke, and consumption of 0.1 to 15.0 g/d was associated with a lower risk of hypertension in females.⁷⁸

Sodium, Potassium, Phosphorus, and Magnesium • In a meta-regression analysis of 133 RCTs, a 100–
mmol/d (2300–mg/d) reduction in sodium was

associated with a 7.7-mm Hg (95% –5.0) lower SBP and a 3.0-mm Hg to –1.4) lower DBP among people mm Hg SBP/DBP. The association people with SBP/DBP $\leq 131/78$ mm mmol/d reduction in sodium was 1.46-mm Hg (95% CI, –2.7 to –0.20) lower SBP and a 0.07-mm Hg (95% CI, –1.5 to 1.4) lower DBP.⁷⁹ The effects of sodium reduction on BP appear to be stronger in individuals who are older, are Black, and have hypertension.⁸⁰

- In a systematic review and nonlinear dose-response meta-analysis of 14 prospective cohort studies

and 1 case-control study, a 1-g/d increment in sodium intake was associated with a 6% increase in stroke risk (RR, 1.06 [95% CI, 1.02–1.10]), and a 1-unit increment in dietary sodium-to-potassium ratio (millimoles per millimole) was associated with a 22% increase in stroke risk (RR, 1.22 [95% CI, 1.04–1.41]).⁸¹

- In a meta-analysis of 133 RCTs with 12 197 participants, interventions with reduced sodium versus usual sodium resulted in a mean reduction of 130 mmol (95% CI, 115–145) in 24-hour urinary sodium, 4.26 mm Hg (95% CI, 3.62–4.89) in SBP, and 2.07 mm Hg (95% CI, 1.67–2.48) in DBP.⁸² The results also showed a dose-response relationship between each 50-mmol reduction in 24-hour sodium excretion and a 1.10-mm Hg (95% CI, 0.66–1.54) reduction in SBP and a 0.33-mm Hg (95% CI, 0.04–0.63 mm Hg) reduction in DBP.

BP-lowering effects of sodium reductions were stronger in older people, populations who are not

White, and those with higher baseline SBP levels. • A meta-analysis of 20 studies including a total of

616 905 adults showed that individuals with high sodium intake had a higher adjusted risk of CVD compared with individuals with low sodium intake (rate ratio, 1.19 [95% CI, 1.08–1.30]).⁸³ For every 1-g increase in dietary sodium intake, the risk of CVD increased 6%.

0.83–0.94]) and a 12% decrease in ischemic stroke risk (RR, 0.88 [95% CI, 0.81–0.95]) compared with the lowest magnesium intake category. After further adjustment for calcium intake, the inverse association remained for total stroke (RR, 0.89 [95% CI, 0.80–0.99]).⁸⁵

Dietary Supplements

- A 2017 AHA science advisory summarized available evidence and suggested fish oil supplementation only for secondary prevention of CHD and SCD (Class IIa recommendation) and for secondary prevention of outcomes in patients with HF (Class IIa recommendation).⁸⁶

- A meta-analysis of 38 RCTs of omega-3 fatty acids, stratified by EPA monotherapy and EPA+DHA therapy, with 149 051 participants showed that omega-3 fatty acids reduced cardiovascular mortality and improved cardiovascular outcomes.⁸⁷ EPA

monotherapy was associated with more cardiovascular risk reduction than with EPA+DHA. Omega-3 fatty acids were associated with reducing cardiovascular mortality (RR, 0.93 [95% CI, 0.88–0.98]; $P=0.01$), nonfatal MI (RR, 0.87 [95% CI, 0.81–0.93]; $P=0.0001$), CHD events (RR, 0.91 [95% CI, 0.87–0.96]; $P=0.0002$), MACEs (RR, 0.95 [95% CI, 0.92–0.98]; $P=0.002$), and revascularization (RR, 0.91 [95% CI, 0.87–0.95]; $P=0.0001$). There were also higher RR reductions with EPA monotherapy

(0.82 [95% CI, 0.68–0.99]) than with EPA+DHA (0.94 [95% CI, 0.89–0.99]) for cardiovascular mortality, nonfatal MI (EPA, 0.72 [95% CI, 0.62–0.84]; EPA+DHA, 0.92 [95% CI, 0.85–1.00]), CHD events

(EPA, 0.73 [95% CI, 0.62–0.85]; EPA+DHA, 0.94 [95% CI, 0.89–0.99]), and MACEs and revascularization. Incident AF was increased with omega-3 fatty acids (RR, 1.26 [95% CI, 1.08–1.48]). EPA

monotherapy was associated with a higher risk of total bleeding (RR, 1.49 [95% CI, 1.20–1.84]) and with AF (RR, 1.35 [95% CI, 1.10–1.66]).

- An observational study of 197 761 US veterans assessed omega-3 fatty acid supplement use and fish intake years on ischemic stroke over 3.2 years (2.2–4.3 years) and incident nonfatal CAD over 3.6 years (2.4–4.7 years). Omega-3 fatty acid supplement use was independently associated with a decreased risk of ischemic stroke (HR, 0.88 [95% CI, 0.81–0.95]) but not with nonfatal

- In an RCT of 25 871 adults age and females ≥ 55 years of daily supplementation of 2000 marine n-3 fatty acids on the and CVD were examined.⁹⁰ on major cardiovascular CI, 0.85–1.12). cancer (HR, 1.06). or any secondary acid supplementation had no diovascular events (HR, 0.92 invasive cancer (HR, 1.03 [95% CI, 0.93–1.13]), or any secondary outcomes.
- A secondary RCT data analysis study conducted across 3 years with 161 patients with advanced HF assessed the effects of daily vitamin D supplementation of 4000 IU on lipid parameters (TC, HDL-C, LDL-C, TC/HDL-C ratio, LDL-C/HDL-C ratio, and triglycerides) and vascular calcification parameters (fetuin-A and nonphosphorylated undercarboxylated matrix Gla protein). Long-term vitamin D supplementation did not improve lipid profiles and did not affect vascular calcification markers in these patients. In addition, no sex-specific vitamin D effects were found.⁹¹ A similar study, a post hoc analysis of the Effect of Vitamin D on Mortality in Heart Failure trial, assessing daily vitamin D₃ highest subgroup). Similarly, WHI RCT. another study and vitamin D tal calcium carbonate and 400 IU vitamin D₃/d) moderated therapy on CVD events Females reporting prior were randomized to the gen (0.625 mg/d) mg/d) trial. and those without supple- mentation of 4000 IU also found no improvement in cardiac function among patients with advanced HF. However, subgroup analyses among those ≥ 50 years of age indicated improvements of 2.73% in LVEF (95% CI, 0.14%–5.31%) at the 12-month follow-up and 2.60% (95% CI, –2.47% to 7.67%) improvement at the 36-month follow-up.⁹²
- The VITAL-HF, an ancillary study of the VITAL RCT, examined whether vitamin D₃ (2000 IU/d) or marine omega-3 fatty acids (n-3; 1 g/d, including EPA 460 mg+DHA 380 mg) were associated with

(n=10 739) were randomized to the conjugated equine estrogen trial (0.625 mg/d). In the conjugated equine estrogen trial, receiving calcium and vitamin D was associated with lowered stroke risk (HR, 0.49 [95% CI, 0.25–0.97]). In both trials, in females with a low intake of vitamin D, a significant synergist effect of calcium and vitamin D and hormone therapy on LDL-C was observed ($P=0.03$).⁹⁴ A meta-analysis of 14 RCTs with 1088 participants 4 to 19 years of age concluded that the evidence does not support vitamin D supplementation for improving cardiometabolic health in children and adolescents.⁹⁵ Another review article similarly reported that vitamin D supplementation had no beneficial effects on SBP and DBP in children and adolescents.⁹⁶

- An umbrella review of 10 systematic reviews and meta-analyses examined the relationship between vitamin C supplementation and CVD biomarkers (ie, cardiovascular arterial stiffness, BP, lipid profile, endothelial function, and glycemic control) and found weak evidence for salutary effects from vitamin C supplementation on CVD biomarkers.

However, subgroup analyses revealed that specific groups of participants (ie, those who were older or with higher BMI, elevated CVD risk, and lower intake of vitamin C) may benefit from vitamin C

first HF-related hospitalization or recurrent hospitalization for HF among 25 871 adults with HF between 2011 and 2017. No significant relationships were found between either vitamin D or n-3 fatty acid supplementation and first HF hospitalization. However, marine n-3 supplementation (326 events) significantly reduced recurrent HF hospitalization compared with placebo (379 events; HR, 0.86

supplementation).⁹⁷

[95% CI, 0.74–0.998]; $P=0.048$).⁹³

- A secondary analysis of the WHI examining the efficacy of calcium and vitamin D supplementation on AF prevention found that calcium and vitamin D had no reduction in incidence of AF compared

- A 2-sample mendelian randomization study including 7781 individuals of European descent examined the relationship between vitamin E and risk of CAD and found higher vitamin E to be associated with a higher risk of CAD and MI. Specifically, each 1-mg/L increase in vitamin E was significantly associated with CAD (OR, 1.05 [95% CI, 1.03–1.06]) and MI (OR, 1.04 [95% CI, 1.03–1.05]); elevated TC (SD, 0.043 [95% CI, 0.038–0.04]), LDL-C (SD, 0.021 [95% CI, 0.016–0.027]), and triglycerides (SD, 0.026 [95% CI, 0.021–0.031]); and lower levels of HDL-C (SD, –0.019 [95% CI, –0.024 to –0.014]).⁹⁸
- Although a relationship between baseline CVD risk factors and vitamin D deficiency was present, no significant association was found between baseline 25-hydroxyvitamin D serum levels and

Eating Patterns

incident AF (HR, 0.92 [95% CI, 0.66–1.28] in the lowest versus

- A meta-analysis of 7 RCTs with 425 participants for an average duration of 8.6 weeks found that, compared with breakfast consumption, breakfast

skipping led to modest weight loss (WMD, -0.54 kg [95% CI, -1.05 to -0.03 kg]) but a modest increase in LDL-C (WMD, 9.24 mg/dL [95% CI, 2.18 – 16.30 mg/dL]).⁹⁹ Another meta-analysis of 23 RCTs with 1397 participants reported that fasting and energy-restricting diets resulted in significant reductions in SBP (WMD, -1.88 mm Hg [95% CI, -2.50 to -1.25]) and DBP (WMD, -1.32 mm Hg [95% CI, -1.81 to -0.84]), and the SBP-lowering effects were [95% CI, -5.88 to -0.69]) than energy restriction (WMD, -1.09 mm Hg [95% CI, -1.70 to -0.47]).¹⁰⁰ Data from the French longitudinal study NutriNet-Santé (103 389 participants, 79% females, 42.6 years of age followed up for a median time of 7.2 years) reported 2036 incident cases of CVD.¹⁰¹ Each 1-hour delay in the time of the first meal of the day was associated with higher risk of CVD (HR, 1.06 [95% CI, 1.01 – 1.12]). Time of last meal was not associated with CVD risk (HR, 1.13 [95% CI, 0.99 – 1.29]). Each additional hour of nighttime fasting was associated with reduced risk of cerebrovascular disease (HR, 0.93 [95% CI, 0.87 – 0.99]) but not risk of CVD or CHD. Overall, findings were stronger in females than in males.

Historically, in the first quarter of each year, fresh veg-etables experience a seasonal peak in prices. The prices for fresh vegetables are predicted to increase 1.9% in 2024 (prediction interval, -3.0% to 7.0%). Data from Euromonitor International show that in 2023 consumers' most desired attribute in a food or beverage product globally is "low price" followed by "health properties." In 2021,

- Data from the NHANES 1999 to 2014, with 185 398 PY of follow-up, assessed associations between meal frequency, meal skipping, and meal intervals and CVD mortality.¹⁰² Compared with eating 3 meals per day, eating 1 meal per day was associated with higher all-cause (HR, 1.30 [95% CI, 1.03 – 1.64]) and CVD (HR, 1.83 [95% CI, 1.26 – 2.65]) mortality in fully adjusted models. Eating >3 meals per day was not significantly associated with all-cause and CVD mortality. Skipping breakfast compared with not skipping breakfast was associated with increased risk of CVD mortality (HR, 1.40 [95% CI, 1.09 – 1.78]). Skipping breakfast (HR, 1.11 [95% CI, 0.98 – 1.26]), lunch (HR, 1.12 [95% CI, 1.01 – 1.24]), and dinner (HR, 1.16 [95% CI, 1.02 – 1.32]) was associated with increased risk of all-cause mortality.

such as taste, branding, and sustainable positioning was lower in 2023 than in 2021.

Cost of a Healthy Diet

• A systematic review of studies published between 2000 and 2019 found moderate- to good-quality evidence supporting the use of pricing incentives to increase consumption or purchases of fruits and vegetables.¹⁰⁵ Providing incentives electronically on >1 occasion for ≥24 weeks and allowing redemption in stores are associated with successful programs.

Healthy Diet and Health Care Cost Savings

• A study evaluated the health care costs associated with following the healthy US-style eating pattern (measured by the HEI) and the healthy Mediterranean-style eating pattern (measured by the Mediterranean diet score) and found that a 20% increase in compliance with the HEI was estimated to result in annual cost savings in the United States of \$31.5 billion (range, \$23.9–\$38.9) billion.¹⁰⁶ Half of the cost savings were attributed to the reduction in costs associated with CVD, whereas the other half were attributed to cancer and type 2 diabetes cost reductions. Similarly, a 20% increase in conformance with the Mediterranean diet score resulted in annual cost savings of \$16.7 billion (range, \$6.7–\$25.4) billion.¹⁰⁶ The biggest contributors to these costs savings were HD (\$5.4 billion), type 2 diabetes (\$4.6 billion), AD (\$2.6 billion), stroke (\$1.0 billion), and, to a lesser degree, site-specific cancer (<\$1 billion).

• Based on combined data from NHANES 2013 to 2016 and a community-based randomized trial of cash and subsidized CSA intervention, a micro-

simulation model
was developed to

Cost

The US Department of Agriculture reported that the food-at-home prices will increase by 2.9% (prediction interval, 0.5%–5.3%) in 2024. This is a deceleration relative to the reported increase of 8.6% (prediction interval, 5.6%–11.8%) in 2023.¹⁰³ The retail price of eggs increased 1.8% in January 2024 after an

increase of 8.9% in December 2023, albeit 28.6% below prices seen in January 2023. The price for fresh vegetables increased by 2.9% in January 2024 but was almost 1% lower than prices seen in January 2023, at which time the prices remained elevated after a peak in December 2022.

measured by the HEI) on CVD and type 2 diabetes in US adults with low income.¹⁰⁸ Implementation of the model in the short term (10-year time horizon) and long term (life-course time horizon) demonstrated that both a cash transfer (\$300) and subsidized CSA (\$300/y subsidy) lowered total discounted DALYs accumulated over the life course attributable to CVD and diabetes complications from 24 797 per 10 000 people (95% CI, 24 584–25 001) at baseline to 23 463 per 10 000 (95% CI, 23 241–23 666) under the cash intervention and 22 304 per

10 000 (95% CI, 22 084–22 intervention. Both mental cost-effectiveness prevented DALY, with the effective in the short term and cost-effective in the long term. ingas to society of –\$191 100 (95% CI, –191 767 to –188 vention and –\$93 182 per –93 707 to –92 503) for the

evidence illustrating the SSB daily intake and CVD. This review also of an SSB tax because of its ing SSB consumption in In the United States, a model (CVD PREDICT) was effectiveness. CVD from imposing a penny-per- Cost savings were identified

Cost-Effectiveness of Sodium Reduction and SSB Tax

- A global cost-effectiveness analysis modeled the cost-effectiveness of a so-called soft regulation national policy to reduce sodium intake in countries around the world using the UK experience (government-supported industry agreements, gov- ernment monitoring of industry compliance,

public health campaign).¹⁰⁹ Model estimates were based on sodium intake, BP, and CVD data from 183 countries. Country-specific cost data were used to estimate the cost-effectiveness ratio, defined

ment (\$106.56 billion) and private sector (\$15.60 billion). A 100% price pass-through led to reductions of 4494 (2.06%) lifetime MI events (95% UI, 2640–6599) and 1540 (1.42%) total IHD deaths (95% UI, 995–2118) compared with no tax and to a gain of 0.020 lifetime QALYs. The lifetime cost to the beverage industry is \$0.92 billion (or \$49.72 billion if electing to absorb half of the proposed SSB tax).¹¹²

Global Trends in Key Dietary Factors

Several countries and US cities have implemented SSB

as purchasing power parity–adjusted international taxes.

dollars (equivalent to country-specific purchasing power of US \$1) per DALY saved over 10 years.

Globally, the estimated average cost-effectiveness ratio was \$204 (international dollars) per DALY (95% CI, 149–322) saved. The estimated cost-effectiveness ratio was highly

favorable in high-, middle-, and low-income countries.

- A US study examined the cost-effectiveness of implementing voluntary sodium target reformulation among people ever working in the food system

- In Mexico, a 1–peso/L excise tax was implemented in January 2014. In a study using store purchase data from 6645 Mexican households, posttax volume of beverages purchased decreased by 5.5% in 2014 and by 9.7% in 2015 compared with the predicted volume of beverages purchased based on pretax trends. Although all socioeconomic groups experienced declines in SSB purchases, the low-est socioeconomic group had the greatest decline in SSB purchases (9.0% in 2014 and 14.3% in 2015).^{.113}

and those in the processed food industry and found benefits in both. Achieving FDA reformulations across 10 years could lead to 20-year health gains in those who had ever worked in the food system of 180 000 QALYs (95% UI, 150 000–209 000) and health care–related savings of \$5.2 (95% UI, \$3.5– \$8.3) billion with an incremental cost-effectiveness ratio of \$62 000 (95% UI, 1000–171 000) per each QALY gained. Those working in the processed food industry could see similar improvements of 32 000 gained QALYs (95% UI, 27 000–37 000), health cost savings of \$1 (95% UI, \$0.7–\$1.6) billion, and an incremental cost-effectiveness ratio of \$486 000 (95% UI, \$148 000–\$1 094 000) for each QALY gained. The long-term reformulation would cost the industry \$16.6 (95% UI, \$12–\$31) billion. This highlights that potential health benefits and cost savings are greater than the costs associated with sodium reformulation.^{.110}

 - A policy review of worldwide consumption of SSBs found that SSB consumption has increased significantly, which is problematic given the mounting

- Data from 3 waves (2004–2018) of the Health Workers Cohort Study Mexico were used to examine the change in probability of belonging to 1 of 4 categories of soft drink consumption (non, low, medium, high) after the tax was implemented.¹¹⁴ After the tax, the prevalence of medium or high consumers decreased from 50% to 43%, and the prevalence of nonconsumers increased from 10% to 14%. The probability of being a nonconsumer of soft drinks increased by 4.7% (95% CI, 0.3%–9.1%) and that of being a low consumer increased by 8.3% (95% CI, 0.6%–16.0%) compared with the pretax period. The probability of being in the medium and high levels of soft drink consumption decreased by 6.8% (95% CI, 0.5%–13.2%) and 6.1% (95% CI, 0.4%–11.9%), respectively.
- In Berkeley, CA, a 1-cent/oz SSB excise tax was implemented in January 2015.¹¹⁵ According to store-level data, posttax year 1 SSB sales declined by 9.6% compared with SSB sales predicted from pretax trends. In comparison, SSB sales increased

by 6.9% in non-Berkeley stores in adjacent cities. Three years after the tax was implemented, these declines were sustained across demographically diverse Berkeley neighborhoods compared with sales in the neighboring locales of San Francisco and Oakland.¹¹⁶ Another global trend is the mean sodium intake among adults worldwide documented as 3950 mg/d in 2010.¹¹⁷ Across world regions, mean

Africa (2180 mg/d). Across countries, the lowest observed mean national intakes were $\approx$ 1500 mg/d.

Between 1990 and 2010, global mean sodium intake appeared to remain relatively stable, although data on trends in many world regions were suboptimal. Successful population-level sodium initiatives tend to use multiple strategies

Global Burden

(See Table 5-5 and Chart 5-1)

- Based on 204 countries and territories in 2021, among regions, age-standardized mortality rates attributable to dietary risks were highest for central Asia and lowest for high-income Asia Pacific (Chart 5-1).

There were 7.22 (95% UI, 1.96–

and include structural activities such as food product reformulation. For example, the United Kingdom initiated a nation-wide salt reduction program in 2003 to 2004 that included consumer awareness campaigns, progressively lower salt targets for various food categories, clear nutritional labeling, and working with industry

was 86.26 (95% UI, 23.35–128.98) per 100 000 (Table 5-5).

- A report from the GBD Study 2019 estimated the impact of 15 dietary risk factors on mortality and DALYs worldwide using a comparative risk assessment approach.¹¹⁹ An estimated 7.9 million deaths (95% UI, 6.5–9.8 million; 14% of all deaths) and 188 million DALYs (95% UI, 156–225 million; 7% of all DALYs) were attributable to dietary risks in 2019.

The leading dietary risk factors were high sodium intake (1.9 [95% UI, 0.5–4.2] million deaths), low whole grain intake (1.8 [95% UI, 0.9–2.3] million deaths), and low legume intake (1.1 [95% UI, 0.3–1.8] million deaths).

Mean sodium intake in the United Kingdom decreased by 15% from 2003 to 2011,¹¹⁸ along with concurrent decreases in BP (3.0/1.4 mm Hg) in patients not taking antihypertensive medication, stroke mortality (42%), and

CHD mortality (40%; $P < 0.001$ for all comparisons). These findings remained statistically significant after adjustment for changes in demographics, BMI,

– Countries with low-middle SDI and middle SDI scores had the highest age-standardized rates of diet-related deaths (119 [95% UI, 96–147] and 116 [95% UI, 92–147] deaths per 100 000 population), whereas countries with high SDI scores had the lowest age-standardized rates of diet-related deaths (56 [95% UI, 47–69] deaths per 100 000 population). and other dietary factors.

Table 5-1. Population-Level Measurement of Diet in the AHA's Life Essential 8 for CVH

Domain	CVH metric	Method of measurement	Quantification of CVH metric: adults (
Health behaviors	Diet	Measurement: Self-reported daily intake of a DASH-style eating pattern Example tools for measurement: DASH diet score ^{120,121} (populations); MEPA ¹²² (individuals)	Quantiles of DASH-style diet adherence or HEI-2015 (population) Scoring (population): <u>Points</u> <u>Quantile</u> 100 (top/ideal) 80 75th–94th percentile 50 50th–74th percentile 25 25th–49th percentile 0 1st–24th percentile (bottom/ least ideal quartile) Scoring (individual): <u>Points</u> <u>MEPA score</u> (points) 16 80 12–14

AHA indicates American Heart Association; CVH, cardiovascular health; DASH, Dietary Approaches to Stop Hypertension; HEI, Healthy Eating Index; and MEPA, Mediterranean Eating Pattern for Americans.

*Cannot meet these metrics until solid foods are being consumed.

Notes on implementation:

Diet: See . For adults and children, a score of 100 points for the CVH diet metric should be assigned for the top (95th percentile) or a score of 15 to 16 on the MEPA (for individuals) or for those in the ≥95th percentile on the DASH score or HEI-2015 (for populations). The 75th to 94th percentile should be assigned 80 points, given that there is likely improvement that can be made even among those in this top quartile. For individuals, the MEPA points are stratified for the 100-point scoring system approximately by quantiles. In children, a modified MEPA is suggested on the basis of age-appropriate foods. The writing group recognizes that the quantiles may need to be adjusted or recalibrated at intervals with population shifts in eating patterns. In children, the scoring applies only once solid foods are being consumed. For now, the reference population for quantiles of HEI or DASH score should be the National Health and Nutrition Examination Survey sample from 2015 to 2018. The writing group acknowledges that this may need to change or be updated over time. Clinicians should use judgment in assign-ing points for culturally contextual healthy diets. For additional notes on scoring in children, see .

Source: Adapted from Lloyd-Jones et al.¹ Supplemental Material. Copyright © 2022, American Heart Association, Inc.

Table 5-2. Scoring Criteria for the DASH-Style Diet Score

Component	Foods (NHANES 24-h recall)	Scoring criteria	Note
Fruits	All fruits and fruit juices	Quintile 1: 1 point Quintile 2: 2 points Quintile 3: 3 points Quintile 4: 4 points Quintile 5: 5 points	Higher score represents more ideal intake Quintile 1 is lowest consumption; quintile 5 is highest consumption
Vegetables	All vegetables except potatoes and		
Nuts and legumes	Nuts and peanut butter, dried		
Whole grains	Brown rice, dark breads, cooked cereal, whole grain -		
Low-fat dairy	Skim milk, yogurt, cottage cheese	Quintile 1: 5 points Quintile 2: 4 points Quintile 3: 3 points Quintile 4: 2 points Quintile 5: 1 point	Reverse scoring in that higher quintiles represent less ideal intake Quintile 1 is lowest consumption; quintile 5 is highest consumption
Sodium	Sum of sodium content of all foods		
Red and processed meats	Beef, pork, lamb, deli meats, organ meats, hot dogs,		
Sweetened beverages	Carbonated and noncarbonated		

The DASH diet score is assessed and points scored using the methods of Fung et al.¹²³ Quintiles of point score should be assigned using the most recent or most relevant NHANES data, appropriate to the question being addressed.

DASH indicates Dietary Approaches to Stop Hypertension; and NHANES, National Health and Nutrition Examination Survey.

Source: Reproduced with permission from Fung et al.¹²³ Copyright © 2008, American Medical Association. All rights reserved, including those for text and data mining, artificial intelligence training, and similar technologies.

Table 5-3. Scoring Criteria for the Mediterranean Eating Pattern for Americans*

Screener item	Question	Scoring criteria	Score
Olive oil	How much olive oil do you consume per day (including that used in frying, meals)	≥2 servings of olive oil per day	1: If scoring condition met 0: If scoring condition not met (range, 0–16)
Green leafy vegetables	How many servings of green leafy vegetables do you consume	≥7 servings of green leafy vegetables per week	
Other vegetables	How many servings of other vegetables do you consume	≥2 servings of other vegetables per day	
Berries	How many servings of berries do you consume per week?	≥2 servings of berries per week	
Other fruit	How many servings of other fruit do you consume per week?	≥1 servings of other fruit per day	
Meat	How many servings of red meat, hamburger, bacon, or sausage do	≤3 servings of red meat, hamburger, bacon, or sausage per	
Fish	How many servings of fish or shellfish/seafood do you	≥1 serving of fish per week	
Chicken	How many servings of chicken do you consume per week?	≤5 servings of chicken per week	
Cheese	How many servings of full-fat or regular cheese or cream cheese	≤4 servings of full-fat or regular cheese or cream cheese per	
Butter/cream	How many servings of butter or cream do you consume	≤5 servings of butter or cream per week	
Beans	How many servings of beans do you consume per week?	≥3 servings of beans per week	
Whole grains	How many servings of whole grains do you consume per day?	≥3 servings of whole grains per day	
Sweets and pastries	How many servings of commercial sweets, candy bars, pastries, cookies, or cakes do	≤4 servings of commercial sweets, candy bars, pastries, cookies, or cakes per week	
Nuts	How many servings of nuts do you consume per week?	≥4 servings of nuts per week	
Fast food	How many times per week do you consume meals from fast-	≤1 meal at a fast-food restaurant per week	
Alcohol	How much alcohol do you drink per week?	>0 or ≤2 servings of alcohol per day for men and >0 or ≤1 servings of	

*The Mediterranean Eating Pattern for Americans screener is successful at capturing several components of the Mediterranean style pattern.¹²² Source: Reprinted from Lloyd-Jones et al¹ Supplemental Material. Copyright © 2022, American Heart Association, Inc.

Table 5-4. Population Mean Consumption* of Food Groups and Nutrients of Interest, by Sex and Race and Ethnicity Among US Adults ≥20 Years of Age, NHANES 2017 to 2018

	NH White males		NH Black males		Mexican American males		NH White females		NH Black females		Mexican American females	
	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines
Foods												
Whole grains,	0.9±0.8	7.1	0.7±1.1	3.1	0.6±0.9	2.5	0.8±0.6	3.4	0.7±1.1	3.6	0.7±0.9	2.5
Whole fruit,	1.3±1.2	8.8	1.1±2.4	5.9	1.7±2.2	7.1	1.3±1.0	7.6	1.1±1.9	6.2	1.7±1.9	13.2
Total fruit,	1.7±1.4	13.5	1.7±2.9	11.9	2.2±2.4	12.1	1.5±1.2	10.0	1.8±2.5	13.7	2.2±2.3	19.3

Nonstarchy vegeta-bles,	2.0±1.1	5.8	1.5±1.8	2.1	2.1±1.7	5.6	2.3±1.2	9.3	1.9±2.3	8.4	2.3±1.8	9.5
Starchy vegetables,	0.9±0.7	NA	0.9±1.2	NA	0.7±0.9	NA	0.9±0.7	NA	0.9±1.2	NA	0.7±0.9	NA
Legumes, servings/	1.2±1.8	21.4	1.2±3.9	18.2	3.4±6.1	40.6	1.2±1.6	21.9	0.99±3.3	17.0	2.8±5.1	42.1

(Continued)

Table 5-4. Continued

	NH White males		NH Black males		Mexican American males		NH White females
	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption	% Meeting guidelines	Average consumption
Fish and shellfish,	1.0±1.8	15.0	1.5±4.2	21.6	1.5±3.8	19.3	1.1±1.5
Nuts and seeds,	5.8±6.7	36.0	4.0±11.1	21.9	3.6±8.2	22.5	6.1±6.0
Unprocessed	3.6±2.5	NA	2.9±4.1	NA	4.2±4.3	NA	2.6±1.9
Processed	2.4±1.8	58.8	2.0±3.2	66.6	2.1±2.8	68.0	1.7±1.4
SSBs,	7.3±7.3	55.6	9.8±12.4	38.6	9.9±10.7	37.9	6.4±6.7
Sweets and bakery desserts,	4.2±4.0	51.9	3.3±6.4	65.2	4.5±6.8	58.6	3.8±3.2
Refined	5.1±1.5	7.9	5.1±2.8	7.1	6.6±2.9	1.3	5.1±1.6
Nutrients							
Total calories	2415±541	NA	2284±1220	NA	2450±967	NA	1797±398
EPA/DHA, mg/d	0.079±0.107	6.5	0.09±0.213	9.0	0.082±0.140	10.0	0.083±0.114
α-Linoleic acid, g/d	1.75±0.64	47.8	1.71±0.97	48.7	1.66±0.72	41.7	1.84±0.62
n-6 PUFAs, %	8.0±2.99	NA	9.88±10.2	NA	7.74±5.75	NA	11.5±5.04
Saturated fat, %	12.4±2.2	24.3	11.3±4.0	32.0	11.1±3.3	34.6	12.3±2.1
Ratio of (PUFAs + MUFA)	1.8±0.5	11.2	2.3±2.6	29.4	1.9±1.2	12.9	2.2±0.6
Dietary cholesterol,	299±137	61.7	320±275	55.6	315±195	55.1	304±130
Carbohydrate	44.4±6.1	NA	46.0±12.8	NA	46.7±9.2	NA	46.3±6.2
Dietary fiber, g/d	15.1±4.4	4.1	13.7±8.3	3.8	18.5±8.9	14.6	16.7±4.3
Sodium, g/d	3.4±1.3	6.5	3.4±3.98	11.3	3.4±0.94	6.9	3.4±0.65
Added sugar, %	11.8±25.0	37.9	17.8±43.2	23.5	13.0±21.3	38.3	17.8±9.6

Values for average consumption are mean±SD. Data are from NHANES 2017 to 2018, derived from two 24-hour dietary recalls per person, with population SD adjusted for within-person vs between-person variation. All values are energy adjusted by individual regressions or percent energy, and for comparability, means and proportions are reported for a 2000-kcal/d diet. To obtain actual mean consumption levels, the group means for each food or nutrient can be multiplied by the group-specific total calories (kilocalories per day) divided by 2000 kcal/d. The calculations for foods use the US Department of Agriculture Food Patterns Equivalent Database on composition of various mixed dishes, which incorporates partial amounts of various foods (eg, vegetables, nuts, processed meats) in mixed dishes; in addition, the characterization of whole grains is now derived from the US Department of Agriculture database instead of the ratio of total carbohydrate to fiber.

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; NA, not available; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; and SSB, sugar-sweetened beverage.

*All intakes and guidelines adjusted to a 2000-kcal/d diet. Servings are defined as follows: whole grains, 1-oz equivalents; fruits and vegetables, 1/2-cup equivalents; legumes, 1/2 cup; fish/shellfish, 3.5 oz or 100 g; nuts and seeds, 1 oz; unprocessed red or processed meat, 3.5 oz or 100 g; SSBs, 8 fl oz; and sweets and bakery desserts, 50 g. Guidelines are defined as follows: whole grains, 3 or more 1-oz equivalent (eg, 21 g whole wheat bread, 82 g cooked brown rice, 31 g Cheerios) servings/d; fruits, ≥2 cups/d; nonstarchy vegetables, ≥2.5 cups/d; legumes, ≥1.5 cups/wk; fish or shellfish, 2 or more 100-g (3.5-oz) servings/wk; nuts and seeds, 4 or more 1-oz servings/wk; processed meats (bacon, hot dogs, sausage, processed deli meats), 2 or fewer 100-g (3.5-oz) servings/wk (one-fourth of discretionary calories); SSBs (defined as ≥50 cal/8 oz, excluding 100% fruit juices), ≤36 oz/wk (approximately one-fourth of discretionary calories); sweets and bakery desserts, 2.5 or fewer 50-g servings/wk (approximately one-fourth of discretionary calories); EPA/DHA, ≥0.250 g/d¹²⁴; α-linoleic acid, ≥1.6/1.1 g/d (males/females); saturated fat, <10% energy; dietary cholesterol, <300 mg/d; dietary fiber, ≥28 g/d; sodium, <2.3 g/d; ratio of (PUFAs+MUFA)/SFAs, ≥2.5; and added sugars, ≤6.5% total energy intake. No dietary targets are listed for starchy vegetables and unprocessed red meats because of their positive association with long-term weight gain and their positive or uncertain relation with diabetes and cardiovascular disease.

†Including white potatoes (chips, fries, mashed, baked, roasted, mixed dishes), corn, plantains, green peas. Sweet potatoes, pumpkin, and squash are considered red-orange vegetables by the US Department of Agriculture and are included in nonstarchy vegetables.

Source: Unpublished analyses courtesy of Dr Junxiu Liu, Icahn School of Medicine at Mount Sinai, using NHANES.¹²⁵

Table 5-5. Deaths Caused by Dietary Risks Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	7.22 (1.96 to 10.77)	3.98 (1.05 to 5.84)	3.24 (0.90 to 4.92)
Percent change (%) in total number,	50.76 (39.27 to 61.68)	57.07 (41.67 to 70.99)	43.66 (31.08 to 55.33)
Percent change (%) in total number,	18.78 (12.36 to 24.66)	18.90 (10.41 to 28.14)	18.63 (11.53 to 26.43)
Rate per 100,000, age	86.26 (23.35 to 128.98)	106.00 (28.65 to 156.32)	69.49 (19.44 to 105.66)
Percent change (%) in rate, age	−35.68 (−39.86 to −31.47)	−33.03 (−38.80 to −27.03)	−38.89 (−43.40 to −33.88)
Percent change (%) in rate, age	−13.85 (−18.15 to −9.63)	−13.51 (−19.27 to −6.98)	−14.25 (−19.24 to −8.76)
PAF (%), all ages, 2021	10.63 (2.90 to 15.94)	10.57 (2.83 to 15.68)	10.71 (3.01 to 16.34)
Percent change (%) in PAF, all	2.39 (−5.39 to 7.73)	3.43 (−5.49 to 10.18)	1.26 (−5.80 to 7.02)
Percent change (%) in PAF, all	−7.16 (−10.23 to −4.12)	−8.39 (−12.22 to −4.70)	−5.64 (−9.00 to −1.67)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and PAF, population attributable fraction.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹²⁶

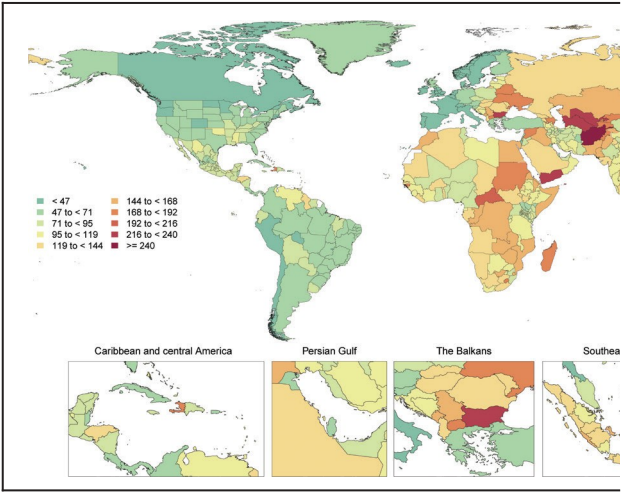


Chart 5-1. Age-standardized global mortality rates attributable to dietary risks per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study

REFERENCES

1. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhanc-ing the American Heart Association's construct of

cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/cir.0000000000001078

2. Anderson CAM, Thorndike AN, Lichtenstein AH, Van Horn L, Kris-Etherton PM, Foraker R, Spees C. Innovation to create a healthy and sustainable food system: a science advisory from the American Heart Association. *Circulation*.

5. Woodruff RC, Zhao L, Ahuja JKC, Gillespie C, Goldman J, Harris DM, Jackson SL, Moshfegh A, Rhodes D, Sebastian RS, et al. Top food category contributors to sodium and potassium intake—United States, 2015–2016. *MMWR Morb Mortal Wkly Rep.* 2020;69:1064–1069. doi: 10.15585/mmwr.mm6932a3
6. Clarke LS, Overwyk K, Bates M, Park S, Gillespie C, Cogswell ME. Temporal trends in dietary sodium intake among adults aged ≥ 19 years—United States, 2003–2016. *MMWR Morb Mortal Wkly Rep.* 2021;70:1478–1482. doi: 10.15585/mmwr.mm7042a4
7. Liu J, Rehm CD, Onopa J, Mozaffarian D. Trends in diet quality among youth in the United States, 1999–2016. *JAMA.* 2020;323:1161–1174. doi: 10.1001/jama.2020.0878
3. Lloyd-Jones DM, Ning H, Labarthe D, Brewer LP, Sharma G, Rosamond W, Foraker RE, Black T, Grandner MA, Allen NB, et al. Status of cardiovascular health in US adults and children using the American Heart Association's new "Life's Essential 8" metrics: prevalence estimates from the National Health and Nutrition Examination Survey (NHANES), 2013–2018. *Circulation.* 2022;146:822–835. doi: 10.1161/CIRCULATIONAHA.122.060911
4. US Department of Agriculture and US Department of Health and Human Services. Dietary Guidelines for Americans, 2020–2025. 9th ed. 2015. Accessed May 6, 2024.

8. Shan Z, Rehm CD, Rogers G, Ruan M, Wang DD, Hu FB, Mozaffarian D, Zhang FF, Bhupathiraju SN. Trends in dietary carbohydrate, protein, and fat intake and diet quality among US adults, 1999-2016. *JAMA*. 2019;322:1178–1187. doi: 10.1001/jama.2019.13771
9. Liu J, Micha R, Li Y, Mozaffarian D. Trends in food sources and diet quality among US children and adults, 2003-2018. *JAMA Netw Open*. 2021;4:e215262. doi: 10.1001/jamanetworkopen.2021.5262
10. Cowan AE, Tooze JA, Gahche JJ, Eicher-Miller HA, Guenther PM, Dwyer JT, Potischman N, Bhadra A, Carroll RJ, Bailey RL. Trends in overall and micronutrient-containing dietary supplement use in US adults and

- children, NHANES 2007-2018. *J Nutr.* 10.1093/in/nxac168
11. Anderson CE, Martinez CE, Ritchie LD, SE. Longer special Supplemental Nutrition Children (WIC) participation duration is age 5 years. *J Nutr.* 2022;152:1974–1982. doi: 10.1093/in/nxac168
 12. Buszkiewicz JH, Bobb JF, Hurvitz PM, A, Moonev SJ, Cruz M, Gupta S, Lozano P. ment have independent obesogenic power? tories of weight gain. *Int J Obes (Lond).* 10.1038/s41366-021-00836-z
 13. Vinvard M, Zimmer M, Herrick KA, Storv M. ing Index-2015 scores vary by types of food *Nutrients.* 2021;13:2717. doi: 10.3390/nu13082717
 14. May-Wilson S, Matoba N, Wade KH, Hottenga J-J, Concas MP, Mangino M, Grzeszkowiak EJ, Menni C, Gasparini P, Timpson NJ, et al. Large-scale GWAS of food liking reveals genetic determinants and genetic correlations with distinct neurophysiological traits. *Nat* overweight and obese adults. *Clin Nutr.* 10.1016/j.clnu.2018.04.002
 28. Garcia-Arellano A, Martínez-González Hébert JR, Corella D, Shivanna N, et al. Dietary inflammatory index and the SUN and PREDIMED studies. *Clin* 10.1016/j.clnu.2018.05.003
 29. Collin LJ, Judd S, Safford M, Vaccarino beverage consumption with mortality of data from the REGARDS study. 10.1001/jamanetworkopen.2019.3121
 30. Ramne S, Alves Dias J, González-G, Ericson H, Johansson I, Sonestedt *Commun.* 2022;13:2743. doi: 10.1038/s41467-022-30187-w
 15. Ferguson JF, Allayee H, Gerszten RE, Ideraabdullah F, Kris-Etherton PM,

- intake and mortality is nonlinear and dependent on sugar source in 2 Swedish population-based prospective cohorts. *Am J Clin Nutr*. 2019;109:411–423. doi: 10.1093/ajcn/nqy268
31. Shahdadian F, Saneei P, Milajerdi A, Esmailzadeh A. Dietary glycemic index, glycemic load, and risk of mortality from all causes and cardiovascular diseases: a systematic review and dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr*. 2019;110:921–937. doi: 10.1093/ajcn/nqz061
- Ordovás JM, Rimm EB, Wang TJ, Bennett BJ; on behalf of the American Heart Association Council on Functional Genomics and Translational Biology, Council on Epidemiology and Prevention, and Stroke Council. Nutrigenomics, the microbiome, and gene-environment interactions: new directions in cardiovascular disease research, prevention, and treatment: a scientific statement from the American Heart Association. *Circ Cardiovasc Genet*. 2016;9:291–313. doi: 10.1161/hcg.0000000000000030
16. Merino J, Dashti HS, Sarnowski C, Lane JM, Todorov PV, Udler MS, Song Y, Wang H, Kim J, Tucker C, et al. Genetic analysis of dietary intake identifies new loci and functional links with metabolic traits. *Nat Hum Behav*. 2022;6:155–163. doi: 10.1038/s41562-021-01182-w
17. Vasishta S, Ganesh K, Umakanth S, Joshi MB. Ethnic disparities attributed to the manifestation in and response to type 2 diabetes: insights from metabolomics. *Metabolomics*. 2022;18:45. doi: 10.1007/s11306-022-01905-8

32. Jenkins DJA, Dehghan M, Mente A, Bangdiwala SI, Rangarajan S, Srichaikul K, Mohan V, Avezum A, Díaz R, Rosengren A, et al; PURE Study Investigators. Glycemic index, glycemic load, and cardiovascular disease and mortality. *N Engl J Med*. 2021;384:1312–1322. doi: 10.1056/NEJMoa2007123
33. Virtanen HEK, Voutilainen S, Koskinen TT, Mursu J, Kokko P, Ylilauri MPT, Tuomainen T-P, Salonen JT, Virtanen JK. Dietary proteins and protein sources and risk of death: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr*. 2019;109:1462–1471. doi: 10.1093/ajcn/nqz025
34. Pala V, Sieri S, Chiodini P, Masala G, Palli D, Mattiello A, Panico S, Tumino R, Frasca G, Fasanelli F, et al. Associations of dairy product consumption with mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC)–Italy cohort. *Am J Clin Nutr*. 2019;110:1220–1230. doi: 10.1093/ajcn/nqz183
18. Tobi EW, Slieker RC, Luijk R, Dekkers KF, Stein AD, Xu KM, Slagboom PE, van Zwet EW, Lumey LH, Heijmans BT; Biobank-based Integrative Omics Studies Consortium. DNA methylation as a mediator of the association between prenatal adversity and risk factors for metabolic disease in adulthood.

35. Ding M, Li J, Qi L, Ellervik C, Zhang X, Manson JE, Stampfer M, Chavarro JE, Rexrode KM, Kraft P, et al. Associations of dairy intake with risk of mortality in women and men: three prospective cohort studies. *BMJ*. 2019;367:l6204. doi: 10.1136/bmj.l6204
19. Huang JV, Cardenas A, Colicino E, Schooling CM, Rifas-Shiman SL, Agha G, Zheng Y, Hou L, Just AC, Litonjua AA, et al. DNA methylation in blood as a mediator of the association of mid-childhood body mass index with cardio-metabolic risk score in early adolescence. *Epigenetics*. 2018;13:1072–1087. doi: 10.1080/15592294.2018.1543503
20. Qi L, Heianza Y, Li X, Sacks FM, Bray GA. toward precision weight-loss dietary interventions: findings from the POUNDS Lost Trial. *Nutrients*. 2023;15:3665. doi: 1510.3390/nu15163665
21. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, Desai M, King AC. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *JAMA*. 2018;319:667–679. doi: 10.1001/jama.2018.0245
22. Cole JB, Florez JC, Hirschhorn JN. Comprehensive genomic analysis of dietary habits in UK Biobank identifies hundreds of genetic associations. *Nat Commun*. 2020;11:1467. doi: 10.1038/s41467-020-15193-0

36. Chen Z, Glisic M, Song M, Aliahmad HA, Zhang X, Moumdjian AC, Gonzalez-Jaramillo V, van der Schaft N, Bramer WM, Ikram MA, et al. Dietary protein intake and all-cause and cause-specific mortality: results from the Rotterdam Study and a meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2020;35:411–429. doi: 10.1007/s10654-020-00607-6
37. Naghshi S, Sadeghi O, Willett WC, Esmailzadeh A. Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ*. 2020;370:m2412. doi: 10.1136/bmj.m2412
38. Qi XX, Shen P. Associations of dietary protein intake with all-cause, cardiovascular disease, and cancer mortality: a systematic review and meta-analysis of cohort studies. *Nutr Metab Cardiovasc Dis*. 2020;30:1094–1105. doi: 10.1016/j.numecd.2020.03.008
39. Amba V, Murphy G, Etemadi A, Wang SM, Abnet CC, Hashemian M. Nut and peanut butter consumption and mortality in the National Institutes of Health-AARP Diet and Health Study. *Nutrients*. 2019;11:1508. doi: 10.3390/nu11071508
23. Ding M, Ellervik C, Huang T, Jensen MK, Curhan GC, Pasquale LR, Kang JH, Wiggs JL, Hunter DJ, Willett WC, et al. Diet quality and genetic association with body mass index: results from 3 observational studies. *Am J Clin Nutr*. 2018;108:1291–1300. doi: 10.1093/ajcn/nqy203
24. Westerman K, Liu Q, Liu S, Parnell LD, Sebastiani P, Jacques P, DeMeo DL, Ordovás JM. A gene-diet interaction-based score predicts response to dietary fat in the Women's Health Initiative. *Am J Clin Nutr*. 2020;111: 893–902. doi: 10.1093/ajcn/nqaa037
25. Shan Z, Guo Y, Hu FB, Liu L, Qi Q. Association of low-carbohydrate and low-fat diets with mortality among US adults. *JAMA Intern Med*. 2020;180: 513–523. doi: 10.1001/jamainternmed.2019.6980
26. Wang DD, Li Y, Bhupathiraju SN, Rosner BA, Sun Q, Giovannucci EL, Rimm EB, Manson JE, Willett WC, Stampfer MJ, et al. Fruit and vegetable intake and mortality: results from 2 prospective cohort studies of US men and women and a meta-analysis of 26 cohort studies. *Circulation*. 2021;143:1642–1654. doi: 10.1161/CIRCULATIONAHA.120.048996
27. Park Y-MM, Choi MK, Lee S-S, Shivappa N, Han K, Steck SE, Hébert JR, Merchant AT, Sandler DP. Dietary inflammatory potential and risk of mortality in metabolically healthy and unhealthy phenotypes among

40. Zamora-Ros R, Cayssials V, Cleries R, Redondo ML, Sánchez M-J, Rodríguez-Barranco M, Sánchez-Cruz J-J, Mokoroa O, Gil L, Amiano P, et al. Moderate egg consumption and all-cause and specific-cause mortality in the Spanish European Prospective Into Cancer and Nutrition (EPIC-Spain) study. *Eur J Nutr*. 2019;58:2003–2010. doi: 10.1007/s00394-018-1754-6

41. Mazidi M, Katsiki N, Mikhailidis DP, Banach M. Dietary choline is positively related to overall and cause-specific mortality: results from individuals of the National Health and Nutrition Examination Survey and pooling prospective data. *Br J Nutr*. 2019;122:1262–1270. doi: 10.1017/S0007114519001065

42. Chester DN, Goldman JD, Ahuja JK, Moshfegh AJ. *Dietary Intakes of Choline: What We Eat in America, NHANES 2007-2008*. US Department of Agriculture; 2010:1–4. FSRG Dietary Data Brief No. 9.

43. Estruch R, Ros E, Salas-Salvado J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al. Retraction and republication: primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279-90. *N Engl J Med*. 2018;378:2441–2442. doi: 10.1056/NEJMc1806491

44. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Fitó M, Chiva-Blanch G, Fiol M, Gómez-Gracia E, Arós F, Lapetra J, et al; PREDIMED Study Investigators. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:e6–e17. doi: 10.1016/S2213-8587(19)30074-9
45. Rosato V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies. *Eur J Nutr*. 2019;58:173–191. doi: 10.1007/s00394-017-1582-0
46. Chen GC, Neelakantan N, Martin-Calvo N, Koh W-P, Yuan J-M. *Epidemiol*. 2019;34:337–349. doi: 10.1007/s10654-019-00504-7
47. Becerra-Tomas N, Blanco Mejia S, Vigiouliou E, Khan T, Kendall CWC, Kahleova H, Rahelić D, Sievenpiper JL, Salas-Salvadó J. Mediterranean diet, cardiovascular disease and mortality in
61. Liu Q, Matthan NR, Manson JE, Howard BV, Tinker LF, Neuhauser ML, Van Horn LV, Rossouw JE, Allison MA, Martin LW, et al. Plasma phospho-lipid fatty acids and coronary heart disease risk: a matched case-control study within the Women's Health Initiative observational study. *Nutrients*. 2019;11:1672. doi: 10.3390/nu11071672
62. Chen J, Sun B, Zhang D. Association of dietary n3 and n6 fatty acids intake with hypertension: NHANES 2007–2014. *Nutrients*. 2019;11:1232. doi: 10.3390/nu11061232
63. Kouli G-M, Panagiotakos DB, Kyrou I, Magriplis E, Georgousopoulou EN, Chrysoshoou C, Tsigos C, Tousoulis D, Pitsavos C. Olive oil consumption and 10-year (2002-2012) cardiovascular disease incidence: the ATTICA study. diabetes: a systematic review and meta-analysis of prospective cohort studies and randomized clinical trials. *Crit Rev Food Sci Nutr*. 2020;60:1207–1227. doi: 10.1080/10408398.2019.1565281

- mic load and cardiometabolic risks in the US, Europe and Asia: a dose-response meta-analysis. *Nutr Metab Cardiovasc Dis*. 2020;30:853–871. doi: 10.1016/j.numecd.2019.12.050
65. Wan Y, Wang F, Yuan J, Li J, Jiang D, Zhang J, Li H, Wang R, Tang J, Huang T, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomised controlled-feeding trial. *Gut*. 2019;68:1417–1429. doi: 10.1136/gutjnl-2018-317609
48. Chiavaroli L, Viguioliouk E, Nishi SK, Blanco Mejia S, Rahelić D, Kahleová H, Salas-Salvadó J, Kendall CW, Sievenpiper JL. DASH dietary pattern and cardiometabolic outcomes: an umbrella review of systematic reviews and meta-Analyses. *Nutrients*. 2019;11:338. doi: 10.3390/nu11020338
49. Yang ZQ, Yang Z, Duan ML. Dietary Approach to Stop Hypertension diet and risk of coronary artery disease: a meta-analysis of prospective cohort studies. *Int J Food Sci Nutr*. 2019;70:668–674. doi: 10.1080/09637486.2019.1570490
50. Filippini T, Malavolti M, Whelton PK, Naska A, Orsini N, Vinceti M. Blood pressure effects of sodium reduction: dose-response meta-analysis

66. Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, De Henauw S, Michels N, Devleesschauwer B, Schlesinger S, et al. Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. *Crit Rev Food Sci Nutr*. 2019;59:1071–1090. doi: 10.1080/10408398.2017.1392288
 67. Qin P, Li Q, Zhao Y, Chen Q, Sun X, Liu Y, Li H, Wang T, Chen X, Zhou Q, et al. Sugar and artificially sweetened beverages and risk of obesity, type 2 diabetes mellitus, hypertension, and all-cause mortality: a dose-response meta-analysis of experimental studies. *Circulation*. 2021;143:1542–1567. doi: 10.1161/CIRCULATIONAHA.120.050371
-
51. Matsumoto S, Beeson WL, Shavlik DJ, Siapco G, Jaceldo-Siegl K, Fraser G, Knutsen SF. Association between vegetarian diets and cardiovascular risk factors in non-Hispanic White participants of the Adventist Health Study-2.

68. Schwingshackl L, Neuenschwander M, Hoffmann G, Buyken AE, Schlesinger S. Dietary sugars and cardiometabolic risk factors: a network meta-analysis on isocaloric substitution interventions. *Am J Clin Nutr.* 2020;111:187–196. *J Nutr Sci.* 2019;8:e6. doi: 10.1017/jns.2019.1
doi: 10.1093/ajcn/nqz273
52. Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA Intern Med.* 2019;179:1335–1344. doi: 10.1001/jamainternmed.2019.2195
53. Prentice RL, Aragaki AK, Howard BV, Chlebowski RT, Thomson CA, Van Horn L, Tinker LF, Manson JE, Anderson GL, Kuller LE, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer,

69. Marshall S, Petocz P, Duve E, Abbott K, Cassettari T, Blumfield M, Fayet-Moore F. The effect of replacing refined grains with whole grains on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials with GRADE clinical recommendation. *J Acad Nutr Diet*. 2020;120:1859–1883.e31. doi: 10.1016/j.jand.2020.06.021
70. Wang Y, Duan Y, Zhu L, Fang Z, He L, Ai D, Jin Y. Whole grain and cereal fiber intake and the risk of type 2 diabetes: a meta-analysis. *Int J Mol Epidemiol*. 2019;10:38–46.
54. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Méjean C, Andrianasolo RM, Chazelas E, Deschasaux M, Hercberg S, Galan P, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). *BMJ*. 2019;365:l1451. doi: 10.1136/bmj.l1451
55. Jayedi A, Soltani S, Abdolshahi A, Shab-Bidar S. Healthy and unhealthy dietary patterns and the risk of chronic disease: an umbrella review of meta-analyses of prospective cohort studies. *Br J Nutr*. 2020;124:1133–1144. doi: 10.1017/S0007114520002330
56. Dong T, Guo M, Zhang P, Sun G, Chen B. The effects of low-carbohydrate

71. Zhang B, Xiong K, Cai J, Ma A. Fish consumption and coronary heart disease: a meta-analysis. *Nutrients*. 2020;12:2278. doi: 10.3390/nu12082278
72. Zhong VW, Van Horn L, Greenland P, Carnethon MR, Ning H, Wilkins JT, Lloyd-Jones DM, Allen NB. Associations of processed meat, unprocessed red meat, poultry, or fish intake with incident cardiovascular disease and all-cause mortality. *JAMA Intern Med*. 2020;180:503–512. doi: 10.1001/jamainternmed.2019.6969
73. Liu K, Hui S, Wang B, Kaliannan K, Guo X, Liang L. Comparative effects of different types of tree nut consumption on blood lipids: a network meta-analysis of clinical trials. *Am J Clin Nutr*. 2020;111:219–227. doi: 10.1093/ajcn/nqz280
74. Liang L, Hui S, Wang B, Kaliannan K, Guo X, Liang L. Diets on cardiovascular risk factors: a meta-analysis. *PLoS One*. 2020;15:e0225348. doi: 10.1371/journal.pone.0225348
57. Mazidi M, Mikhailidis DP, Sattar N, Toth PP, Judd S, Blaha MJ, Hernandez AV, Penson PE, Banach M. Association of types of dietary fats and all-cause and cause-specific mortality: a prospective cohort study and meta-analysis of prospective studies with 1,164,029 participants. *Clin Nutr*. 2020;39:3677–3686. doi: 10.1016/j.clnu.2020.03.028
58. Kang ZQ, Yang Y, Xiao B. Dietary saturated fat intake and risk of stroke: systematic review and dose-response meta-analysis of prospective cohort studies. *Nutr Metab Cardiovasc Dis*. 2020;30:179–189. doi: 10.1016/j.numecd.2019.09.028
59. Astrup A, Magkos F, Bier DM, Brenna JT, de Oliveira Otto MC, Hill JO, King JC, Mente A, Ordovas JM, Volek JS, et al. Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76:844–857. doi: 10.1016/j.jacc.2020.05.077
60. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655–666. doi: 10.1001/jama.295.6.655

74. Zhang X, Chen X, Xu Y, Yang J, Du L, Li K, Zhou Y. Milk consumption and multiple health outcomes: umbrella review of systematic reviews and meta-analyses in humans. *Nutr Metab.* 2021;18:1–18. doi: 10.1186/s12986-020-00527-y
75. Zhang K, Chen X, Zhang L, Deng Z. Fermented dairy foods intake and risk of cardiovascular diseases: a meta-analysis of cohort studies. *Crit Rev Food Sci Nutr.* 2020;60:1189–1194. doi: 10.1080/10408398.2018.1564019
76. Martínez-López S, Sarriá B, Mateos R, Bravo-Clemente L. Moderate consumption of a soluble green/roasted coffee rich in caffeoylquinic acids reduces cardiovascular risk markers: results from a randomized, cross-over, controlled trial in healthy and hypercholesterolemic subjects. *Eur J Nutr.* 2019;58:865–878. doi: 10.1007/s00394-018-1726-x
77. Suliga E, Koziel D, Ciesla E, Rebak D, Głuszek-Osuch M, Głuszek S. Consumption of alcoholic beverages and the prevalence of metabolic syndrome and its components. *Nutrients.* 2019;11:2764. doi: 10.3390/nu11112764
78. Suliga E, Koziel D, Ciesla E, Rebak D, Głuszek-Osuch M, Naszydlowska E, Głuszek S. The consumption of alcoholic beverages and the prevalence of cardiovascular diseases in men and women: a cross-sectional study. *Nutrients.* 2019;11:1318. doi: 10.3390/nu11061318

79. Graudal N, Hubeck-Graudal T, Jurgens G, et al. Association between dietary sodium and blood pressure: a meta-analysis of 133 randomized controlled trials. *Am J Clin Nutr*. 2010;92:1000-1007. doi: 10.1093/ajcn/nqz384
80. Sacks FM, Svetkey LP, Vollmer WM, et al. Effect of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: DASH-Sodium Collaborative Group. *N Engl J Med*. 2001;344:3-10. doi: 10.1056/NEJM0107063440301
81. Javedi A, Ghomashi F, Zargar MS, Shahmoradian L, et al. Sodium-to-potassium ratio and risk of stroke: a meta-analysis. *Clin Nutr*. 2018;37:1016-1023. doi: 10.1016/j.clnu.2018.05.017
82. Huang L, Trieu K, Yoshimura S, Neal R, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: a systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
83. Lackland DT, Leung AA, Anderson CAM, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: a systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
84. Graudal N, Hubeck-Graudal T, Jurgens G, et al. Association between dietary sodium and blood pressure: a meta-analysis of 133 randomized controlled trials. *Am J Clin Nutr*. 2010;92:1000-1007. doi: 10.1093/ajcn/nqz384
85. Sacks FM, Svetkey LP, Vollmer WM, et al. Effect of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: DASH-Sodium Collaborative Group. *N Engl J Med*. 2001;344:3-10. doi: 10.1056/NEJM0107063440301
86. Javedi A, Ghomashi F, Zargar MS, Shahmoradian L, et al. Sodium-to-potassium ratio and risk of stroke: a meta-analysis. *Clin Nutr*. 2018;37:1016-1023. doi: 10.1016/j.clnu.2018.05.017
87. Huang L, Trieu K, Yoshimura S, Neal R, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: a systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
88. Lackland DT, Leung AA, Anderson CAM, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: a systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
89. Graudal N, Hubeck-Graudal T, Jurgens G, et al. Association between dietary sodium and blood pressure: a meta-analysis of 133 randomized controlled trials. *Am J Clin Nutr*. 2010;92:1000-1007. doi: 10.1093/ajcn/nqz384
90. Sacks FM, Svetkey LP, Vollmer WM, et al. Effect of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: DASH-Sodium Collaborative Group. *N Engl J Med*. 2001;344:3-10. doi: 10.1056/NEJM0107063440301
91. Javedi A, Ghomashi F, Zargar MS, Shahmoradian L, et al. Sodium-to-potassium ratio and risk of stroke: a meta-analysis. *Clin Nutr*. 2018;37:1016-1023. doi: 10.1016/j.clnu.2018.05.017
92. Huang L, Trieu K, Yoshimura S, Neal R, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: a systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
93. Lackland DT, Leung AA, Anderson CAM, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: a systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
94. Graudal N, Hubeck-Graudal T, Jurgens G, et al. Association between dietary sodium and blood pressure: a meta-analysis of 133 randomized controlled trials. *Am J Clin Nutr*. 2010;92:1000-1007. doi: 10.1093/ajcn/nqz384
95. Haughey H, Laursen RP, Ritz C, et al. Effects of vitamin D supplementation in children and adolescents: a meta-analysis of randomized controlled trials. *Eur J Clin Nutr*. 2010;64:1007-1015. doi: 10.1007/s00394-019-02150-x
96. Abboud M. Vitamin D supplementation in children and adolescents: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr*. 2020;74:1163-1173. doi: 10.1007/s00394-019-02150-x
97. Ashor AW, Brown R, Keenan PD, et al. Vitamin D supplementation in children and adolescents: a systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315

Limited evidence for a beneficial effect of vitamin C supplementa-tion on biomarkers of cardiovascular diseases: an umbrella review of systematic reviews and meta-analyses. *Nutr Res.* 2019;61:1–12. doi:

10.1136/bmj.m315

83. Wang YJ, Yeh TL, Shih MC, Tu Y-K, Chien K-L. Dietary sodium intake and risk of cardiovascular disease: a systematic review and dose-response meta-analysis. *Nutrients.* 2020;12:2934. doi: 10.3390/nu12102934 84.

McClure ST, Rebholz CM, Mitchell DC, Selvin E, Appel LJ. The associa-

10.1016/j.nutres.2018.08.005

tion of dietary phosphorus with blood pressure: results from a secondary analysis of the PREMIER trial. *J Hum Hypertens.* 2019;34:132–142. doi:

98. Wang T, Xu L. Circulating vitamin E levels and risk of coronary artery disease and myocardial infarction: a mendelian randomization study. *Nutrients*. 2019;11:2153. doi: 10.3390/nu11092153
99. Bonnet JP, Cardel MI, Cellini J, Hu FB, Guasch-Ferré M. Breakfast skipping, body composition, and cardiometabolic risk: a systematic review and meta-analysis of randomized trials. *Obesity (Silver Spring)*. 2020;28:1098–1109. doi: 10.1038/s41371-019-0231-x
85. Zhao B, Hu L, Dong Y, Xu J, Wei Y, Yu D, Xu J, Zhang W. The effect of magnesium intake on stroke incidence: a systematic review and meta-analysis with trial sequential analysis. *Front Neurol*. 2019;10:852. doi: 10.3389/fneur.2019.00852
86. Siscovick DS, Barringer TA, Fretts AM, Wu JHY, Lichtenstein AH, Costello RB, Kris-Etherton PM, Jacobson TA, Engler MB, Alger HM, et al; on behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. *Circulation*. 2017;135:e867–e884. doi: 10.1161/cir.0000000000000482
87. Khan SU, Lone AN, Khan MS, Virani SS, Blumenthal RS, Nasir K, Miller M, Michos ED, Ballantyne CM, Boden WE, et al. Effect of omega-3 fatty acids on cardiovascular outcomes: a systematic review and meta-analysis. *EClinicalMedicine*. 2021;38:100997. doi: 10.1016/j.eclinm.2021.100997
88. Ward RE, Cho K, Nguyen XM, Vassy JL, Ho YL, Quaden RM, Gagnon DR, Wilson PWF, Gaziano JM, Djoussé L. Omega-3 supplement use, fish intake, and risk of non-fatal coronary artery disease and ischemic stroke in the Million Veteran Program. *Clin Nutr*. 2019;39:574–579. doi: 10.1016/j.clnu.2019.03.005
89. Hadi A, Askarpour M, Salamat S, Ghaedi E, Symonds ME, Miraghajani M. Effect of flaxseed supplementation on lipid profile: an updated systematic review and dose-response meta-analysis of sixty-two randomized controlled trials. *Pharmacol Res*. 2020;152:104622. doi: 10.1016/j.phrs.2019.104622
90. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Gordon D, Copeland T, D'Agostino D, et al; Vital Research Group. Vitamin D

100. Kord-Varkaneh H, Nazary-Vannani A, Mokhtari Z, Salehi-Sahlabadi A, Rahmani J, Clark CCT, Fatahi S, Zanghelini F, Hekmatdoost A, Okunade K, et al. The influence of fasting and energy restricting diets on blood pressure in humans: a systematic review and meta-analysis. *High Blood Press Cardiovasc Prev.* 2020;27:271–280. doi: 10.1007/s40292-020-00391-0

101. Palomar-Cros A, Andreeva VA, Fezeu LK, Julia C, Bellicha A, et al. Dietary circadian rhythms and cardiovascular disease risk in the prospective NutriNet-Santé cohort. *Nat Commun.* 2023;14:7899. doi: 10.1038/s41467-023-43444-3

102. Sun Y, Rong S, Liu B, Du Y, Wu Y, Chen L, Xiao Q, Snetselaar L, et al. Meal skipping and shorter meal intervals are associated with increased risk of all-cause and cardiovascular disease mortality among US adults. *J Acad Nutr Diet.* 2023;123:417–426.e3. doi: 10.1016/j.jand.2022.08.119

103. US Department of Agriculture and Economic Research Service. Summary findings: food price outlook. 2024. Accessed May 6, 2024. /

104. Euromonitor International. Voice of the consumer: Lifestyles Survey 2023: key insights. 2023. Accessed March 1, 2024.

105. Healthy Food America. Healthy food pricing incentives: a systematic review of current evidence. June 2019. Accessed October 25, 2024.

106. Scrafford CG, Bi X, Multani JK, Murphy MM, Schmier JK, Barraj LM. Health economic evaluation modeling shows potential health care cost savings with increased conformance with healthy dietary patterns among adults in the United States. *J Acad Nutr Diet.* 2019;119:599–616. doi: 10.1016/j.jand.2018.10.002

91. Zittermann A, Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, Knabbe C, Börgermann J, Berthold HK, Pilz S, et al. Daily supplementation with supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* 2019;380:33–44. doi: 10.1056/NEJMoa1809944

4000 IU vitamin D3 for three years does not modify cardiovascular risk

107. Deleted in proof. markers in patients with advanced heart failure: the effect of vitamin D on mortality in heart failure trial. *Ann Nutr Metab.* 2019;74:62–68. doi:

108. Basu S, O'Neill J, Sayer E, Petrie M, Bellin R, Berkowitz SA. Population health impact and cost-effectiveness of community-supported agriculture among low-income US adults: a microsimulation analysis. *Am J Public Health*. 2020;110:119–126. doi: 10.2105/AJPH.2019.305364
109. Webb M, Fahimi S, Singh GM, Khatibzadeh S, Micha R, Powles J, Mozaffarian D. Cost effectiveness of a government supported policy strategy to decrease sodium intake: global analysis across 183 nations. *BMJ*.
92. Zittermann A, Ernst JB, Prokop S, Fuchs U, Gruszka A, Dreier J, Kuhn J, Knabbe C, Berthold HK, Gouni-Berthold I, et al. Vitamin D supplementation of 4000IU daily and cardiac function in patients with advanced heart failure: the EVITA trial. *Int J Cardiol*. 2019;280:117–123. doi: 10.1016/j.ijcard.2019.01.027
93. Djousse L, Cook NR, Kim E, Bodar V, Walter J, Bubes V, Luttmann-Gibson H, Mora S, Joseph J, Lee IM, et al; VITAL Research Group. Supplementation with vitamin D and/or omega-3 fatty acids and incidence of heart failure hospitalization: vITAL-Heart Failure. *Circulation*. 2019;141:784–786. doi: 10.1161/CIRCULATIONAHA.119.044645
94. Jiang X, Nudy M, Aragaki AK, Robbins JA, Manson JE, Stefanick ML, O'Sullivan DM, Shikany JM, LeBlanc ES, Kelsey AM, et al.

- 2017;356:i6699. doi: 10.1136/bmj.i6699
110. Collins B, Kyridemos C, Pearson-Stuttard J, Huang Y, Bandosz P, Wilde P, Kersh R, Capewell S, Mozaffarian D, Whitsel LP, et al. FDA sodium reduction targets and the food industry: are there incentives to reformulate? Microsimulation cost-effectiveness analysis. *Milbank Q.* 2019;97:858–880. doi: 10.1111/1468-0009.12402
111. Park H, Yu S. Policy review: Implication of tax on sugar-sweetened beverages for reducing obesity and improving heart health. *Health Policy Technol.* 2019;8:92–95. doi: 10.1016/j.hlpt.2018.12.002
112. Wilde P, Huang Y, Sy S, Abrahams-Gessel S, Jardim TV, Paarlberg R, Mozaffarian D, Micha R, Gaziano T. Cost-effectiveness of a US national sugar-sweetened beverage tax with a multistakeholder approach: who

- pays and who benefits. *Am J Public Health*. 2019;109:276–284. doi: 10.2105/AJPH.2018.304803
113. Colchero MA, Rivera-Dommarco J, Popkin BM, Ng SW. In Mexico, evidence of sustained consumer response two years after implementing a sugar-sweetened beverage tax. *Health Aff (Millwood)*. 2017;36:564–571. doi: 10.1377/hlthaff.2016.1231
114. Sanchez-Romero LM, Canto-Osorio F, Gonzalez-Morales R, Colchero MA, Ng S-W, Ramirez-Palacios P, Salmerón J, Barrientos-Gutiérrez T. Association between tax on sugar sweetened beverages and soft drink consumption in adults in Mexico: open cohort longitudinal analysis of Health Workers Cohort Study. *BMJ*. 2020;369:m1311. doi: 10.1136/bmj.m1311
115. Silver LD, Ng SW, Ryan-Ibarra S, Taillie LS, Induni M, Miles DR, Poti JM, Popkin BM. Changes in prices, sales, consumer spending, and beverage consumption one year after a tax on sugar-sweetened beverages in Berkeley, California, US: a before-and-after study. *PLoS Med*. 2019;15:e1002783. doi: 10.1371/journal.pmed.1002783
119. GBD Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1223–1249. doi: 10.1016/S0140-6736(20)30752-2
120. Mellen PB, Gao SK, Vitolins MZ, Goff DC Jr. Deteriorating dietary habits among adults with hypertension: DASH dietary adherence, NHANES 1988–1994 and 1999–2004. *Arch Intern Med*. 2008;168:308–314. doi: 10.1001/archinternmed.2007.119
121. Gao S. Diet and Exercise: Behavioral Management of Hypertension and Diabetes [dissertation]. University of Washington; 2006.
122. Cerwinski LA, Rasmussen HE, Lipson S, Volgman AS, Tananev CC. Evaluation of a dietary screener: the 2017;14:e1002283. doi: 10.1371/journal.pmed.1002283

123. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart dis-ease and stroke in women. *Arch Intern Med*. 2008;168:713–720. doi:
116. Lee MM, Falbe J, Schillinger D, Basu S, McCulloch CE, Madsen KA. Sugar-sweetened beverage consumption 3 years after the Berkeley, California, sugar-sweetened beverage tax. *Am J Public Health*. 2019;109:637–639. doi: 10.2105/AJPH.2019.304971
117. Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, Engell RE, Lim SS, Danaei G, Mozaffarian D. Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open*. 2013;3:e003733. doi: 10.1001/archinte.168.7.713

124. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation*. 2010;121:2271–2283. doi: 10.1161/circulationaha.109.924977
125. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2024. 10.1136/bmjopen-2013-003733
118. He FJ, Brinsden HC, MacGregor GA. Salt reduction in the United Kingdom: a successful experiment in public health. *J Hum Hypertens*. 2014;28:345–352. doi: 10.1038/jhh.2013.105
126. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed July 1, 2024.

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Prevalence and Secular

Youths

Prevalence in

[Click here to return to the Table \(See Table 6-1\)](#)

[Click here to return to the](#)

Classification of

- BMI is calculated as weight in by height in meters squared. defined as a BMI ≥ 30.0 kg/m² sity as a BMI ≥ 40 kg/m².^{1,2} defined as BMI ≥ 25.0 but < 30
- Obesity in adults can be further 1 (BMI $30 - < 35$ kg/m²) and kg/m²); severe obesity is ≥ 40 kg/m²).^{1,2}
- For children and adolescents, as BMI ≥ 95 th percentile and BMI $\geq 120\%$ of the 95th in children is defined as BMI percentile.
- Abdominal obesity is also defined cm (40 in) in males and ≥ 88
- Lower BMI thresholds have been for Asian adults, with to < 27.5 kg/m² and obesity as Accordingly, the American has lowered the BMI cut point screening in Asian adults to viduals of South Asian, descent, the respective WC with disease risk are ≥ 90 cm cm in females.⁵
- It should be noted that the risk betes conferred by an across racial and ethnic estimated among Black adults in Asian people.³ Even among lations, the BMI cut point for from 22 to 26 kg/m², and for varies from 26 to 31 kg/m².^{3,7}

- According to NHANES data 2020 (before the COVID-19 children and adolescents 2 to prevalence of obesity was males, and 18.5% for increased with age, being of age, 20.7% for those 6 to 22.2% for those 12 to 19
- There were significant racial obesity.⁸ The highest among Hispanic male and NH According to NHANES data the prevalence of obesity cents 2 to 19 years of age NH White males and females, NH Black males and females, Asian males and females, and Hispanic males and females,
- Among youths, percent body by BMI categories. In 2018 in youths 8 to 19 years fat was highest among and males (28.2%).⁹ There ence in percent body fat White females, and Asian and 32.7%, respectively). lower among NH Black males with NH White or Asian males respectively. Among female Asian females had lower than NH White females
- There are regional/geographic lence of obesity in youths An analysis of pooled data dren and adolescents (N=14 scores to be higher in the South and West compared adjustment for
- According to data from the National Survey of Children's Health from 2021 to 2022, 17% of

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published

data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

youths 10 to 17 years of age had obesity, with 7 states having youths obesity rates significantly above the national average exceeding 20% (ie, West Virginia, Kentucky, New Mexico, Mississippi, Louisiana, Texas, and Tennessee).¹¹

Youth Secular Trends

(See Chart 6-1)

- Comparing data across NHANES survey years shows that the prevalence of overweight, obesity,

and severe obesity among all children and adolescents 2 to 19 years of age increased from 10.2%, 5.2%, and 1.0% in 1971 to 1974 to 16.1%, 19.3%, and 6.1%, respectively, in 2017 to 2018 (Chart 6-1).¹² For males, the prevalence increased from

10.3%, 5.3%, and 1.0% in 1971 to 1974 to 14.7%, 20.5%, and 6.9% in 2017 to 2018. For females, the prevalence increased from 10.1%, 5.1%, and 1.0% in 1971 to 1974 to 17.6%, 18.0%, and 5.2% in 2017 to 2018.¹³

- Comparing NHANES data from 1999 to 2006 among youths 8 to 19 years of age increased from 25.6% to 26.3% ($P < 0.01$) among males and from 33.0% to 33.7% ($P = 0.01$) among females.¹⁴
- Another analysis using NHANES data examined the change in prevalence of obesity in children and adolescents (2–19 years of age) between the 2011 to 2012 and 2021 to March 2020 periods

of severe obesity among adults ≥ 20 years of age in the United States was 9.2% with greater prevalence in females (11.7%) than males (6.6%; Table 6-3).⁸ Significant disparities were noted by racial and ethnic groups with the greatest prevalence of severe obesity among Black females (19.1%).

- In that same time frame (2017–March 2020), the age-adjusted prevalence of severe obesity stratified by age and found that obesity prevalence increased significantly from 16.7% to 20.9% for male youths ($P_{\text{trend}} = 0.0084$) but not significantly for female youths ($P_{\text{trend}} = 0.35$).

This study also reported that the prevalence of obesity increased significantly in children 2 to 5 years of age but not in children 6 to 11 years of age or adolescents 12 to 19 years of age.¹⁵

- Using 2022 data from the BRFSS (Chart 6-2), the CDC reported that all US states had an obesity prevalence >20% (ie, 1 in 5 adults), 22 states had an obesity prevalence between 30% and 35%, 19 states had an obesity prevalence of 35% to 40%, and 3 states had an obesity prevalence ≥40%.¹⁶ There were regional differences with the Midwest and South having the highest prevalence of obesity in the United States followed by the Northeast and the West. These data are striking because 10 years ago no state had an adult obesity prevalence >35%.¹⁶ By state, the highest prevalence of obesity was in West Virginia (41.3%) and the lowest in Colorado (24.9%) and the District of Columbia (24.8%; unpublished NHLBI tabulation using

Adults

BRFSS¹⁶).

Prevalence in Adults

Secular Trends in Adults

(See Tables 6-2 and 6-3 and Chart 6-2)

(See Chart 6-3)

- According to NHANES data from 2017 through March 2020 (before the pandemic), the age-adjusted prevalence of overweight or obesity

among adults ≥20 years of age in the United States was 71.2%.⁸ The prevalence of obesity was 41.9% and was similar for males (41.8%) and females (41.8%;

- The age-adjusted trends in overweight, obesity, and severe obesity in US adults from 1960 to 1962 to 2017 to 2018 using NHANES data are shown in Chart 6-3.¹⁹
- Comparing NHANES data from 1999 to 2000 with data from 2017 to 2018 shows that the prevalence of obesity increased from 27.5% (95% CI, 24.3%– among NH Black females. Among adults ≥20 years of age, according to data from NHANES 2017 through March 2020 (before the pandemic), the prevalence of obesity for males and females was 43.1% and 39.6% for NH White adults, 40.4% and 57.9% for NH Black adults, 17.6% and 14.5% for NH Asian adults, and 45.2% and 45.7% for Hispanic adults, respectively (Table 6-2).⁸
- This prevalence of obesity by age categories for adults ≥20 years of age from this same time frame (2017–March 2020) was 39.8% in younger adults 20 to 39 years of age, 44.3% in middle-aged adults 40 to 59 years of age, and 41.5% in adults ≥60 years of age (Table 6-2).⁸
- There were significant disparities by racial and ethnic groups with the highest prevalence of obesity
- In data from NHANES 2017 through March 2020

30.8%) to 43% (95% CI, 37.6%–48.6%) among US males with severe obesity increasing from 3.1% to 6.9%. All racial and ethnic groups experienced an increase in obesity and severe obesity during this time frame except for Black males, for whom the obesity prevalence did not increase after 2005 to 2006. The increase in obesity biennially was greater among Mexican American males (3%) than NH White males (1.4%; $P<0.001$).²⁰

- Among females, the prevalence of obesity increased from 33.4% (95% CI, 29.8%–37.1%) in 1999 to 41.9% (95% CI, 37.8%–46.1%) in 2017 to 2018; severe obesity increased from 6.2% to 11.5%. This same pattern of increase was seen among NH White females and NH Black females, whereas Mexican American females experienced a rise in obesity, but severe obesity increased only (before the pandemic) after 2009 to 2010.²⁰

- An analysis using BRFSS data of *Income and Education* (See Tables 6-1 through 6-3) that the prevalence of obesity with a 0.6% increase in BMI, pandemic period of March compared with the 2019 to March 2020.²¹
- A recent analysis from the AHA trends using NHANES data March 2020 forecasted that if the prevalence of rise from 43.1% in 2020 to highest prevalence and groups were in the 20 to 44 and groups.
- There were significant of obesity in the United States est prevalence of obesity in (college degree or above) and FPL) groups according to ≥ 20 years of age from 2017 (before the pandemic).⁸ In prevalence of obesity was less than a high school individuals with a high school and 34.2% for individuals with above. In terms of family

Social Determinants of Health and Health Equity

Urbanization

- There are differences in obesity prevalence by urbanization status. Children and adolescents from rural locations had a 30% higher odds of being overweight or obese compared with children and adolescents living in urban locations (OR, 1.30 [95% CI, 1.11–1.52]) according to survey data from 2019 through 2020.²³ An analysis of preschoolers also found that indexed BMI was higher among children living in rural areas than children living in urban areas (β , 0.13 [95% CI, 0.09–0.42]), suggesting that the rural-urban disparity may begin as early as 3 to 4 years of age.²⁴
- Also among US adults, obesity prevalence is higher in rural compared with urban counties (OR, 1.035 [95% CI, 1.03–1.04]).²⁵ Using BRFSS data from 2016, the CDC reported that the prevalence of obesity in adults was higher among nonmetropolitan county residents compared with those living in metropolitan areas (34.2% versus 28.7%;

$P < 0.001$).²⁶

- Rurality may further moderate Black and White racial disparities in obesity with a higher odds of obesity for Black adults compared with White adults living in rural areas (OR, 2.03 [95% CI, 1.71–2.4]) versus the odds of Black adults compared with White adults living in urban areas (OR, 1.83 [95% CI, 1.78–1.88], race-rural interaction, $P < 0.05$).²⁵
- In contrast, a recent analysis reported that obesity-related cardiovascular mortality in the United States from 1999 through 2020 was greater among Black adults who lived in urban communities than those living in rural communities (6.8 versus 5.9 per 100 000 population), whereas the reverse was true for all of the other racial and ethnic groups (rural: range, 2.2–5.4 per 100 000 population; urban: range, 0.9–3.5 per 100 000 population).²⁷

the prevalence of obesity was 43.9% for those with income $\leq 130\%$ FPL, 46.5% for those with income $>130\%$ to 350% FPL, and 39% for individuals with income $>350\%$ FPL (Table 6-2).

- Similar patterns of disparity by education and income were seen for the prevalence of severe obesity (Table 6-3).⁸
- According to 2022 BRFSS data, the prevalence of obesity among US adults was highest among those with incomes of $< \$15\,000$ (38.2%) and $\$15\,000$ to $< \$25\,000$ (38.4%) and then steadily fell across income groups to a prevalence of 34.1% for those with income $\geq \$75\,000$.²⁸ That same 2022 BRFSS data showed that the prevalence of obesity also decreased with higher education with prevalences of 37.6% for less than high school, 35.7% for high school graduate, 35.9% for some college or technical school, and 27.2% for college graduate.²⁸
- There was also significant disparity by SES among youths and adolescents. According to data from NHANES 2017 through March 2020, the prevalence of obesity among children and adolescents 2 to 19 years of age was greatest among those with low family income. Prevalence of obesity was 25.8%, 21.2%, and 11.5% for those with a family income level of $\leq 130\%$ FPL, $>130\%$ to 350% FPL, and $>350\%$ FPL, respectively (Table 6-1).⁸

Composite Social Determinants

- According to data from the NHIS from 2013 to 2017, there was a graded association with increasing burden of social determinants of health such as economic stability; neighborhood, physical environment, and social cohesion; community and social context; food insecurity; education; and health care system being associated with a higher prevalence of obesity. For example, in adjusted models, for the fourth quartile of unfavorable social determinants of health compared with the first quartile, there was a 15%, 50%, and 70% higher prevalence of overweight, obesity class 1 or 2, and obesity class 3, respectively.²⁹

Family History and Genetics

- Genetic variation contributes to overweight and obesity,³⁰ with heritability estimates ranging from 40% to 70%.³¹
- Monogenic or mendelian causes of obesity include variants with strong effects in genes that control appetite and energy balance (eg, *LEP*, *MC4R*, *POMC*). Obesity that occurs in the context of genetic syndromes (eg, Prader-Willi syndrome) also can reflect monogenic or mendelian causes.³² Monogenic obesity inherited in a mendelian pattern is generally rare and associated with other organ-specific abnormalities.
- Polygenic obesity has a heritability pattern similar to that of complex diseases.³³ Numerous GWASs have identified >1100 independent loci associated with polygenic obesity.³³ These GWASs have estimated that common genetic variants may account for >20% of the variation in BMI.³⁴
- In a GWAS of African ancestral populations, only <30% of BMI and waist-to-hip loci identified in European ancestral populations were also associated in African ancestry.³⁵
- One GWAS in children identified 3 new loci with susceptibility for childhood BMI with a GRS (combining these 3 with 12 other previously identified loci) explaining 2% of variations in childhood BMI.³⁶ • *FTO* (first intron of fat mass and

adults, there was a 13-kg gradient in weight and a 25-fold gradient in risk of severe obesity across increasing deciles of polygenic scores.⁴⁴ Similarly, a weight gradient was seen after birth to early childhood of up to 12-kg difference by 18 years of age.

However, obesity-related genetic risks are not deterministic; in the same analysis, 17% of people of normal weight were in the top decile of polygenic risk.⁴⁴ In another analysis, GRS explained 5.2% of BMI variance, and gene-by-environment interaction explained an additional 1.9%.⁴⁵

- However, there is considerable uncertainty in obesity GRSs. A study of N=291 273 unrelated White British UK Biobank participants reported that only 0.4% of participants assigned to the 90% BMI GRS threshold had corresponding 95% credible intervals fully contained in the top decile, demonstrating considerable uncertainty.⁴⁶
- In the Bogalusa Heart Study with >40 years of follow-up, a GRS performed in childhood was found to be modestly associated with mid-life BMI (correlation coefficient, 0.27; $P=1.94\times 10^{-8}$) and associated with a 26% higher risk of later life obesity ($P=3.50\times 10^{-6}$) in White participants.⁴⁷ However, the GRS did not independently predict later-life cardiometabolic health in Black adults, emphasizing the need to develop GRS in more diverse populations.
- Polygenic risk associated with higher BMI is associated with increased risk for CAD, HF, and mortality.³⁸ A mendelian randomization study has shown that a high-BMI GRS is associated with shorter life span, defined as a younger age at death compared with the reference group in the UK Biobank (HR per 1-SD BMI GRS for increase in mortality, 1.07 [95% CI, 1.05–1.09]).⁴⁸
- Mendelian randomization analysis also was used to evaluate the health consequences of obesity across a spectrum of human diseases. In data from the UK Biobank, a high GRS for obesity was associated with a 70% increased risk for diabetes (OR, 1.70 [95% CI, 1.62–1.79]), a 35% increased risk for hypertension (OR, 1.35 [95% CI, 1.31–1.38]), a 27% increased risk for CAD (OR, 1.27 [95% CI, 1.19–1.36]), a 23% increased risk for ischemic stroke (OR, 1.23 [95% CI, 1.02–1.48]), a 33% increased risk for HF (OR, 1.33 [95% CI, 1.14–1.54]), and a 40% increased risk for VTE (OR, 1.40 [95% CI, 1.30–1.49]).⁴⁹
- Genetic variants may also influence responsiveness to weight loss interventions.⁵⁰ A GWAS (N=1166) conducted in a low-calorie diet intervention trial identified 2 loci, *NKX6.3/MIR486* and *RBSG4*, that were associated with degree of weight loss. Both loci were replicated in a second low-calorie diet intervention study (N=789).⁵⁰

- Genetic variants also may affect gain in the context of a example, the *MTIF3* lead ously identified BMI locus. ated with greater weight loss interventions in 2 RCTs, with G allele being associated with (95% CI, −1.75 to −0.53) arm compared with a mean of (95% CI, −0.30 to 0.95) in the
- Environmental exposures may interact with common variants to affect obesity traits. In a study of >500 000 predominantly European ancestral populations, 4 significant loci were identified that modified the effect of current smoking on obesity traits: *INPP4B*, *CHRNA4*, *VEGFA*, and *RSPO3*.⁵² *INPP4B* was previously identified in obesity⁵³ and smoking⁵⁴ GWASs, whereas *VEGFA* lead variants were identified in a gene-by-smoking study of rheumatoid arthritis.⁵⁵

Behavioral/Technology Interventions for Obesity Prevention

- A Cochrane systematic review and meta-analysis of studies from 2015 through 2021 was conducted to evaluate the effectiveness of obesity prevention interventions for children 6 to 18 years of age. Among 140 RCTs (183 063 participants), this meta-analysis found a small beneficial effect on BMI reduction for school-based interventions (SMD, −0.03 kg/m² [95% CI, −0.05 to −0.01]) but not interventions that were after-school programs or community or home based.⁵⁶
- Another meta-analysis of technology-based interventions in youths (telemedicine or digital technology) in an intensive lifestyle lost at least 10% of their body lower risk for a cardiovascular follow-up (HR, 0.80 [95% CI, with those who gained or lost
- A meta-analysis of 54 RCTs pants with obesity found that of weight reduction, usually rated fat with or without associated with a reduction in all-nology mHealth tools) found only small effects on pediatric obesity, with a standardized difference in weight outcomes of only −0.13 and 79% of included studies not demonstrating a significant difference between the treatment and comparator groups.⁵⁷
- Another systematic review and meta-analysis of RCT examined the effectiveness of technology-based interventions for weight loss maintenance (duration, 3–30 months) in adults and found that those interventions were similar to usual care but less effective than in-person interventions with 1.36-kg (95% CI, −0.29–2.43) higher weight regain.⁵⁸
- A systematic review and meta-analysis of RCTs demonstrated that lifestyle interventions did prevent cumulative weight gain among nonobese adults (−1.15 kg [95% CI, −1.50 to −0.80]); however, further study is needed to determine the feasibility for implementation and cost-effectiveness for these

- Bariatric surgery is effective for weight loss, but meta-analysis of >65 000 patients 20 to 79 years bariatric surgery, the average total weight loss at 5 Roux-en-Y gastric bypass, 18.8% (95% CI, 18.0%–(95% CI, 10.2%–13.1%) for the adjustable gastric bypass was associated with more adverse events.⁶² • Another meta-analysis including studies with >10 years of follow-up showed that gastric bypass adjustable gastric band conferred 46%, and sleeve common across all 3 procedures.⁶³
- The weight reduction with bariatric surgery is associated with a lower rate of mortality (HR, 0.51 [95% (median, 6.1 years) than usual care for obesity management. There were greater survival benefits among individuals with diabetes (HR for mortality, 0.41 [95% CI, 0.37–0.45]) than those without diabetes (HR, 0.71 [95% CI, 0.59–0.84]).⁶⁴
- A meta-analysis of 39 observational studies with follow-up ranging from 2 to 24 years found that bariatric surgery was associated with reduced risk for all-cause mortality (HR, 0.55 [95% CI, 0.49–0.62]) and CVD mortality (HR, 0.59 [95% CI, 0.47–0.73]) compared with nonsurgical control.⁶⁵ In addition, bariatric surgery was associated with reduced risk of HF (HR, 0.50 [95% CI, 0.38–0.66]), MI (HR, 0.58 [95% CI, 0.43–0.76]), and stroke (HR, 0.64 [95% CI, 0.53–0.77]) with a nonsignificant favor- programs.⁵⁹
- A subanalysis from the Look AHEAD trial demonstrated that participants (with baseline BMI ≥25 kg/

able trend for reduction in AF (HR, 0.82 [95% CI, 0.64–1.06]).

Pharmacotherapy

- Metformin has weight-reduction effects. In a meta-analysis of 21 trials, metformin compared with control conferred a modest reduction in BMI overall with a WMD of -0.98 kg/m^2 (95% CI, -1.2 to -0.72), which was greater among individuals with simple obesity (WMD, -1.31 [95% CI, -2.07 to -0.54]) compared with those with obesity with type 2 diabetes.
- The older FDA-approved antiobesity medications orlistat, naltrexone-bupropion, phentermine-topiramate, and liraglutide have been shown to confer a placebo-corrected weight reduction of $\approx 5\%$ to 10% .⁶⁷
- SGLT-2 inhibitor medications can confer modest weight loss. In a recent meta-analysis of 116 RCTs, including patients with and without type 2 diabetes, SGLT-2 inhibitors conferred a mean weight reduction of -1.79 kg (95% CI, -1.93 to -1.66) compared with placebo.⁶⁸ This effect was seen for all SGLT-2 inhibitor drugs and across diabetes status.
- Among patients with type 2 diabetes, systematic reviews and meta-analyses have shown that GLP1-RAs have conferred weight loss, but there are differences among the specific types and doses of GLP1-RAs (mean weight loss difference ranging from -0.48% to -6.2%).⁶⁹
- It is notable that among patients with type 2 diabetes and obesity, GLP1-RAs also significantly reduce MACEs (RR, 0.88 [95% CI, 0.81 – 0.96]).⁷⁰
- More recently, GLP1-RAs have emerged as effective drug achieved significant weight loss in a dose-dependent manner.⁷³ The highest dose of tirzepatide (15 mg subcutaneous weekly) conferred an average 17.8% greater weight reduction compared with placebo, with a mean weight loss of 23.6 kg (52.0 lb) at 72 weeks.
- Newer GLP1-RAs have been recently studied in phase 3 trials. Retatrutide, a novel pharmacological options for weight loss with cardiovascular safety among patients with overweight/obesity but without type 2 diabetes,^{71–73} as well as cardiovascular benefit among those with obesity and established CVD.⁷⁴ In the STEP 1 trial, among patients with overweight/obesity, semaglutide 2.4 mg/wk conferred 12.4% greater weight reduction, which is a treatment difference of -12.7 kg (28 lb), compared with placebo at 68 weeks.⁷¹ Similar weight loss results were seen with other phase 3 trials of semaglutide in the STEP 2 through 8 trials.⁷⁵ In all trials, there were more gastrointestinal side effects in the GLP1-RA-treated group, but most gastrointestinal side effects were mild to moderate and transient.
- Dual agonists of glucose-dependent insulinotropic peptide and glucagon-like peptide 1 are also emerging pharmacotherapies for weight loss. Tirzepatide, a dual glucose-dependent insulinotropic peptide/ glucagon-like peptide 1 agonist, was studied in the SURMOUNT-1 trial of 2539 adult patients without type 2 diabetes who were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) or overweight ($\text{BMI} \geq 27 \text{ kg/m}^2$) with a history of weight-related comorbidities and showed that this

demonstrated to confer a 22.1% greater reduction in body weight at 48 weeks compared with placebo in individuals with overweight or obesity at its highest dose of 12 mg subcutaneous weekly.⁷⁶ Orforglipron, a daily oral nonpeptide GLP1-RA, was shown to confer 12.4% greater weight reduction compared with placebo at 36 weeks among individuals with overweight/obesity.⁷⁷ These agents are not yet approved by the FDA but are moving forward for additional study in phase 3 trials.

- Currently, liraglutide, semaglutide, and tirzepatide are the GLP1-RA agents approved by the FDA for long-term weight management in adults with obesity or with BMI ≥ 27 kg/m² in the setting of at least 1 weight-related condition such as type 2 diabetes, hypertension, or dyslipidemia, in conjunction with a reduced-calorie diet and increased PA.
- It should be noted that GLP1-RAs are a treatment for weight management, not a cure. Weight regain is common after cessation of therapy. In the STEP 1 trial, 1 year after the discontinuation of the subcutaneous semaglutide 2.4 mg/wk, participants regained two-thirds of their prior weight loss.⁷⁸ Similar regain of lost weight was seen after cessation of tirzepatide in the SURMONT-4 trial compared with those who continued treatment.⁷⁹
- GLP1-RAs have also been shown to reduce cardiovascular events among individuals with overweight or obesity but without diabetes. A meta-analysis of 9 weight-loss RCTs of patients with overweight and obesity but without diabetes demonstrated that cardiovascular events were fewer in individuals treated with GLP1-RAs compared with placebo (8.7% versus 11.2%; RR, 0.81 [95% CI, 0.70–0.92]).⁸⁰
- Furthermore, the SELECT trial was a dedicated cardiovascular outcome trial evaluating semaglutide that enrolled patients with overweight or obesity and established CVD but without diabetes.⁷⁴ SELECT demonstrated that semaglutide compared with placebo reduced MACEs by 20% in this population (HR, 0.80 [95% CI, 0.72–0.90]) while conferring an $\approx 9\%$ weight loss (estimated treatment difference, -8.51% [95% CI, -8.75% to -8.27%]). Although data did not meet hierarchical testing for superiority, a 19% reduction in all-cause mortality was also

demonstrated with semaglutide (HR, 0.81 [95% CI, 0.71–0.93]).⁷⁴ The weight loss with semaglutide in SELECT was more modest than in the previous weight loss trials with a reduction of –8.5% (95% CI, –8.8 to –8.3) compared with placebo.

Furthermore, subgroup analysis of SELECT demonstrated no interaction of baseline BMI category with the MACE reduction conferred by semaglutide, with a significant MACE reduction seen even for those with a BMI of ≥ 27 to <30 kg/m² (HR, 0.74 [95% CI, 0.60–0.91]).⁷⁴ These findings suggest that the cardiovascular reduction conferred by semaglutide may not be entirely explained by only its weight reduction effects. After SELECT, the FDA has added a new indication for semaglutide to reduce the risk of cardiovascular events among adults with overweight and obesity and CVD but without diabetes.

- The STEP-HFpEF trials evaluated patients with BMI ≥ 30 kg/m² and HFpEF with and without diabetes and demonstrated that semaglutide conferred a weight reduction of –8.4% (95% CI, –9.2 to –7.5), as well as significant improvement in symptoms (change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, 7.5 points [95% CI, 5.3–9.8]). A reduction in time to first HF event (HR, 0.27 [95% CI, 0.12–0.56]) was also noted, although the trial was not specifically powered for clinical outcomes.⁸¹

- GLP1-RAs have also been evaluated for treatment of obesity-related conditions such as MASLD. Among patients with type 2 diabetes and MASLD, a meta-analysis showed that GLP1-RAs significantly reduced BMI (WMD, –1.57 kg/m² [95% CI, –2.72 to –0.39]), as well as WC and body weight.⁸²

Furthermore, another recent meta-analysis evaluating GLP1-RA in patients with MASLD or metabolic dysfunction–associated steatohepatitis found that semaglutide conferred a significant improvement in liver fat content (mean difference, –4.97% [95% CI, –6.65% to –3.29%]), as well as an improvement in liver enzymes.⁸³ In addition, the dual-agonist tirzepatide was found to be more effective than placebo for resolution in metabolic dysfunction–associated steatohepatitis without worsening of fibrosis (difference, 53 percentage points [95% CI, 37–69]; $P<0.001$).⁸⁴

- GLP1-RAs have also been evaluated for treatment in youths with obesity. In a meta-analysis of 9 studies including 574 children and adolescents with obesity, GLP1-RAs conferred modest reductions in BMI (WMD, –1.24 kg/m² [95% CI, –1.71 to 0.77]) and reductions in body weight (WMD, –1.50 kg [95% CI, –2.50 to –0.50]), showing efficacy and safety in youths with obesity.⁸⁵

Mortality

- Obesity-related cardiovascular deaths increased

3-fold in the United States between 1999 to 2020, with AAMR rising from 2.2 to 6.6 per 100 000

population.²⁷ The age-adjusted obesity-related

cardiovascular mortality was noted to be

highest among Black individuals (6.7 per 100 000 population),

followed by American Indian individuals

or Alaska Native individuals (3.8 per 100 000 population),

and lowest among Asian individuals

or Pacific Island individuals (0.9 per 100 000 population).²⁷

- According to data from the NHIS from 1999

through 2018, there was a 21% to 108% increase

in mortality for BMI ≥ 30 kg/m² (HR, 1.21 for BMI 30–34.9

kg/m²; HR, 1.44 for BMI 35.0–39.9 kg/m²; and HR,

2.08 for BMI ≥ 40 kg/m²) compared with a BMI of 22.5 to 24.9

kg/m².⁸⁶ For older adults

≥ 65 years of

age, there was no

- Being overweight or obese was associated with a 21% (RR, 1.21 [95% CI, 1.08–1.35]) and 52% (RR, 1.52 [95% CI, 1.31–1.77]) increased risk of SCD compared with being normal weight in a meta-analysis of >10 studies.⁹⁰
- When US data from 2016 were modeled, excess weight (BMI ≥ 25 kg/m²) was attributed to 1300 excess deaths per day, nearly 500 000 excess deaths per year, and a loss of life expectancy of 2.4 years compared with a BMI 20 to 25 kg/m²; this was a higher excess mortality than for smoking.⁹¹ This relative excess in mortality attributed to increased weight was twice as high for females compared with males (21.9% versus 13.9%) and higher for Black NH adults compared with White NH adults (22.8% versus 17.0%).
- According to GBD data, deaths attributed to elevated BMI (≥ 25 kg/m²) in Asia increased 265% from 1990 to 2019.⁹² In 1990, the death burden attributed to elevated BMI was higher in females than males, but the burden in

of developing CVD at an earlier age translates to a greater proportion of years lived with CVD morbidity.⁹⁴ In a meta-analysis of individuals with type 2 diabetes, there was a linear association between BMI and risk of CVD incidence with an RR of 1.12 (95% CI, 1.04–1.20) for each 5-unit increase in BMI.⁹⁵

Coronary Heart Disease

- Mendelian randomization studies among participants of predominantly European ancestry suggest a causal role of obesity and CAD (OR, 1.49 [95% CI, 1.39–1.60]) per 1 SD of genetically predicted BMI, although this is accounted for in part by intermediate factors such as hypertension, lipids, and diabetes.⁹⁶ After these potential cardiovascular risk mediators were accounted for, the OR for

Complications of Obesity

Cardiovascular Disease

- Obesity is associated with increased risk of adverse cardiovascular outcomes. An umbrella review examined 12 systematic reviews including 53 meta-analyses, >500 cohort studies, and 12 mendelian randomization studies.⁹³ This study found that for every 5–kg/m² increase in measured BMI, the

RR was 1.07 (95% CI, 1.02–1.12) for stroke, 1.15 (95% CI, 1.12–1.20) for CHD, 1.23 (95% CI, 1.17–1.30) for AF, 1.41 (95% CI, 1.32–1.50) for HF, and 1.49 (95% CI, 1.40–1.60) for hypertension. Mendelian randomization analyses suggest that obesity is causally related to CVD: for each 5–kg/m² increase in genetically determined BMI, the RR was 1.19 (95% CI, 1.03–1.37) for CHD, 1.23 (95% CI, 1.13–1.33) for PAD, 1.64 (95% CI, 1.47–1.82) for hypertension, and 1.92 (95% CI, 1.12–3.30) for

for each 5-unit increase in BMI.⁹³

Stroke

- In a meta-analysis of 13 observational cohort studies, the RR for ischemic stroke was 1.36 (95% CI, 1.25–1.47) for each 5-unit increase in BMI.⁹³
- In the HUNT cohort of 14 139 individuals who had their BMI measured 4 times over a 42-year period, overweight and obesity over adulthood were associated with a higher risk for ischemic stroke (HR, 1.29 [95% CI, 1.11–1.48] and 1.27 [95% CI, 0.96–1.67], respectively) compared with normal weight over adulthood.⁹⁸
- However, a prior mendelian randomization study in 694 649 subjects of primarily European descent did not find an association between genetically predicted BMI and cerebrovascular disease but did find an association between genetically predicted waist-hip-ratio and both ischemic and hemorrhagic stroke.⁹⁹

HF, but no association with stroke was seen.⁹³

- In an analysis pooling data from 10 large US prospective cohorts, lifetime risks for incident CVD were higher in middle-aged adults with overweight and obesity compared with individuals with normal weight.⁹⁴ The HR for incident CVD in males was 1.21 (95% CI, 1.14–1.28) for overweight, 1.67 (95% CI, 1.55–1.79) for obesity,

Heart Failure

and 3.14 (95% CI, 2.48–3.07) for morbid obesity. The HR for incident CVD in females was 1.32 (95% CI, 1.24–1.40) for overweight, 1.85 (95% CI, 1.72–1.99) for obesity, and 2.53 (95% CI, 2.20–2.91) for morbid obesity. Although the overweight group had a longevity similar to that of the normal BMI group, an increased risk

- In a meta-analysis of 32 observational cohort studies, the RR for HF was 1.41 (95% CI, 1.32–1.50) for each 5-unit increase in BMI.⁹³
- Another recent systematic review and meta-analysis of 35 studies including >1 million participants found that the RR of HF was 1.42 (95% CI, 1.40–1.42) for each 5–kg/m² higher BMI, 1.28 (95% CI, 1.26–1.31) for each 10-cm higher WC, and 1.33 (95% CI, 1.28–1.37) per each 0.1–unit higher waist-to-hip ratio.¹⁰⁰ The association of adiposity with HF was higher for HFpEF than for HFrEF; per 5–kg/m² higher BMI, the RR of HFpEF was 1.42 (95% CI, 1.33–1.51) and the RR for HFrEF was 1.13 (95% CI, 1.05–1.22).

- In a meta-analysis, a J-shaped relationship between BMI and HF risk. weight. the OR for incident HF 0.95–1.58) for underweight, for overweight, 1.62 (95% CI, 1.30–2.21) and 1.73 (95% CI, 1.30–2.21) that same analysis, intentional cardiac surgery was associated with improvement in LV diastology ($P < 0.0001$).¹⁰¹
- A pooled analysis across 10 cohorts examined the lifetime risk of HF.⁹⁴ For males, compared with normal weight, the lifetime risk of HF was an HR of 1.22 (95% CI, 1.07–1.40) for overweight, 1.95 (95% CI, 1.68–2.27) for obesity, MASLD, which is also strongly associated with incident HF odds of incident HF according analysis (OR, 1.60 [95% CI, 1.21–2.11]).
- Despite the increased risk of obesity, many studies have shown an “obesity paradox” wherein outcomes for patients with HF and obesity are more favorable than for individuals with HF without obesity. For example, in a study of individuals with HF with severe obesity, the HR for HF was 1.37 (95% CI, 1.21–1.55) for overweight, 2.28 (95% CI, 2.00–2.60) for obesity, and 5.26 (95% CI, 3.65–7.57) for severe obesity. For females, the HR for HF was 1.37 (95% CI, 1.21–1.55) for overweight, 2.28 (95% CI, 2.00–2.60) for obesity, and 5.26 (95% CI, 3.65–7.57) for severe obesity.

kg/m²). In a primary care cohort including 47 531 individuals with HF, there was a U-shaped relation-ship between BMI and mortality with an increased mortality risk for those with underweight (HR, 1.59 [95% CI, 1.45–1.75]) and with class III obesity (HR, 1.23 [95% CI, 1.17–1.29]) compared with healthy weight, with a decrease risk of mortality associated with overweight and class I or class II obesity.¹⁰⁶

4.32 (95% CI, 3.39–5.19) for severe obesity.

There was a stronger association of higher

Atrial Fibrillation

dent HF compared with other CVD subtypes.⁹⁴

For example, for severe obesity (BMI ≥40 kg/m²) compared with normal weight, the HR for incident HF was 5.26 (95% CI, 3.65–7.57) for males and 4.32 (95% CI, 3.39–5.19) for females, whereas the HRs for MI and stroke were 1.98 (95% CI, 1.42–2.78) and 0.75 (95% CI, 0.35–1.60) and 1.80 (95% CI, 1.41–2.30) and 1.01 (95% CI,

0.73–1.39) for MI and stroke in males and females, respectively.

Greater risk for HF compared with MI and stroke events was also seen for the overweight (BMI, 25.0–29.9 kg/m²) and obesity (BMI, 30.0–39.9 kg/m²) categories as well.

- Obesity is a strong risk factor for AF; it is associated with incident AF and persistent AF.¹⁰⁷
- Mendelian randomization studies support a causal relationship between BMI and AF risk. Genetically determined central adiposity from the UK Biobank (European ancestry) was associated with increased risk of AF, with an OR of 1.63 (95% CI, 1.26–2.12) for WC, 1.36 (95% CI, 1.11–1.67) for WHR, and 1.43 (95% CI, 1.34–1.53) for percent truncal fat.¹⁰⁸ • Similar associations have been seen for measured BMI in observational studies. In a meta-analysis of 31 observational cohort studies, the RR for AF was 1.23 (95% CI, 1.17–1.30) for each 5-unit increase

- Cumulative weight (ie, BMI-years) over a lifetime has a stronger association with incident HF. In an analysis from MESA, BMIs at 20 and 40 years of age were more strongly associated with increased risk of incident HF than BMI measured in mid to late adulthood (45–84 years of age).¹⁰² Even after accounting for present weight at later adulthood, higher BMI per 5 kg/m² (determined by self-reported weight) at 20 years of age was independently associated with an HR of incident HF of 1.27 (95% CI, 1.07–1.50), and at 40 years of age, the HR was 1.36 (95% CI, 1.18–1.57).¹⁰²
- Regionality of fat distribution influences HF risk.¹⁰³ Visceral adipose tissue, but not subcutaneous adipose tissue, was associated with incident

in BMI.⁹³

HFpEF in the MESA cohort. For each 1-SD increment in visceral adipose tissue, the HR was 2.24 (95% CI, 1.44–3.49), and for subcutaneous adipose tissue, the HR was 1.30 (95% CI, 0.79–2.12).¹⁰⁴

- Another recent meta-analysis found that both visceral fat (RR, 1.08 [95% CI, 1.04–1.12]) and pericardial fat (RR, 1.08 [95% CI, 1.06–1.10]) were associated with incident HF.¹⁰⁰

- In a large meta-analysis of 25 studies including >2 million participants, each 5-kg increase in weight was associated with a 28% greater risk of AF (RR, 1.28 [95% CI, 1.20–1.38]).¹⁰⁹ The association between BMI and AF was not linear, although there was a generally stronger association with AF with increasing BMI levels. However, even a BMI of 22.5 to 24.0 kg/m² (HR, 1.09 [95% CI, 1.04–1.13]) compared with 20 to 22.5 kg/m² (reference) also had an increased risk, with the greatest risk of AF seen for a BMI ≥40 kg/m² (HR, 3.45 [95% CI, 2.56–4.64]).
- Weight reduction may prevent AF. In a meta-analysis of patients with a history of catheter ablation for AF, those who lost weight experienced a lower risk of recurrent AF than those who did not (RR, 0.35 [95% CI, 0.18–0.67]). The reduced risk of AF after ablation was seen predominantly among patients who lost ≥10% of weight (RR, 0.18 [95% CI, 0.03–0.89]) but not for patients with <10% of weight loss (RR, 1.00 [95% CI, 0.51–1.96]).¹¹⁰ There was also a lower risk of recurrent AF among patients who lost weight before the ablation procedure.

- Weight loss of $\geq 5\%$ after treatment with an SGLT-2 inhibitor has been associated with reduced risk of new-onset AF in patients with type 2 diabetes (HR, 0.39 [95% CI, 0.22–0.68]).¹¹¹
- GLP1-RAs, which confer weight reduction, have been shown to reduce AF risk in individuals with type 2 diabetes compared with other glucose-lowering medications (OR, 0.17 [95% CI, 0.04–0.61] versus insulin, and OR, 0.18 [95% CI, 0.04–0.66] versus nonsulfonylureas in a network meta-analysis).¹¹² However, whether GLP1-RA treatment in individuals with overweight/obesity but without diabetes can prevent AF warrants further investigation.
- For patients with overweight/obesity and AF, current AHA guidelines recommend a $\geq 10\%$ reduction in weight, a BMI $< 27 \text{ kg/m}^2$, and at least a 2-MET increase in PA. Bariatric surgery could be considered in appropriate candidates.¹⁰⁷

COVID-19

- Obesity is a risk factor for severe COVID-19 and COVID-19–associated mortality.¹¹³ In a meta-analysis of 186 studies including > 1.3 million patients, the RR of mortality in COVID-19 associated with obesity was 1.45 (95% CI, 1.31–1.61) compared with those with a BMI $< 30 \text{ kg/m}^2$ with an increased risk of death of 1.12 (95% CI, 1.08–1.18) for every 5-kg/ m^2 increase in BMI.¹¹⁴ This relationship was J shaped with the lowest risk of COVID-19–associated mortality around a BMI of 22 to 24 kg/ m^2 .

$> 200\,000$ participants, children and adolescents with obesity were ≈ 5 times more likely to have obesity in adulthood. Approximately 55% of children (7–11 years of age) with obesity will have obesity in adolescence (12–18 years of age), and $\approx 80\%$ of adolescents with obesity will still have obesity in adulthood (≥ 20 years of age), with

- In the AHA COVID-19 registry, obese patients were more likely to be hospitalized with COVID-19 than non-obese patients and had greater multivariable-adjusted risk for the composite outcome of in-hospital death or mechanical ventilation (OR for class 1, 2, and 3 obesity: 1.28 [95% CI, 1.09–1.51], 1.57 [95% CI, 1.29–1.91], and 1.80 [95% CI, 1.47–2.20], respectively).¹¹⁵ There was a significant interaction with age, with severe obesity being associated with a greater risk of in-hospital death only for individuals ≤ 50 years of age (HR, 1.36 [95% CI, 1.01–1.84]). Obese patients also had greater risk of VTE (HR, 1.81 [95% CI, 1.22–2.98]).
- The STOP-COVID registry of 5133 patients admitted to critical care units with COVID-19 during March to July 2020 found that CVD risk factors rather than preexisting CVD were the major contributors to 28-day CVD events and mortality, with BMI ranking second (only after age) as the strongest predictor of risk.¹¹⁶

Complications in Youths

- Overweight and obesity in youths frequently track into adulthood. In a meta-analysis including

- 5–7), which is 19 years earlier than those who had weight status at 25 years of age (95% CI, 24–27).¹¹⁸ In the prospective the i3C Consortium, which examined childhood risk factors at 3 to 19 years of age a mean follow-up of 35 years, elevated BMI was 1.38–1.53]) per 1–z score increase in childhood weight in childhood, high-normal BMI status (HR, 1.92 [95% CI, 1.62–2.27]), and obese status (HR, increased risk of adult CVD events.
- In another meta-analysis of 22 studies including >5 million youths 2 to 19 years of age, childhood and adolescent BMI per 1-SD increment conferred a 12% increased risk of CHD in adulthood (HR, 1.12 [95% CI, 1.01–1.25]).¹²⁰ The associations did not change significantly after adjustment for SES or differ by sex.
 - A mendelian randomization study determined that genetically predicted childhood obesity was associated with mild obesity-related diabetes in adulthood (OR, 7.30 [95% CI, 4.17–12.78]) and severe insulin-resistant diabetes in adulthood (OR, 2.76 [95% CI, 1.60–4.74]).¹²¹
 - A recent cohort study assessed 801 019 youths 3 to 17 years of age in a health care system in Southern California and found that even high-normal body weight between the 60th and 84th percentiles of BMI for age was associated with incident hypertension (HR, 1.26 [95% CI, 1.20–1.33]) over 5 years compared with youths in the 40th to 59th percentile.¹²² Risk of incident hypertension was even greater for overweight (85th–94th percentile: HR, 1.91 [95% CI, 1.81–2.00]), moderately obese (95th–96th percentile: HR, 2.77 [95% CI, 2.61–2.94]), and severely obese (≥97th percentile: HR, 4.94 [95% CI, 4.72–5.18]).
 - In an NHANES analysis, obesity in youths (3–19 years of age) was associated with increased prevalence of cardiometabolic risk factors, including greater SBP and DBP, lower HDL-C, and higher levels of triglycerides and HbA1c, particularly in males.¹²³

Health Care Use and Cost

- Adjusted to 2019 US dollars, a from MEPS, a nationally and controlling for sity was associated with \$2053 in excess costs per individuals with obesity with normal weight.¹²⁴ Severe ated with excess annual costs \$2777–\$3413) per person 1-unit increase in BMI >30 with an additional \$253 (95% per year per person.
 - Obesity in children was CI, \$14–\$201) in excess costs billion in medical spending ing \$310 (95% CI, \$124–\$474)
- Medical expenditures associated were greater among J-shaped relationship tures and BMI with the lowest a BMI of 20.5 kg/m² for adult m² for adult males.
- In another MEPS analysis, it was the total direct medical cost noninstitutionalized adults in \$260.0 billion in 2016, more 2001 (\$124.2 billion).¹²⁵
- Globally, the GBD Study 2021 BMI ranked 7 (ie, in the top tors attributable to the burden 95 (95% CI, 1.12–2.91) to CVD and 3.7 (95% CI, resulting from any cause).¹²⁸ DALYs from all causes 1560 per 100 000 (95% CI.
- Data from the GBD Study (≥25 kg/m²) related DALYs annually from 2000 to 2019 predicted to increase by 2020 and 2030. The highest were observed in Eastern middle-SDI countries.¹²⁹ High- the lowest obesity-related
- Based on 204 countries and age-standardized mortality BMI among regions were Asia Pacific and highest for Africa, North Africa and the (Chart 6-4). Globally, high (95% UI, 1.85–5.66) million increase of 154.13% (95% UI, compared with 1990 (Table 6-
- Trends in global CVD 100 000 by measure from YLLs, mortality, and DALYs shown in Chart 6-5.¹³⁰

Global Burden of Disease

(See Tables 6-4 and 6-5 and Charts 6-4 and 6-5)

- According to WHO statistics, in 2022, it was estimated that among adults ≥18 years of age globally, 16% (890 million) were obese and 43% (2.5 billion) were overweight, with the worldwide prevalence of obesity doubling between 1990 and 2022.¹²⁶
- In 2022, an estimated 37 million children <5 years of age were overweight and >390 million youths 5 to 19 years of age were overweight, including 160 million (8%) living with obesity.¹²⁶
- The World Obesity Federation's 2024 Obesity Atlas reported that in 2020, 42% of adults globally had overweight or obesity, and this was projected to rise to 54% by 2023. In 2020, 1.39 billion and 0.81 billion adults had overweight (≥25–30 kg/m²) and obesity (≥30 kg/m²), respectively, and this was projected to increase to 1.77 billion and 1.53 billion, respectively, by 2023.¹²⁷
- The prevalence of obesity is increasing more rapidly in lower-income countries. In this same report, it was further estimated that 79% of adults and 88% of children with overweight and obesity will live in low- and middle-income countries by 2035.¹²⁷

- Although the rate of increase in obesity prevalence seems to be declining in most high-income countries, the prevalence rate continues to rise in many low- and middle-income countries.¹²⁷ Data from the Non-Communicable Disease Risk Factor Collaboration reported that increases in BMI in rural areas accounted for >55% of the global rise in mean BMI from 1985 to 2017 and >80% of the rise in some low- and middle-income regions.¹³¹ These data challenge the notion that urbanization is responsible for the obesity epidemic and call attention to the need for improvement in prevention strategies and CVH in rural areas.
- Overweight and obesity contribute to significant economic costs globally. A recent analysis estimated that the negative economic impact of overweight and obesity in 2019 across 161 countries was 2.2% of the global GDP.¹³² Furthermore, if these trends continue at same rate, the economic impact of overweight and obesity is estimated to rise to 3.3% of the global GDP by 2060, with the largest increases being concentrated in lower-resource countries.
- The World Obesity Federation estimated that the economic impact of an elevated BMI could reach as much as \$4.32 trillion annually by 2035, which is ≈3% of the GDP, an increase from \$1.96 trillion or 2.4% of the global GDP in 2020.¹²⁷

Table 6-1. Prevalence of Children and Adolescents 2 to 19 Years of Age With Obesity, by Demographic Characteristics: United States, 2017 to March 2020

Characteristic	Both sexes		Males		Females	
	Sample size, n	Prevalence percentage	Sample size, n	Prevalence percentage	Sample size, n	Prevalence percentage (95%)
Total	4749	19.7 (17.9–21.6)	2410	20.9 (18.9–22.9)	2339	18.5 (16.3–21.0)
Age group, y						
2–5	1141	12.7 (10.8–14.8)	566	13.6 (10.8–16.8)	575	11.8 (9.3–14.8)
6–11	1765	20.7 (17.9–23.7)	894	22.9 (19.5–26.5)	871	18.5 (15.2–22.1)
12–19	1843	22.2 (19.7–24.8)	950	22.6 (19.7–25.7)	893	21.7 (18.1–25.7)
Race and ethnicity						
NH White	1471	16.6 (13.7–19.8)	743	17.6 (14.8–20.7)	728	15.4 (11.2–20.5)
NH Black	1270	24.8 (21.6–28.1)	662	18.8 (15.9–22.1)	608	30.8 (26.0–35.8)
NH Asian	420	9.0 (6.5–12.2)	208	13.1 (8.8–18.4)	212	5.2 (2.3–9.9)
Hispanic	1143	26.2 (22.4–30.2)	562	29.3 (23.1–36.0)	581	23.0 (19.6–26.6)
Family income relative to FPL						
≤130	1748	25.8 (22.8–29.1)	864	26.4 (22.4–30.8)	884	25.2 (22.3–28.3)
130–350	1514	21.2 (18.5–24.0)	789	20.7 (17.6–24.1)	725	21.7 (18.3–25.3)
>350	956	11.5 (8.9–14.5)	471	15.1 (11.1–19.8)	485	8.2 (5.0–12.5)

Obesity is defined as a body mass index greater than or equal to the age- and sex-specific 95th percentile of the 2000 Centers for Disease Control and Prevention growth charts. Children and adolescents were included and categorized into age categories based on age at examination in months. Pregnant females were excluded from the analysis. FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al⁸ using National Health and Nutrition Examination Survey.¹³³

Table 6-2. Prevalence of Adults ≥20 Years of Age With Obesity, by Demographic Characteristics: United States, 2017 to March 2020

Characteristic	Both sexes		Males		Females	
	Sample size, n	Prevalence percentage (95%)	Sample size, n	Prevalence percentage	Sample size, n	Prevalence percentage (95%)
Total (age adjusted)	8295	41.9 (39.4–44.3)	4051	41.8 (37.7–45.9)	4244	41.8 (39.3–44.4)
Total age (crude)	8295	41.9 (39.4–44.3)	4051	41.6 (37.4–45.8)	4244	42.1 (39.6–44.8)
Age group, y						
20–39	2489	39.8 (35.3–44.3)	1177	39.9 (33.1–47.0)	1312	39.6 (34.9–44.3)
40–59	2765	44.3 (41.3–47.4)	1320	45.9 (41.0–50.9)	1445	42.8 (38.7–47.1)
≥60	3041	41.5 (38.4–44.7)	1554	38.4 (32.9–44.1)	1487	44.2 (40.5–47.9)
Race and ethnicity						
NH White	2866	41.4 (37.9–44.9)	1432	43.1 (37.4–48.9)	1434	39.6 (36.2–43.0)
NH Black	2213	49.9 (47.2–52.6)	1058	40.4 (36.3–44.6)	1155	57.9 (54.0–61.7)
NH Asian	1014	16.1 (13.6–18.9)	466	17.6 (13.7–22.2)	548	14.5 (11.4–18.1)
Hispanic	1806	45.6 (42.9–48.2)	880	45.2 (41.7–48.8)	926	45.7 (42.4–49.1)
Family income relative to FPL						
≤130	2019	43.9 (41.7–46.1)	892	38.6 (33.6–43.8)	1127	47.9 (44.0–51.7)
130–350	2815	46.5 (43.6–49.4)	1400	43.9 (40.5–47.3)	1415	48.8 (44.5–53.0)
>350	2312	39.0 (34.2–43.9)	1189	42.4 (34.9–50.2)	1123	35.1 (31.1–39.3)

Education						
Less than high	1538	40.1 (36.5–43.8)	803	35.3 (30.4–40.6)	735	45.3 (41.0–49.7)
High school diploma	4709	46.4 (44.0–48.9)	2259	45.9 (41.9–50.0)	2450	46.8 (43.9–49.8)
College degree or	2037	34.2 (30.1–38.5)	984	36.3 (29.0–44.1)	1053	32.2 (28.5–36.1)

Obesity is defined as a body mass index ≥ 30 kg/m². Except when reported as crude estimates, estimates were age adjusted by the direct method to the projected US Census 2000 population using the age groups 20 to 39, 40 to 59, and ≥ 60 years. Statistical comparisons were not performed on crude estimates. Pregnant individuals were excluded from the analysis.

FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al⁸ using National Health and Nutrition Examination Survey.¹³³

Table 6-3. Prevalence of Adults ≥20 Years of Age With Severe Obesity, by Demographic Characteristics, United States, 2017 to March 2020

Characteristic	Both sexes		Males	
	Sample size, n	Prevalence percentage (95% CI)	Sample size, n	Prevalence percentage (95% CI)
Total (age adjusted)	8295	9.2 (8.0–10.6)	4051	6.6 (5.3–8.1)
Total age (crude)	8295	9.0 (7.8–10.3)	4051	6.4 (5.1–8.0)
Age group, y				
20–39	2489	9.7 (7.7–12.0)	1177	7.0 (4.7–10.1)
40–59	2765	10.7 (8.9–12.8)	1320	8.1 (5.5–11.5)
≥60	3041	6.1 (5.2–7.2)	1554	3.5 (2.6–4.5)
Race and ethnicity				
NH White	2866	9.5 (7.9–11.3)	1432	6.8 (5.1–8.9)
NH Black	2213	14.0 (11.9–16.3)	1058	7.9 (6.3–9.7)
NH Asian	1014	1.8 (1.0–2.8)	466	2.4 (0.9–5.1)
Hispanic	1806	7.4 (6.1–8.9)	880	6.0 (4.2–8.4)
Family income				

Severe obesity is defined as a body mass index ≥ 40 kg/m². Except when reported as crude estimates, estimates were age adjusted by the direct method to the projected US Census 2000 population using the age groups 20 to 39, 40 to 59, and ≥ 60 years. Statistical comparisons were not performed on crude estimates. Pregnant individuals were excluded from the analysis.

FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al⁸ using National Health and Nutrition Examination Survey.¹³³

Table 6-4. DALYs and Mortality of Individuals With Obesity From the GBD Study 2019

	DALYs				Mortality			
	n (Year 2019)	Age-standardized DALYs per 100 000 in 2019	Annual percent age change	P value	n (Year 2019)	Age-standardized death rate per 100 000	Annual percentage change 2000–	P value
Overall	160 265 357 (105 969)	1933 (1277–2640)	0.48 (0.38–0.58)	<0.001	5 019 360 (3 223 364–7 110)	62.59 (39.92–89.13)	–0.01 (–0.13 to 0.11)	0.881
Sex								
Male	82 840 928 (52 774 866–115)	2070 (1312–2889)	0.74 (0.63–0.85)	<0.001	2 477 387 (1 515 677–3 568 860)	66.55 (39.76–97.21)	0.33 (0.15–0.52)	<0.001
Female	77 424 429 (53 176)	1790 (1229–2417)	0.25 (0.17–0.34)	<0.001	2 541 973 (1 683 590–3 561 055)	58.14 (38.53–81.39)	–0.27 (–0.38 to –0.16)	<0.001
WHO region								
Africa	12 324 913 (8 371)	2221 (1486–3025)	0.87 (0.80–0.95)	<0.001	361 539 (237 293–499 448)	79.20 (50.92–111.98)	0.86 (0.78–0.94)	<0.001
Eastern Mediterranean	17 923 202 (12 584 59–)	3721 (2591–4954)	1.04 (0.92–1.15)	<0.001	522 392 (352–707 166)	130.97 (87.38–179.78)	1.01 (0.87–1.14)	<0.001

(Continued)

Table 6-4. Continued

	DALYs				Mortality			
	n (Year 2019)	Age-standardized DALYs per 100 000 in 2019	Annual percent age change	P value	n (Year 2019)	Age-standardized death rate per 100 000	Annual percentage change 2000–	P value
Europe	32 474 360 (22 183)	2206 (1519–2946)	–0.90 (–1.10 to –0.70)	<0.001	1 243 937 (810 492–1	75.41 (49.74–103.02)	–1.16 (–1.41 to –0.89)	<0.001
Region of Americas	30 395 450 (21 207 720–39 622	2457 (1725–3200)	0.17 (0.09–0.26)	<0.001	940 265 (625 116–1 268	72.83 (48.62–97.90)	–0.27 (–0.44 to –0.10)	0.002
Southeast Asia	33 558 095 (20 816 783–46 899	1786 (1096–2513)	2.63 (2.48–2.77)	<0.001	918 795 (550 880–1 327	53.60 (31.54–78.85)	2.37 (1.93–2.81)	<0.001
Western Pacific	33 058 032 (16 759	1229 (624–1963)	1.22 (0.98–1.46)	<0.001	1 015 716 (483 041–1	38.38 (18.10–64.89)	0.87 (0.48–1.26)	<0.001
SDI								
High	26 809 080 (18 213 631–36 348	1631 (1121–2198)	–0.14 (–0.19 to –0.09)	<0.001	901 712 (573 462–1 289	45.65 (29.76–63.76)	–1.02 (–1.20 to –0.84)	<0.001
High-middle	39 587 645 (26 141	1982 (1312–2706)	–0.91 (–1.09 to –0.73)	<0.001	1 376 628 (877 166–1	69.14 (44.00–98.24)	–1.21 (–1.44 to –0.99)	<0.001
Middle	55 465 889 (36 710 764–	2119 (1388–2920)	1.26 (1.18–1.35)	<0.001	1 647 (1 051 542–2 333 137)	68.92 (43.02–99.26)	1.05 (0.92–1.19)	<0.001
Low-middle	28 007 122 (17 469	1892 (1174–2682)	2.41 (2.18–2.63)	<0.001	804 748 (490 930–1 158	60.34 (36.27–88.37)	2.07 (1.79–2.36)	<0.001
Low	10 276 830 (6 088	1698 (990–2492)	1.87 (1.79–1.94)	<0.001	285 468 (162 714–429 330)	55.55 (31.38–85.09)	1.68 (1.59–1.78)	<0.001

Data in the parentheses are 95% uncertainty intervals.

DALY indicates disability-adjusted life-year; GBD, Global Burden of Disease; SDI, sociodemographic index; and WHO World Health Organization.

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Table 6-5. Deaths Caused by High BMI Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	3.71 (1.85 to 5.66)	1.70 (0.86 to 2.64)	2.01 (0.98 to 3.08)
Percent change (%) in total number, 2000–2021	154.13 (138.15 to 170.49)	168.61 (148.95 to 187.41)	143.08 (125.70 to 162.94)
Rate per 100,000, age 20–79, 2021	42.81 (36.71 to 48.87)	43.79 (36.29 to 51.45)	41.99 (34.92 to 49.16)
Rate per 100,000, age 20–79, 2000–2021	44.23 (22.01 to 67.64)	44.90 (23.01 to 70.17)	43.26 (21.08 to 66.05)
Percent change (%) in rate, age 20–79, 2000–2021	8.15 (1.37 to 15.14)	15.06 (6.35 to 22.98)	4.06 (–3.28 to 11.93)
Percent change (%) in rate, age 20–79, 2000–2021	3.38 (–0.84 to 7.83)	4.85 (–0.20 to 10.42)	2.60 (–2.47 to 8.09)
PAF (%), all ages, 2021	5.46 (2.74 to 8.27)	4.50 (2.29 to 6.83)	6.67 (3.22 to 10.14)
Percent change (%) in PAF, all ages, 2000–2021	72.59 (62.49 to 83.38)	76.83 (66.55 to 88.24)	71.39 (60.75 to 83.63)
Percent change (%) in PAF, all ages, 2000–2021	11.66 (8.11 to 15.42)	10.82 (7.45 to 14.61)	12.99 (8.99 to 17.10)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

BMI indicates body mass index; GBD, Global Burden of Diseases, Injuries, and Risk Factors; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³⁴

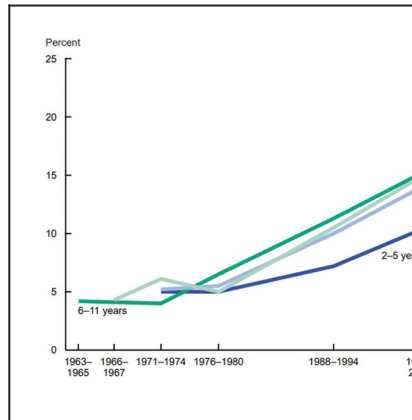


Chart 6-1. Trends in obesity among children and adolescents 2 to 19 years of age, by age, United States, 1963 to 1965 through 2017 to 2018.

Obesity is a body mass index at or above the 95th percentile from the sex-specific BMI-for-age Centers for Disease Control and Prevention Growth Charts.

Source: Reprinted from Fryar et al¹² using National Health and Nutrition Examination Survey.¹³³

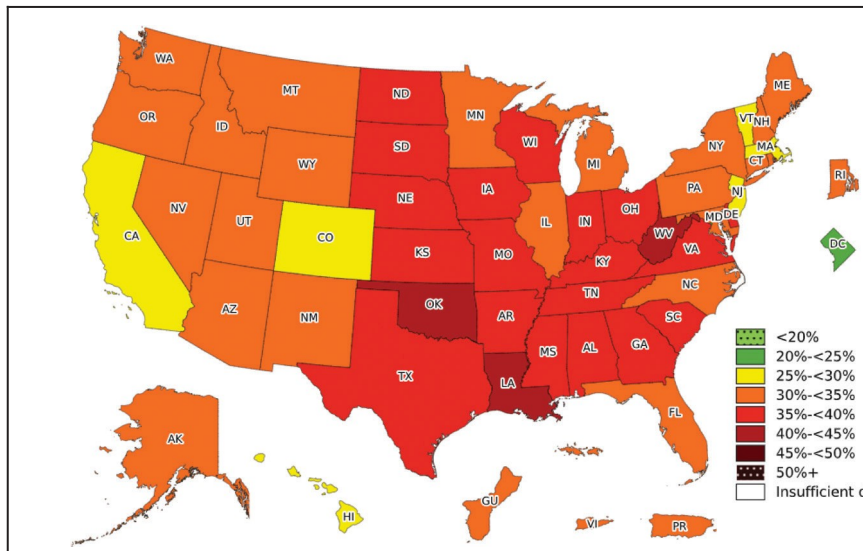


Chart 6-2. Prevalence of self-reported obesity among US adults by state and territory, BRFSS, 2022.

BRFSS indicates Behavioral Risk Factor Surveillance System.
*Sample size <50, the relative standard error (dividing the standard error by the prevalence) $\geq 30\%$, or no data

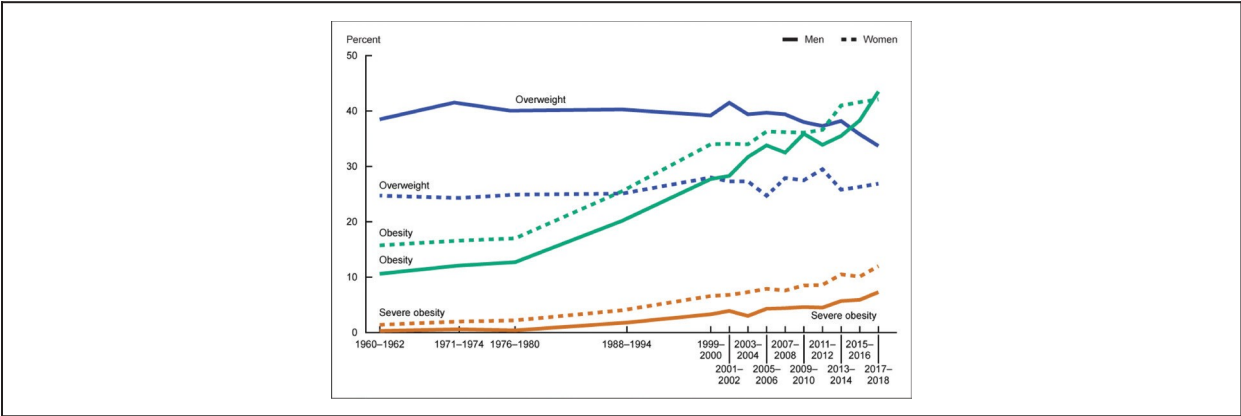


Chart 6-3. Age-adjusted trends in overweight, obesity, and severe obesity among males and females 20 to 74 years of age: United States, 1960 to 1962 through 2017 to 2018.

Data are age adjusted by the direct method to US Census 2000 estimates using age groups 20-39, 40-59, and 60-74. Overweight is body mass index of 26.0-29.9 kg/m². Obesity is body mass index at or above 30.0 kg/m². Severe obesity is body mass index at or above 40.0 kg/m². Pregnant women are excluded from the analysis. Source: Reprinted from Fryar et al¹⁹ using National Health and Nutrition Examination Survey.¹³³

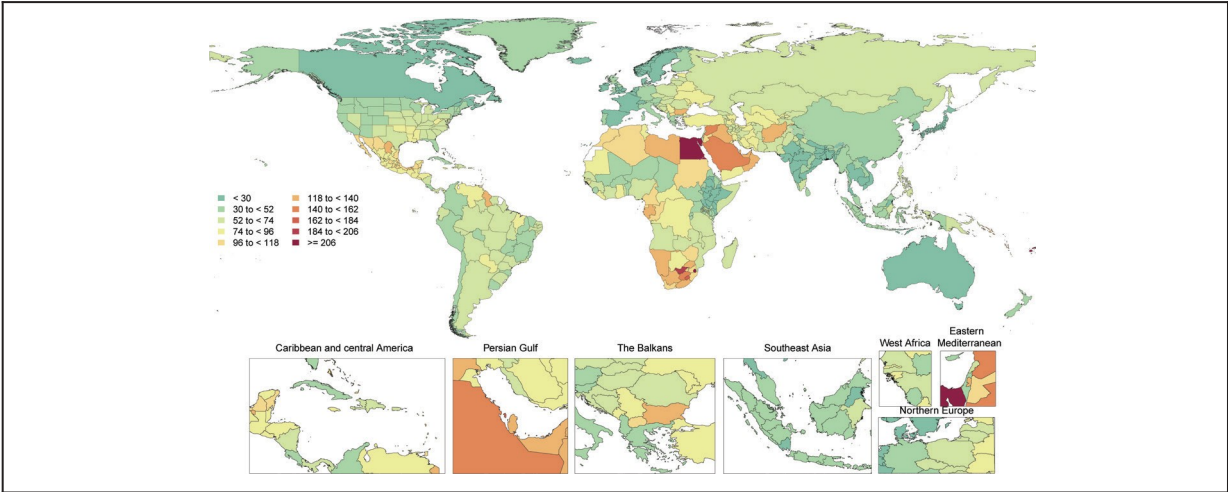


Chart 6-4. Age-standardized mortality rates attributable to high BMI per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. BMI indicates body mass index; and GBD, Global Burden of Diseases, Injuries, and Risk Factors. Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹³⁴

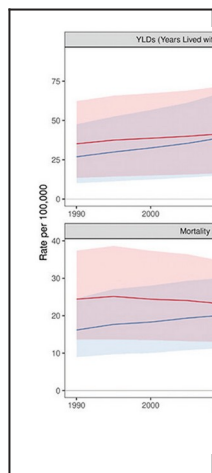


Chart 6-5. Global CVD attributable to high BMI estimates per 100 000 by measure with shaded 95% uncertainty, trends from 1990 to 2022 for YLD, YLL, mortality, and DALYs for all ages and age standardized.

10. Bekelman TA, Dabelea D, Ganiban JM, Law A, McGovern Reilly A, Althoff KN, Mueller N, Camargo CA Jr, Duarte CS, Dunlon AL, et al: Program Collaborators for Environmental Influences on Child Health Outcomes (ECHO). Regional and sociodemographic differences in average BMI among US children in the ECHO program. *Obesity (Silver Spring)*. 2021;29:2089–2099. doi: 10.1002/obv.23235
11. State of Childhood Obesity. Accessed February 22, 2024.
12. Flegal DM, Carroll MD, Afari J. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. *NCHS Health E-Stats*. 2020. Accessed October 22, 2024.
13. Carroll MD, Flegal DM. Total and high-density lipoprotein cholesterol in adults: United States, 2015–2018. *NCHS Data Brief*. 2020;290:1–8.
14. Stierman B, Onden CL, Yanovski JA, Martin CB, Sarafrazi N, Hales CM. Changes in adiposity among children and adolescents in the United States, 1999–2006 to 2011–2018. *Am J Clin Nutr*. 2021;114:1495–1504. doi: 10.1093/ajcn/nqab237
15. Hu K, Staiano AE. Trends in obesity prevalence among children and ado-

BMI indicates body mass index; CVD, cardiovascular disease; DALY, disability-adjusted life year; YLD, years of life lived with disability or injury; and YLL, years of life lost to premature mortality.

Source: Reprinted from Mensah et al.¹³⁰

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lescents aged 2 to 19 years in the US from 2011 to 2020. *JAMA Pediatr.* 2022;176:1037–1039. doi: 10.1001/jamapediatrics.2022.2052

16. Centers for Disease Control and Prevention. Adult obesity prevalence maps. U.S. Department of Health and Human Services; 2023. Accessed October 25, 2024.

17 . Deleted in proof.

18. Deleted in proof.

19. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. *NCHS Health E-Stats.* 2020. Accessed October 22, 2024.

20. Ogden CL, Fryar CD, Martin CB, Freedman DS, Carroll MD, Gu Q,

REFERENCES

1. Centers for Disease Control and Prevention. Defining adult overweight & obesity. Accessed February 22, 2024.

Hales CM. Trends in obesity prevalence by race and Hispanic origin: 1999-2000 to 2017-2018. *JAMA.* 2020;324:1208–1210. doi:

10.1001/jama.2020.14590

21. Restrepo BJ. Obesity prevalence among U.S. adults during the
10.1016/j.amepre.2022.01.012

COVID-19 pandemic. *Am J Prev Med.* 2022;63:102–106. doi:

2. Bianchetti RG, Lavie CJ, Lopez-Jimenez F. Challenges in
cardiovascular evaluation and management of obese patients: JACC
state-of-the-art review. *J Am Coll Cardiol.* 2023;81:490–504. doi:
10.1016/j.jacc.2022.11.031 3. Powell-Wiley TM, Poirier P, Burke LE,
Despres JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE,
Neeland IJ, Sanders P, et al; on behalf of the American Heart Association
Council on Lifestyle and Cardiometabolic Health; Council on

Cardiovascular and Stroke Nursing; Council on
Clinical Cardiology; Council on Epidemiology and
Prevention; and Stroke Council. Obesity and
cardiovascular disease: a scientific statement from the
American Heart Association. *Circulation.* 2021;143:e984–
e1010. doi:

22. Joynt Maddox KE, Elkind MSV, Aparicio HJ, Commodore-Mensah Y, de Ferranti SD, Dowd WN, Hernandez AF, Khavjou O, Michos ED, Palaniappan L, et al; on behalf of the American Heart Association. Forecast-ing the burden of cardiovascular disease and stroke in the United States through 2050: prevalence of risk factors and disease: a presidential advisory from the American Heart Association. *Circulation*. 2024;150:e65–e88. doi: 10.1161/CIR.0000000000001256
23. Crouch E, Abshire DA, Wirth MD, Hung P, Benavidez GA. Rural-urban differences in overweight and obesity, physical activity, and food security among children and adolescents. *Prev Chronic Dis*. 2023;20:E92. doi: 10.1161/CIR.0000000000000973 10.5888/pcd20.230136
4. Hampl SE, Hassink SG, Skinner AC, Armstrong SC, Barlow SE, Bolling CF, Avila Edwards KC, Eneli I, Hamre R, Joseph MM, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. *Pediatrics*. 2023;151:e2022060641. doi: 10.1542/peds.2022-060641
5. Lopez-Jimenez F, Almahmeed W, Bays H, Cuevas A, Di Angelantonio E, le Roux CW, Sattar N, Sun MC, Wittert G, Pinto FJ, et al. Obesity and cardiovascular disease: mechanistic insights and management strategies: a joint position paper by the World Heart Federation and World Obesity Federation. *Eur J Prev Cardiol*. 2022;29:2218–2237. doi: 10.1093/eurjpc/zwac187
6. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: Standards of Care in Diabetes—2024. *Diabetes Care*. 2023;47:S20–S42. doi: 10.2337/dc24-S002
7. Caleyachetty R, Barber TM, Mohammed NI, Cappuccio FP, Hardy R, Mathur R, Banerjee A, Gill P. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2021;9:419–426. doi: 10.1016/S2213-8587(21)00088-7
8. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, Fryar CD, Gu S, Hales CM, Hughes JP, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Rep*. 2021;158:1–21. doi: <https://dx.doi.org/10.15620/cdc:106273>
9. Martin CB, Stierman B, Yanovski JA, Hales CM, Sarafrazi N, Ogden CL. Body fat differences among US youth aged 8-19 by race and Hispanic origin, 2011-2018. *Pediatr Obes*. 2022;17:e12898. doi: 10.1111/ijpo.12898

24. Contreras DA, Martoccio TL, Brophy-Herb HE, Horodynski M, Peterson KE, Miller AL, Senehi N, Sturza J, Kaciroti N, Lumeng JC. Rural-urban differences in body mass index and obesity-related behaviors among low-income preschoolers. *J Public Health (Oxf)*. 2021;43:e637–e644. doi: 10.1093/pubmed/fdaa162

25. Cohen SA, Nash CC, Byrne EN, Mitchell LE, Greaney ML. Black/White disparities in obesity widen with increasing rurality: evidence from a national survey. *Health Equity*. 2022;6:178–188. doi: 10.1089/heq.2021.0149

26. Lundeen EA, Park S, Pan L, O'Toole T, Matthews K, Blanck HM. Obesity prevalence among adults living in metropolitan and nonmetropolitan counties—United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67:653–658. doi: 10.15585/mmwr.mm6723a1

27. Raisi-Estabragh Z, Kobo O, Mieres JH, Bullock-Palmer RP, Van Spall HGC, Breathett K, Mamas MA. Racial disparities in obesity-related cardiovascular mortality in the United States: temporal trends from 1999 to 2020. *J Am Heart Assoc*. 2023;12:e028409. doi: 10.1161/JAHA.122.028409

28. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition, Physical Activity, and Obesity. Data, trend and maps. Accessed February 22, 2024.

29. Javed Z, Valero-Elizondo J, Maqsood MH, Mahajan S, Taha MB, Patel KV, Sharma G, Hagan K, Blaha MJ, Blankstein R, et al. Social determinants

- of health and obesity: findings from a national study of US adults. *Obesity (Silver Spring)*. 2022;30:491–502. doi: 10.1002/oby.23336
30. Riveros-McKay F, Mistry V, Bounds R, Hendricks A, Keogh JM, Thomas H, Henning E, Corbin LJ, Understanding Society Scientific Group, O’Rahilly S, et al, Zeggini E, et al. Genetic architecture of human thinness compared to severe obesity. *PLoS Genet*. 2019;15:e1007603. doi: 10.1371/journal.pgen.1007603
31. Herrera BM, Lindgren CM. The genetics of obesity. *Curr Diab Rep*. 2010;10:498–505. doi: 10.1007/s11892-010-0153-z
32. Kaur Y, de Souza RJ, Gibson WT, Meyre D. A systematic review of genetic syndromes with obesity. *Obes Rev*. 2017;18:603–634. doi: 10.1111/obr.12531
33. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to *Rev Genet*. 2022;23:120–133. doi: 10.1038/s41576-021-00414-z
34. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, et al; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; index with cardiometabolic health from childhood through midlife. *Circ Genom Precis Med*. 2022;15:e003375. doi: 10.1161/CIRCGEN.121.003375
48. Sakaue S, Kanai M, Karjalainen J, Akiyama M, Kurki M, Matoba N, Takahashi A, Hirata M, Kubo M, Matsuda K, et al. Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan. *Nat Med*. 2020;26:542–548. doi: 10.1038/s41591-020-0785-8
49. He C, Zhang M, Li J, Wang Y, Chen L, Qi B, Wen J, Yang J, Lin S, Liu D, et al. Novel insights into the consequences of obesity: a phenotype-wide mendelian randomization study. *Eur J Hum Genet*. 2022;30:540–546. doi: 10.1038/s41431-021-00978-8
- CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MIGen Consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518:197–206. doi:

- ses of weight loss interventions identify a potential role for NKX6.3 in metabolism. *Nat Commun.* 2019;10:540. doi: 10.1038/s41467-019-08492-8 51.
- Papandonatos GD, Pan Q, Pajewski NM, Delahanty LM, Peter I, Erar B, Ahmad S, Harden M, Chen L, Fontanillas P, et al; GIANT Consortium, Diabetes Prevention Program and the Look AHEAD Research Groups. Genetic predisposition to weight loss and regain with lifestyle intervention: analyses from the Diabetes Prevention Program and the Look AHEAD randomized controlled trials. *Diabetes.* 2015;64:4312–4321. doi: 10.2337/db15-0441
- 10.1038/nature14177
35. Ng MCY, Graff M, Lu Y, Justice AE, Mudgal P, Liu CT, Young K, Yanek LR, Feitosa MF, Wojczynski MK, et al; Bone Mineral Density in Childhood Study (BMDCS) Group. Discovery and fine-mapping of
52. Lee WJ, Lim JE, Kang JO, Ha TW, Jung HU, Kim DJ, Baek EJ, Kim HK, adiposity loci using high density imputation of genome-wide association studies in individuals of African ancestry: African Ancestry Anthropometry Genetics Consortium. *PLoS Genet.* 2017;13:e1006719. doi: 10.1371/journal.pgen.1006719

- Chung JY, Oh B. Smoking-interaction loci affect obesity traits: a gene-smoking stratified meta-analysis of 545,131 Europeans. *Lifestyle Genom.* 2022;15:87–97. doi: 10.1159/000525749
53. Kichaev G, Bhatia G, Loh PR, Gazal S, Burch K, Freund MK, Schoech A, Pasaniuc B, Price AL. Leveraging polygenic functional enrichment to improve GWAS power. *Am J Hum Genet.* 2019;104:65–75. doi: 10.1016/j.ajhg.2018.11.008
36. Felix JF, Bradfield JP, Monnereau C, van der Valk RJ, Stergiakouli E, Chesir A, Gaillard R, Feenstra B, Thiering E, Kreiner-Moller E, et al; Bone Mineral Density in Childhood Study (BMDCS) Early Growth Genetics Consortium and Bone Mineral Density in Childhood Study. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. *Hum Mol Genet.* 2016;25:389–403. doi: 10.1093/hmg/ddv472
37. Speakman JR. The “fat mass and obesity related” (FTO) gene: mechanisms of impact on obesity and energy balance. *Curr Obes Rep.* 2015;4:73–91. doi: 10.1007/s13679-015-0143-1
38. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. *Nat Rev Endocrinol.* 2014;10:51–61. doi: 10.1038/nrendo.2013.227
39. Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, Yoon D, Lee MH, Kim DJ, Park M, et al. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat Genet.* 2009;41:527–534. doi: 10.1038/ng.357
40. Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L, Chen CH, Delahanty RJ, Okada Y, Tabara Y, et al; Genetic Investigation of Anthropometric Traits (GIANT) Consortium. Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat Genet.* 2012;44:307–311. doi: 10.1038/ng.1011

54. Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, Datta G, Davila-Velderrain J, McGuire D, Tian C, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet.* 2019;51:237–244. doi: 10.1038/s41588-018-0307-5
55. Chen Y, Dawes PT, Matthey DL. Polymorphism in the vascular endothelial growth factor A (VEGFA) gene is associated with serum VEGF-A level and disease activity in rheumatoid arthritis: differential effect of cigarette smoking. *Cytokine.* 2012;58:390–397. doi: 10.1016/j.cyto.2012.02.018
56. Hodder RK, O'Brien KM, Lorien S, Wolfenden L, Moore THM, Hall A, Yoong SL, Summerbell C. Interventions to prevent obesity in school-aged children 6-18 years: an update of a Cochrane systematic review and meta-analysis including studies from 2015-2021. *EClinicalMedicine.* 2022;54:101635. doi: 10.1016/j.eclinm.2022.101635
57. Fowler LA, Grammer AC, Staiano AE, Fitzsimmons-Craft EE, Chen L, Yaeger LH, Wilfley DE. Harnessing technological solutions for childhood obesity prevention and treatment: a systematic review and meta-analysis of current applications. *Int J Obes (Lond).* 2021;45:957–981. doi: 10.1038/s41366-021-00765-x
58. Mamalaki E, Poulimeneas D, Tsiampalis T, Kouvari M, Karipidou M, Senol-Cosar O, Haas ME, Bick A, et al. Polygenic prediction of weight and obesity trajectories from birth to adulthood. *Cell.* 2019;177:587–596.e9. doi: 10.1016/j.cell.2019.03.028
41. Okada Y, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N, Maeda S, Wen W, Dorajoo R, Go MJ, et al; GIANT Consortium. Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat Genet.* 2012;44:302–306. doi: 10.1038/ng.1086
45. Sulc J, Mounier N, Gunther F, Winkler T, Wood AR, Frayling TM, Heid IM, Robinson MR, Kutalik Z. Quantification of the overall contribution of gene-environment interaction for obesity-related traits. *Nat Commun.* 2020;11:1385. doi: 10.1038/s41467-020-15107-0
42. Monda KL, Chen GK, Taylor KC, Palmer C, Edwards TL, Lange LA, Ng MC, Adeyemo AA, Allison MA, Bielak LF, et al; NABEC Consortium. A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. *Nat Genet.* 2013;45:690–696. doi: 10.1038/ng.2608
46. Ding Y, Hou K, Burch KS, Lapinska S, Prive F, Vilhjalmsdottir B, Sankararaman S, Pasaniuc B. Large uncertainty in individual polygenic risk score estimation impacts PRS-based risk stratification. *Nat Genet.* 2022;54:30–39. doi: 10.1038/s41588-021-00961-5
43. Akbari P, Gilani A, Sosina O, Kosmicki JA, Khromin L, Fang YY, Persaud T, Garcia V, Sun D, Li A, et al. Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. *Science.* 2021;373:eabf8683. doi: 10.1126/science.abf8683
47. Shi M, Chen W, Sun X, Bazzano LA, He J, Razavi AC, Li C, Qi L, Khera AV, Kelly TN. Association of genome-wide polygenic risk score for body mass
44. Khera AV, Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, Distefano

Bathrellou E, Collins CE, Panagiotakos DB, Yannakoulia M. The effectiveness of technology-based interventions for weight loss maintenance: a systematic review of randomized controlled trials with meta-analysis. *Obes Rev*. 2022;23:e13483. doi: 10.1111/obr.13483

59. Martin JC, Awoke MA, Misso ML, Moran LJ, Harrison CL. Preventing weight gain in adults: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev*. 2021;22:e13280. doi: 10.1111/obr.13280

60. Look AHEAD Research Group; Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C, Evans M, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2016;4:913–921. doi: 10.1016/S2213-8587(16)30162-0

61. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, MacLennan G. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ*. 2017;359:j4849. doi: 10.1136/bmj.j4849

62. Arterburn D, Wellman R, Emiliano A, Smith SR, Odegaard AO, Murali S, Williams N, Coleman KJ, Courcoulas A, Coley RY, et al; PCORnet Bariatric Study Collaborative. Comparative effectiveness and safety of bariatric procedures for weight loss: a PCORnet cohort study. *Ann Intern Med*. 2018;169:741–750. doi: 10.7326/M17-2786

63. O'Brien PE, Hindle A, Brennan L, Skinner S, Burton P, Smith A, Crosthwaite G, Brown W. Long-term outcomes after bariatric surgery: a systematic review and meta-analysis of weight loss at 10 or more years for all bariatric procedures.

- dures and a single-centre review of 20-year
tric banding. *Obes Surg*. 2019;29:3–14. doi:
64. Svn NL, Cummins DE, Wang LZ, Lin DJ,
Chew CA, Loo YE, Tai BC, et al. Association
gerv with long-term survival in adults with
stage meta-analysis of matched cohort and
studies with 174 772 participants. *Lancet*.
10.1016/S0140-6736(21)00591-2
65. van Veldhuisen SL, Gorter TM, van Woerden
Hazebroek EJ, van Veldhuisen DJ. Bariatric
ease: a systematic review and meta-
1969. doi: 10.1093/eurheartj/ehac071
66. Pu R, Shi D, Gan T, Ren X, Ba Y, Huo Y, Bai
fects of metformin in obesity treatment in different populations: a meta-
analysis. *Ther Adv Endocrinol Metab*. 2020;11:2042018820926000.
doi: 10.1177/2042018820926000
67. Chakhtoura M, Haber R, Ghezzawi M, Rhayem C, Tcheroyan R,
Mantzoros CS. Pharmacotherapy of obesity: an update on the
available medications and drugs under investigation.
EClinicalMedicine. 2023;58:101882. doi: 10.1016/j.eclinm.2023.101882
68. Cheong AJY, Teo YN, Teo YH, Syn NL, Ong HT, Ting AZH, Chia AZQ,
Chong EY, Chan MY, Lee CH, et al. SGLT inhibitors on weight
and body mass: a meta-analysis of 116 randomized-controlled trials.
Obesity (Silver Spring).
2022;30:117–128. doi: 10.1002/oby.23331
69. Vosoughi K, Salman Roghani R, Camilleri M. Effects of GLP-1 agonists
on proportion of weight loss in obesity with or without diabetes: sys-
tematic review and meta-analysis. *Obesity Med*. 2022;35:100456. doi:
10.1016/j.obmed.2022.100456
70. Uneda K, Kawai Y, Yamada T, Kinguchi S, Azushima K, Kanaoka T,
80. Leite AR, Angélico-Gonçalves A,
M. Leite-Moreira A, Neves JS, Ferreira
pentide-1 receptor agonists on
adults without diabetes: a meta-
trials. *Diabetes Obes Metab*.
81. Butler J, Shah SJ, Petrie MC, Borlaug
Hovind GK, Kitzman DW, Moller DV.
Committees and Investigators.
obesity-related heart failure with
ysis of the STEP-HFpEF and STEP-
2024;403:1635–1648. doi:
82. Nowrouzi-Sohrabi P, Rezaei S, Jalali M,
Keshavarz P, Akhbari H. The effects of
Toya Y, Wakui H, Tamura K. Systematic review and meta-
analysis for preven- tion of cardiovascular
complications using GLP-1 receptor agonists and SGLT-
2 inhibitors in obese diabetic patients. *Sci Rep*.
2021;11:10166. doi: 10.1038/s41598-021-89620-7
71. Wilding JPH, Batterham RL, Calanna S, Davies M, Van
Gaal LF, Lingvay I, McGowan BM, Rosenstock J,
Tran MTD, Wadden TA, et al; STEP 1 Study Group.
Once-weekly semaglutide in adults with overweight or
obesity. *N Engl J Med*. 2021;384:989–1002. doi:
10.1056/NEJMoa2032183
72. Wadden TA, Bailey TS,
Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I,
O'Neil PM, Rubino DM, Skovgaard D, et al; STEP 3
Investigators. Ef- fect of subcutaneous semaglutide vs
placebo as an adjunct to intensive behavioral therapy
on body weight in adults with overweight or obesity:

- for agonists on glycemic control and anthropometric profiles among diabetic patients with non-alcoholic fatty liver disease: a systematic re-view and meta-analysis of randomized controlled trials. *Eur J Pharmacol*. 2021;893:173823. doi: 10.1016/j.ejphar.2020.173823
83. Bandyopadhyay S, Das S, Samajdar SS, Joshi SR. Role of semaglutide in the treatment of nonalcoholic fatty liver disease or non-alcoholic steatohepatitis: a systematic review and meta-analysis. *Diabetes Metab Syndr*. 2023;17:102849. doi: 10.1016/j.dsx.2023.102849
 84. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, Yoneda M, Behling C, Cummings OW, Tang Y, et al; Synergy-Nash Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med*. 2024;391:299–310. doi: 10.1056/nejmoa2401943
 85. Ryan PM, Seltzer S, Hayward NE, Rodríguez DA, Sless RT, Hawkes CP. Safety and efficacy of glucagon-like peptide-1 receptor agonists in children and adolescents with obesity: a meta-analysis. *J Pediatr*. 2021;236:137–147.e13. doi: 10.1016/j.jpeds.2021.05.009
 86. Visaria A, Setoguchi S. Body mass index and all-cause mortality in a 21st century U.S. population: a National Health Interview Survey analysis. *PLoS One*. 2023;18:e0287218. doi: 10.1371/journal.pone.0287218
 87. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol*. 2018;6:944–953. doi: 10.1016/S2213-8587(18)30288-2
 88. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, Romundstad P, Vatten LJ. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ*. 2016;353:i2156. doi: 10.1136/bmj.i2156
 73. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, et al; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387:205–216. doi: 10.1056/NEJMoa2206038
 74. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, et al; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221–2232. doi: 10.1056/NEJMoa2307563
 75. Smith I, Hardy E, Mitchell S, Batson S. Semaglutide 2.4 mg for the management of overweight and obesity: systematic literature review and meta-analysis. *Diabetes Metab Syndr Obes*. 2022;15:3961–3987. doi: 10.2147/DMSO.S392952
 76. Jastreboff AM, Kaplan LM, Frias JP, Wu Q, Du Y, Gurbuz S, Coskun T, Haupt A, Milicevic Z, Hartman ML; Retatrutide Phase 2 Obesity Trial Investigators. Triple-hormone-receptor agonist retatrutide for obesity: a phase 2 trial. *N Engl J Med*. 2023;389:514–526. doi: 10.1056/NEJMoa2301972
 77. Wharton S, Blevins T, Connery L, Rosenstock J, Raha S, Liu R, Ma X, Mather KJ, Haupt A, Robins D, et al; GZGI Investigators. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N Engl J Med*. 2023;389:877–888. doi: 10.1056/NEJMoa2302392
 78. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, Lingvay I, McGowan BM, Oral TK, Rosenstock J, et al; STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab*. 2022;24:1553–1564.

89. Jayedi A, Khan TA, Aune D, Emadi A, Shab-Bidar S. Body fat and risk of all-cause mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Int J Obes (Lond)*. 2022;46:1573–1581. doi: 10.1038/s41366-022-01165-5
90. Chen H, Deng Y, Li S. Relation of body mass index categories with risk of sudden cardiac death. *Int Heart J*. 2019;60:624–630. doi: 10.1536/ihj.18-155
91. Ward ZJ, Willett WC, Hu FB, Pacheco LS, Long MW, Gortmaker SL. Excess mortality associated with elevated body weight in the USA by state and demographic subgroup: a modelling study. *EClinicalMedicine*. 2022;48:101429. doi: 10.1016/j.eclinm.2022.101429
92. Li X, Han F, Liu N, Feng X, Sun X, Chi Y, Hou N, Liu Y. Changing trends of the diseases burden attributable to high BMI in Asia from 1990 to 2019: results from the Global Burden of Disease Study 2019. *BMJ Open*. 2023;13:e075437. doi: 10.1136/bmjopen-2023-075437
93. Kim MS, Kim WJ, Khera AV, Kim JY, Yon DK, Lee SW, Shin JI, Won HH. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and mendelian randomization studies. *Eur Heart J*. 2021;42:3388–3403. doi: 10.1093/eurheartj/ehab454
94. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol*. 2018;3:280–287. doi: 10.1001/jamacardio.2018.0022
95. Zhao Y, Qie R, Han M, Huang S, Wu X, Zhang Y, Feng Y, Yang X, Li Y, Wu Y, et al. Association of BMI with cardiovascular disease incidence and mortality in patients with type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of cohort studies. *Nutr Metab Cardiovasc Dis*. 2021;31:1976–1984. doi: 10.1016/j.numecd.2021.03.003
79. Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, Ahmad NN, Zhang S, Liao R, Bunck MC, et al; SURMOUNT-4 Investigators. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA*. 2024;331:38–48. doi: 10.1001/jama.2023.24945

96. Gill D, Zuber V, Dawson J, Pearson-Stuttard J, Carter AR, Sanderson E, Karhunen V, Levin MG, Wootton RE, Klarin D, et al. Risk factors mediating the effect of body mass index and waist-to-hip ratio on cardiovascular outcomes: mendelian randomization analysis. *Int J Obes (Lond)*. 2021;45:1428–1438. doi: 10.1038/s41366-021-00807-4

97. Silva S, Fatumo S, Nitsch D. Mendelian randomization studies on coronary artery disease: a systematic review and meta-analysis. *Syst Rev*. 2024;13:29. doi: 10.1186/s13643-023-02442-8
98. Horn JW, Feng T, Morkedal B, Aune D, Strand LB, Horn J, Mukamal KJ, Janszky I. Body mass index measured repeatedly over 42 years as a risk factor for ischemic stroke: the HUNT study. *Nutrients*. 2023;15:1232. doi: 10.3390/nu15051232
99. Marini S, Merino J, Montgomery BE, Malik R, Sudlow CL, Dichgans M, Florez JC, Rosand J, Gill D, Anderson CD; International Stroke Genetics Consortium. Mendelian randomization study of obesity and cerebrovascular disease. *Ann Neurol*. 2020;87:516–524. doi: 10.1002/ana.25686
100. Ountade AS, Islam N, Malouf R, Taylor H. Joint review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc*. 2023;12:e029062. doi: 10.1161/JAHA.122.029062
101. Mahajan R, Stokes M, Elliott A, Munawar DA, Khokhar KB, Thiagarajah A, Hendriks J, Linz D, Gallagher C, Kaye D, et al. Complex interaction of obesity, intentional weight loss and heart failure: a systematic review and meta-analysis. *Heart*. 2020;106:58–68. doi: 10.1136/heartjnl-2019-314770
102. Fliotsos M, Zhao D, Rao VN, Ndumele CE, Guallar E, Burke GL, Vaidya D, Delaney JCA, Michos ED. Body mass index from early-, mid-, and older-adulthood and risk of heart failure and atherosclerotic cardiovascular disease: MESA. *J Am Heart Assoc*. 2018;7:e009599. doi: 10.1161/JAHA.118.009599
103. Rao VN, Fudim M, Mentz RJ, Michos ED, Felker GM. Regional adiposity and heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020;22:1540–1550. doi: 10.1002/ejhf.1956
104. Rao VN, Zhao D, Allison MA, Guallar E, Sharma K, Criqui MH, Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, et al. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: results from the American Heart Association COVID-19 Cardiovascular Disease Registry. *Circulation*. 2021;143:135–144. doi: 10.1161/CIRCULATIONAHA.120.051936
116. Vasbinder A, Meloche C, Azam TU, Anderson E, Catalan T, Shadid H, Berlin H, Pan M, O'Hayer P, Padalia K, et al; STOP-COVID Investigators. Relationship between preexisting Cushman M, Blumenthal RS, Michos ED. Adiposity and incident heart failure and its subtypes: MESA (Multi-Ethnic Study of Atherosclerosis). *JACC Heart Fail*. 2018;6:999–1007. doi: 10.1016/j.jchf.2018.07.009
105. Salah HM, Pandey A, Van Spall HGC, Michos ED, McGarrah RW, Fudim M. Meta-analysis of nonalcoholic fatty liver disease and incident heart failure. *Am J Cardiol*. 2022;171:180–181. doi: 10.1016/j.amjcard.2022.02.012
106. Jones NR, Ordonez-Mena JM, Roalke AK, Taylor KS, Goyder CR, Hobbs FR, Taylor CJ. Body mass index and survival in people with heart failure. *Heart*. 2023;109:1542–1549. doi: 10.1136/heartjnl-2023-322459
107. Chung MK, Eckhardt LL, Chen LY, Ahmed HM, Gopinathannair R, Joglar JA, Noseworthy PA, Pack QR, Sanders P, Trulock KM; on behalf of the American Heart Association Electrophysiology and Arrhythmias Committee and Exercise, Cardiac Rehabilitation, and Secondary Prevention Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Lifestyle and Cardiometabolic Health. Lifestyle and risk factor

- from childhood obesity: a systematic review and meta-analysis. *Obes Rev.* 2016;17:95–107. doi: 10.1111/obr.12334
118. Nielsen J, Hulman A, Narayan KMV, Cunningham SA. Body mass index trajectories from childhood to adulthood and age at onset of overweight and obesity: the influence of parents' weight status. *Am J Epidemiol.* 2022;191:1877–1885. doi: 10.1093/aje/kwac124
119. Jacobs DR Jr, Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, Kartiosuo N, Lehtimäki T, Magnussen CG, Viikari JSA, et al. Childhood cardiovascular risk factors and adult cardiovascular events. *N Engl J Med.* 2022;386:1877–1888. doi: 10.1056/NEJMoa2109191
120. Meyer JF, Larsen SB, Blond K, Damsgaard CT, Bjerregaard LG, Baker JL. Associations between body mass index and height during childhood and adolescence and the risk of coronary heart disease in adulthood: a systematic review and meta-analysis. *Obes Rev.* 2021;22:e13276. doi: 10.1111/obr.13276
121. Wei Y, Richardson TG, Zhan Y, Carlsson S. Childhood adiposity and novel subtypes of adult-onset diabetes: a mendelian randomisation and genome-wide genetic correlation study. *Diabetologia.* 2023;66:1052–1056. doi: 10.1007/s00125-023-05883-x
122. Koebeck C, Sidell MA, Li X, Woolford SJ, Kuizon BD, Kunani P. Association of high normal body weight in youths with risk of hypertension. *JAMA Netw Open.* 2023;6:e231987. doi: 10.1001/jamanetworkopen.2023.1987
123. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med.* 2015;373:1307–1317. doi: 10.1056/NEJMoa1502821
124. Ward ZJ, Bleich SN, Long MW, Gortmaker SL. Association of body mass index with health care expenditures in the United States by age and sex. *PLoS One.* 2021;16:e0247307. doi: 10.1371/journal.pone.0247307
125. Cawley J, Biener A, Meyerhoefer C, Ding Y, Zvenyach T, Smolarz BG, Ramasamy A. Direct medical costs of obesity in the United States and the most populous states. *J Manag Care Spec Pharm.* 2021;27:354–366. doi: 10.18553/jmcp.2021.20410
- Effect of weight loss on recurrence of atrial fibrillation after ablative therapy: a systematic review and meta-analysis. *J Interv Card Electrophysiol.* 2022;64:763–771. doi: 10.1007/s10840-022-01168-2
111. Chan YH, Chen SW, Chao TF, Kao YW, Huang CY, Chu PH. The impact of weight loss related to risk of new-onset atrial fibrillation in patients with type 2 diabetes mellitus treated with sodium-glucose cotransporter 2 inhibitor. *Cardiovasc Diabetol.* 2021;20:93. doi: 10.1186/s12933-021-01285-8
112. Shi W, Zhang W, Zhang D, Ren G, Wang P, Gao L, Chen H, Ding C. Comparison of the effect of glucose-lowering agents on the risk of atrial fibrillation: a network meta-analysis. *Heart Rhythm.* 2021;18:1090–1096. doi: 10.1016/j.hrthm.2021.03.007
- modification for reduction of atrial fibrillation: a scientific statement from the American Heart Association. *Circulation.* 2020;141:e750–e772. doi: 10.1161/CIR.0000000000000748
108. Deng Y, Li L, Li Q, Guo J, Cai B, Zhou F, Chang D. Central obesity as a potential causal risk factor for atrial fibrillation: evidence from mendelian randomization study. *Europace.* 2024;26:euae061. doi: 10.1093/europace/euae061
109. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol.* 2017;32:181–192. doi: 10.1007/s10654-017-0232-4
110. Park DY, An S, Murthi M, Kattoor AJ, Kaur A, Ravi V, Huang HD, Vij A.

126. World Health Organization. Obesity and overweight. Accessed March 15, 2024.
127. World Obesity Federation. World Obesity Atlas 2024: no area of the world is unaffected by the consequences of obesity. Accessed March 15, 2024.
128. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: a compass for future health. *J Am Coll Cardiol.* 2022;80:2361–2371. doi: 10.1016/j.jacc.2022.11.005
129. Chong B, Jayabaskaran J, Kong G, Chan YH, Chin YH, Goh R, Kannan S, Ng CH, Loong S, Kueh MTW, et al. Trends and predictions of malnutrition and obesity in 204 countries and territories: an analysis of the Global Burden of Disease Study 2019. *EClinicalMedicine.* 2023;57:101850. doi: 10.1016/j.eclinm.2023.101850
130. Mensah GA, Fuster V, Murray CJL, Roth GA; Global Burden of Cardiovascular Diseases and Risks Collaborators. Global Burden of Cardiovascular Diseases and Risks, 1990-2022. *J Am Coll Cardiol.* 2023;82:2350–2473. doi: 10.1016/j.jacc.2023.11.007
131. NCD Risk Factor Collaboration. Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature.* 2019;569:260–264. doi: 10.1038/s41586-019-1171-x
132. Okunogbe A, Nugent R, Spencer G, Powis J, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for 161 countries. *BMJ Glob Health.* 2022;7:e009773. doi: 10.1136/bmjgh-2022-009773
113. Yang Y, Song Y, Hou D. Obesity and COVID-19 pandemics: epidemiology, mechanisms, and management. *Diabetes Metab Syndr Obes.* 2023;16:4147–4156. doi: 10.2147/DMSO.S441762
114. Mahamat-Saleh Y, Fiolet T, Rebeaud ME, Mulot M, Guihur A, El Fatouhi

133. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2024.
- D, Laouali N, Peiffer-Smadja N, Aune D, Severi G. Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies. *BMJ Open*. 2021;11:e052777. doi: 10.1136/bmjopen-2021-052777
134. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed July 1, 2024.

7. HIGH BLOOD OTHER LIPIDS

See Tables 7-1 and 7-2 and
through 7-5

[Click here to return to the Table](#)

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Cholesterol is a primary causal development of atherosclerosis and blood have traditionally been one used to define CVH in children and component of TC that is most CVD risk and is therefore the pharmacological treatment. HDL-C associated with CVD risk, and high associated with increased risk. More Essential 8 has adopted non-C) as a key metric to assess lipid full lipid panel, including TC, LDL-erides, is normally recommended related CVD risk. Lipoprotein(a), an added apolipoprotein(a), is a factor causally linked to ASCVD epidemiological, mendelian The multisociety 2018 Cholesterol Guideline and the 2019 CVD cal Practice Guidelines focus

of LDL-C—lowering therapy to reduce ASCVD risk.^{2,3} The 2022 ACC expert consensus decision pathway dis-cusses the role of nonstatin therapy in the management of ASCVD risk.⁴

Prevalence of High TC

Youths

(See Chart 7-1)

- Among children 6 to 11 years of age, the mean TC level in 2017 to 2020 was 157.4 mg/dL. For males, it was 157.5 mg/dL; for females, it was 157.2 mg/dL. Mean TC levels among racial and ethnic groups in NHANES 2017 to 2020 were as follows (unpub-

- For NH White children, and 159.5 mg/dL for
- For NH Black children, and 155.3 mg/dL for
- For Hispanic children, 156.5 and 153.1 mg/dL for
- For NH Asian children, and 166.0 mg/dL for
- Among adolescents 12 to 19 mean TC level in 2017 to for males, it was 150.1; for mg/dL. Mean TC levels groups in NHANES 2017 to (unpublished NHLBI
 - For NH White adolescents, males and 162.4 mg/dL for
 - For NH Black adolescents, males and 156.8 mg/dL for
 - For Hispanic adolescents, and 154.9 mg/dL for
 - For NH Asian adolescents, males and 161.0 mg/dL for
- Among youths 6 to 19 years of of elevated TC levels (TC 2016 was 7.1% (95% CI, Among youths 6 to 19 years of ideal TC levels (TC <170 2016 was 71.4% (95% CI, 7-1B).⁶

lished NHLBI tabulation using NHANES₅):

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Na-tive American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Adults (≥20 Years of Age)

(See Table 7-1 and Charts 7-2 through 7-4)

- Among adults ≥20 years of age, the mean TC level was 183.9 mg/dL; for females, it was 190.0 mg/dL. Across 3 NHANES time periods (1999–2002, 2007–2010, and 2017–2020), NH Black adults had the lowest serum TC compared with NH White adults and Mexican American adults (Chart 7-2). Mean TC levels among racial and ethnic groups in tabulation using NHANES₅:
 - For NH White adults, 183.3 mg/dL for males and 191.6 mg/dL for females
 - For NH Black adults, 179.5 mg/dL for males and 182.6 mg/dL for females
 - For Hispanic adults, 185.3 mg/dL for males and 187.4 mg/dL for females
 - For NH Asian adults, 191.4 mg/dL for males and 190.8 mg/dL for females
- The prevalence of TC ≥200 mg/dL and ≥240 mg/dL among US adults ≥20 years of age in 2017 to 2020 (unpublished NHLBI tabulation using NHANES₅) is shown overall and by sex and race and ethnicity in Table 7-1 and Charts 7-3 and 7-4.

• The US Healthy TC level achieved combined and (Chart 7-2).^{5,7}

Prevalence of Abnormal Lipid Subfractions

• Among adults who reported CAD between 2015 and 2020, the age-adjusted mean LDL-C was 94.4 mg/dL (95% CI, 90.3–98.5).⁸ In these adults, 73.5% (95% CI, 68.2%–78.8%) had an LDL-C ≥70 mg/dL, and 88.1% (95% CI, 83.6%–92.6%) had an LDL-C ≥55 mg/dL.

Lipoprotein(a)

Lipoprotein(a) is an LDL-like particle, an apolipoprotein(a) covalently bound to apolipoprotein B₁₀₀ by disulfide bonds. Some professional societies recommend screening of lipoprotein(a) in individuals with a personal or family history of ASCVD or who are at high risk of ASCVD. An update to the 2019 US National Lipid Association scientific statement on the use of lipoprotein(a) in clinical practice recommended that lipoprotein(a) be measured once in every adult for risk stratification and to guide early, more intensive risk factor management.⁹

• Elevated lipoprotein(a), which is defined as ≥125 nmol/L or ≥50 mg/dL and is present in up to 20% of the population, is associated with increased risk of CHD, stroke, valvular aortic stenosis, and even HF and AF.

• Among ≈460 000 middle-aged adults in the UK Biobank enrolled between 2006 and 2010, median serum lipoprotein(a) concentration was 19.6 nmol/L (25th–75th percentile, 7.6–74.8 nmol/L) overall, with median values of 21.8 nmol/L in females and 17.4 nmol/L in males, as well as 19 nmol/L in White adults, 31 nmol/L in South Asian adults, 75 nmol/L in Black adults, and 16 nmol/L in Chinese adults.¹⁰

• Among 16 117 participants in the HCHS/SOL, overall median lipoprotein(a) molar concentration was 19.7 nmol/L, with significant heterogeneity ranging from 12 nmol/L in Mexican participants to 41 nmol/L in those with a Dominican background.¹¹

LDL-C

Youths

See Chart 7-1

• Among
• In 2017 to using NHANES₅, dL. The
– Among and
– Among and
– Among Hispanic adults, 110.5 mg/dL for males and
– Among and
• In 2017 to high LDL- (unpublis Table 7-1).

• In the INTERHEART study, median lipoprotein(a) levels and proportions with lipoprotein(a) >50 mg/dL were 7.8 mg/dL and 3.0% in China, 9.6 mg/dL and 13.0% in Europe, 10.2 mg/dL and 7.0% in Southeast Asia, 11.5 mg/dL and 15.0% in Latin America, 13.8 mg/dL and 9.0% in South Asia, 15.3 mg/dL and 12.0% in the Middle East, and 27.2 mg/dL and 27.0% in Africa.¹²

HDL Cholesterol

Youths

(See Chart 7-1)

• Among children 6 to 11 years of age, the mean HDL-C level in 2017 to 2020 was 55.5 mg/dL. For males, it was 56.6 mg/dL, and for females, it was 54.3 mg/dL. Mean HDL-C levels among racial and

ethnic groups were as follows *Triglycerides*

tabulation using NHANES₅): *Youths*

– For NH White children, 56.8 (See Chart 7-1)

54.8 mg/dL for females

– For NH Black children, 58.5

55.9 mg/dL for females

– For Hispanic children, 55.6

51.3 mg/dL for females

– For NH Asian children, 59.3

58.1 mg/dL for females

- Among children 6 to 11 years of HDL-C (<40 mg/dL) were and 8.9% of females in 2017 NHLBI tabulation using

- Among adolescents 12 to 19 mean HDL-C level was 51.7 was 49.0 mg/dL, and for dL. Mean HDL-C levels groups were as follows NHLBI tabulation):

– For NH White adolescents, and 55.2 mg/dL for females

– For NH Black adolescents, and 55.9 mg/dL for females

– For Hispanic adolescents, and 52.2 mg/dL for females

– For NH Asian adolescents, and 55.3 mg/dL for females

- Low levels of HDL-C (<40 mg/dL) in 19.3% of male adolescents adolescents in 2017 to 2020 tabulation using NHANES₅).

Adults

(See Table 7-1)

- HDL-C is considered low and increased ASCVD risk if <40 <50 mg/dL in females. In lished NHLBI tabulation using mean level of HDL-C for years of age was 53.6 mg/dL. levels among racial and follows:
 - Among NH White adults, and 59.5 mg/dL for females
 - Among NH Black adults, and 59.2 mg/dL for females
 - Among Hispanic adults,

and 55.4 mg/dL for females

– Among NH Asian adults, 46.8 mg/dL for males and 59.8 mg/dL for females

- Age-adjusted prevalence rates of low HDL-C (<40 mg/dL) for 2017 to 2020 are shown

- Limited data are available on dren 6 to 11 years of age.

- Among adolescents 12 to 19 metric mean triacylglyceride level 62.3 mg/dL. For males, it was females, it was 63.1 mg/dL. and ethnic groups were as NHLBI tabulation using

– Among NH White

males and 66.8 mg/dL for

– Among NH Black

males and 44.5 mg/dL for

– Among Hispanic

males and 70.7 mg/dL for

– Among NH Asian

males and 67.9 mg/dL for

- Elevated triacylglycerides (≥90 20.8% of male adolescents adolescents during 2017 to NHLBI tabulation using

Adults

- Triacylglyceride levels of 150 to erally considered borderline. dL are considered elevated, risk of ASCVD have been even <100 mg/dL.¹³ Among years of age, the geometric in 2017 to 2020 was 91.6 NHLBI tabulation using mean triacylglyceride levels were and 85.5 mg/dL for females. and ethnic groups were as
 - Among NH White adults, and 85.9 mg/dL for females
 - Among NH Black adults, and 67.5 mg/dL for females
 - Among Hispanic adults, and 96.2 mg/dL for females
 - Among NH Asian adults, and 84.3 mg/dL for females
- In 2017 to 2020, 19.9% of eride levels (≥150 mg/dL; ulation using NHANES₅).

overall and by sex and race and ethnicity in Table 7-1. Prevalence rates were higher among males than females and were highest among Hispanic males.

Secular Trends in TC and Lipid Subfractions
Youths
(See Chart 7-1)

• Between 1999 and 2016, trends in mean levels of TC, HDL-C, and non-HDL-C among youths 6 to 19 years of age demonstrated improved levels. Levels of LDL-C, triglycerides, and apolipoprotein B also improved among adolescents 12 to 19 years of age

over a similar period (data not available for younger children; Chart 7-1).

- The proportion of youths 6 to 19 years of age with ideal levels of 3 cholesterol measures (TC, HDL-C, and non-HDL-C) increased significantly from 42.1% (95% CI, 39.6%–44.7%) in 2007 to 2008 to 51.4% (95% CI, 48.5%–54.2%) in 2015 to 2016, and the proportion with at least 1 adverse level decreased from 23.1% (95% CI, 21.5%–24.7%) in 2007 to 2008 to 14.6% (95% CI, 13.1%–16.1%) in 2015 to 2016 (Chart 7-1).
- The proportion of adolescents 12 to 19 years of age with ideal levels of 6 cholesterol measures (TC, HDL-C, non-HDL-C, LDL-C, triglycerides, and apolipoprotein B) did not change significantly, from 39.6% (95% CI, 33.7%–45.4%) in 2007 to 2008 to 46.8% (95% CI, 40.9%–52.6%) in 2013 to 2014 (Chart 7-1).

Adults (≥20 Years of Age)

(See Chart 7-2)

- Mean age-adjusted TC levels decreased in the US population from 197 mg/dL in 2007 to 2008 to 189 mg/dL in 2017 to 2018.¹⁴ In females, mean TC decreased from 199 mg/dL in 2007 to 2008 to 192 mg/dL in 2017 to 2018. In males, mean TC decreased from 195 mg/dL in 2007 to 2008 to 185 mg/dL in 2017 to 2018.
- The prevalence of high TC (≥240 mg/dL) has decreased over time, from 18.3% (95% CI, 16.3%–20.3%) of adults in 1999 to 2000 to 10.5% (95% CI, 9.7%–11.3%) in 2017 to 2018.¹⁵

- The age-adjusted prevalence of high LDL-C (≥130 mg/dL) decreased from 42.9% during 1999 to 2000 to 26.2% during 2017 to 2018 (unpublished NHLBI tabulation using NHANES₅).
- Mean HDL-C levels increased statistically significantly between 2007 to 2008 and 2017 to 2018 in female (from 57 to 58 mg/dL; $P_{\text{trend}}=0.002$) and male (from 46 to 47 mg/dL; $P_{\text{trend}}=0.002$).
 - From 1999 to 2020, mean serum TC for adults ≥20 years of age decreased across all subgroups of race and ethnicity (Chart 7-2).
 - Declines in mean TC levels were also observed among adults receiving lipid-lowering medication, from 206 mg/dL in 2005 to 2006 to 187 mg/dL in 2015 to 2016.¹⁶
 - Among adults 20 to 44 years of age in the United States, prevalence of hyperlipidemia (defined as TC ≥200 mg/dL or a health care diagnosis of high cholesterol) decreased from 40.5% in 2009 to 2010 to 36.1% in 2017 to 2020.¹⁷
 - In ≈350 000 patients who were 40 to 79 years of age in the Kaiser Permanente Southern California health system with lipid information before (March 2019–March 2020) and during (December 2020–December 2021) the COVID-19 pandemic, the proportion with elevated TC ≥240 mg/dL increased from 9.9% to 10.8%.¹⁸
- Age-adjusted mean LDL-C decreased among US adults from 116 mg/dL in 2007 to 2008 to 111 mg/dL in 2017 to 2018, with similar patterns in females and males.¹⁴

- US adults declined from 22.2% in 2007 to 2008 to 16.0% in 2017 to 2018.¹⁵
- Geometric mean triglyceride levels decreased between 2007 to 2008 and 2017 to 2018 in female (from 104 to 86 mg/dL) and male (from 122 to 98 mg/dL) adults in the United States.¹⁴
- Among males, age-adjusted levels of apolipoprotein B declined from 98 mg/dL in 2005 to 2006 to 93 mg/dL in 2011 to 2012 and did not change subsequently through 2015 to 2016; among females, age-adjusted mean apolipoprotein B declined from 94 mg/dL in 2005 to 2006 to 91 mg/dL in 2015 to 2016.¹⁹

Family History and Genetics

- GWASs in hundreds of thousands of individuals of diverse ancestry, in addition to the use of electronic health record–based samples and whole-exome sequencing (which offers more comprehensive coverage of the coding regions of the genome), have identified >200 lipid loci.^{20–24}
- A recent multi-ancestry GWAS in 1.65 million individuals has identified 941 lipid-associated genomic regions harboring >1700 distinct variants, with 355 novel genomic loci identified.²⁵ The notable findings also highlight that multi-ancestry PRSs leveraging the GWAS findings from multiple ethnicities are more informative for lipid traits across multiple population groups.^{25,26}
- With the use of whole-genome sequencing across diverse ancestries in 66 000 individuals, 428 million variants were interrogated, and a rare noncoding variant model for blood lipids was characterized.²⁷ Novel associations were replicated in 45 000 independent samples with array-based genotyping.
- Lipoprotein(a), a causal risk factor for CAD, is a highly heritable trait. Whole-genome sequencing (which provides a comprehensive coverage of the entire genome, including both coding and noncoding regions) analysis combining structural variants (mainly LPA KIV2-CN) with sequence variations has elucidated that genetic heritability of lipoprotein(a) is ≈85% in Black individuals and ≈75% in European individuals.²⁸

- Furthermore, CAD risk was stratified by polygenic risk score (PRS) and LDL-C. In individuals with high polygenic risk (highest decile of PRS), the estimate of the HR for each double compared with intermediate PRS group (defined as deciles).²⁹ Relative to LDL-C <100 mg/dL, individuals with high PRS and LDL-C ≥190 mg/dL showed an increased risk (HR, 1.08–4.59) comparable to the risk in those with intermediate PRS and LDL-C ≥190 mg/dL (HR, 2.34 [95% CI, 1.75–3.14]). Conversely, CAD risk in individuals in the low PRS group (lowest decile of PRS) did not follow the stepwise increase in risk relative to LDL-C <100 observed in the other PRS groups.
- In a Norwegian registry-based study, individuals with genetic FH also had a higher risk of severe aortic stenosis (a mean of 65 years of age at diagnosis, ratio, 7.7 [95% CI, 5.2–11.5] of follow-up) compared with the general population (24 incident cases of severe aortic stenosis per 100,000 per year).

expected cases).⁴²

- Among 48 741 individuals 40 to 69 years of age with genotyping array and exome sequencing data from the UK Biobank, a pathogenic variant associated with FH was identified in 0.6%.⁴³ Among participants with a pathogenic variant associated

groups.

pathogenic

- The loci associated with blood lipid levels are often associated with cardiovascular and metabolic traits, including CAD, type 2 diabetes, hypertension, waist-hip ratio, and BMI.³⁰
- Mendelian randomization studies: These studies support a causal link between LDL-C, triglycerides, non-HDL-C, apolipoprotein B, and cardiovascular CVD. However, there is no clear evidence for a causal role of HDL-C or apolipoprotein A1.^{31–36}

Familial Hypercholesterolemia

- FH is an autosomal codominant genetic disorder associated with pathogenic variants in *LDLR*, *APOB*, *LDLRAP1*, and *PCSK9*, which affect LDL-C uptake and clearance.^{37,38} Fewer than 10% of patients with FH have actually been diagnosed.³⁹
- According to a meta-analysis from 11 million individuals worldwide, the pooled estimate of heterozygous FH prevalence was 0.32% (95% CI, 0.26%–0.39%), or 1 in 313 individuals worldwide. The prevalence of homozygous FH was estimated as 1 in 400 000.⁴⁰
- Individuals with the FH phenotype (LDL-C ≥ 190 mg/dL) experience an acceleration in CHD risk by 10 to 20 years in males and 20 to 30 years in

with FH compared with those without a

females.⁴¹ However, individuals with LDL-C ≥ 190 mg/dL and a confirmed pathogenic variant for FH representing lifelong elevation of LDL-C levels have substantially higher odds for CAD than individuals with LDL-C ≥ 190 mg/dL without pathogenic variants.³⁷

- Compared with individuals with LDL-C < 130 mg/dL and no pathogenic variant, those with both LDL-C ≥ 190 mg/dL and a pathogenic variant for FH had a 22-fold increased risk for CAD (OR, 22.3 [95% CI, 10.7–53.2]).
- Compared with individuals with LDL-C < 130 mg/dL and no pathogenic variant, individuals with

variant associated with FH, the risk of premature ASCVD (≤ 55 years of age) was higher (HR, 3.17 [95% CI, 1.96–5.12]).

- Among 2404 adult patients (mean, 45.5 years of age [SD, 15.4 years]) with FH in a multicenter, nationwide cohort study (SAFEHEART), independent predictors of ASCVD over a mean follow-up of 5.5 years (SD, 3.2 years) included traditional clinical risk factors for ASCVD (age [30–59 years versus <30 years: 2.92 (95% CI, 1.14–7.52); ≥ 60 years versus <30 years: 4.27 (95% CI, 1.60–11.48)], male sex [2.01 (95% CI, 1.33–3.04)], HBP [1.99 (95% CI, 1.26–3.15)], overweight [2.40 (95% CI, 1.36–4.23)] or obesity [2.67 (95% CI, 1.47–4.85)], smoking [1.62 (95% CI, 1.08–2.44)], and lipoprotein[a] level >50 mg/dL [1.52 (95% CI, 1.05–2.21)]).⁴⁴ In a 20-year follow-up study, early initiation of statin treatment among 214 children with FH was associated with a decrease in LDL-C by 32%, slowed progression of subclinical atherosclerosis (carotid IMT change, 0.0056 mm/y, not significantly different from unaffected siblings), and lower cumulative incidence of cardiovascular events (1% versus 26%) and death resulting from cardiovascular causes (0% versus 7%) by 39 years of age compared with affected parents.⁴⁵
- In NHANES 1999 to 2014, despite a high frequency of cholesterol screening and awareness ($>80\%$), statin use was low in adults with definite/probable FH (52.3% [SE, 8.2%]) and with severe dyslipidemia (37.6% [SE, 1.2%]).⁴⁶ Among adults with diagnosed FH in the CASCADE FH Registry, 25% achieved LDL-C <100 mg/dL, and 41% achieved LDL-C reduction $\geq 50\%$. Factors associated with $\geq 50\%$ reduction from untreated LDL-C levels were high-intensity statin use (OR, 7.33 [95% CI, 1.86–28.86]; used in 42%) and use of >1 medication to lower LDL-C (OR, 1.80 [95% CI, 1.34–2.41]; used in 45%).⁴⁷

- Among 493 children with diagnosed FH in the CASCADE FH Registry, the mean age at diagnosis was 9.4 years (SD, 4.0 years), the mean highest pretreatment LDL-C was 238 mg/dL (SD, 61 mg/dL); 1 or ≥ 2 additional CVD risk factors were present in 35.1% and 8.7%, respectively; and 64% of participants used lipid-lowering therapy (56% used a statin) with a mean age at initiation of 11.1 years (SD, 3.2 years). Among 315 participants ≥ 10 years of age with either family history of premature CVD, 76.5% were using lipid-lowering therapy (statin in 71.6%, nutraceutical in 7.3%). Only 27.6% of children overall and 39% of children receiving lipid-lowering therapy achieved the recommended

remained clinically stable (no ASCVD events or interventions) over a mean follow-up of 17.2 years (SD, 5.6 years).⁵³

Familial Combined Hyperlipidemia

- Familial combined hyperlipidemia is a complex oligogenic disorder that affects 1% to 3% of the general population, which makes it the most LDL-C of either $\geq 50\%$ decrease from baseline or < 130 mg/dL.⁴⁸ These figures are similar to the medians reported for 8 European countries, although there is substantial variation between countries.⁴⁹

combined hyperlipidemia has a heterogeneous clinical presentation within families and individuals, including fluctuating elevations in LDL-C or triglycerides, as well as elevated apolipoprotein B levels. Environmental interactions are essential in familial combined hyperlipidemia, and metabolic comorbidities are common. Familial combined hyperlipidemia remains underdiagnosed.⁵⁴

- Cascade screening, meaning cholesterol testing for all first-degree relatives of patients with FH,

Screening

effectively identify affected family members who would benefit from therapeutic intervention.⁵⁰ A systematic review of 10 studies of cascade testing for FH identified that the average yield {diagnostic yield=[positive cases (n)/total tested (n)]×100} was 44.8%, and the mean number of new cases

per index case was 1.65.⁵¹

- A 2020 modeling study found that child-parent cascade screening, consisting of universal screening of children at 1 year of age during immunizations followed by cascade screening of relatives, was

- According to BRFSS 2021, the median crude prevalence of adults reporting that they had their blood cholesterol checked within the past 5 years across all states and the District of Columbia was 85.2%. In addition, 10.8% reported that they never had it checked, and 3.5% reported that it was not checked in the past 5 years. The highest age-adjusted percentages of adults who had their blood cholesterol checked in the past 5 years were in the District of Columbia (90.1%) and Puerto Rico (93.5%), whereas the state with the lowest percentage was

more effective than either cascade or child-parent screening in isolation at shortening the time to identify 25%, 50%, and 75% of FH cases in the popula-

Maine (64.7%).⁵⁵

tion; the estimates for the United States were 6, 16, and 30 years of age, respectively, to reach these

- From 2017 to 2018, the proportion of US adults with cholesterol levels screened in the preceding 5 years was 65.8% for Hispanic adults, 75.0% for NH Asian adults, 70.7% for NH Black adults, and 74.1% proportions.⁵²
- In a report of 24 pediatric patients with biallelic (homozygous or compound heterozygous) FH in Germany, the mean age at diagnosis was 6.3 years (SD, 3.4 years), and the mean LDL-C at diagnosis was 752 mg/dL (SD, 193 mg/dL). Twenty-one patients were diagnosed on the basis of clinical lipid deposits (xanthomas/xanthelasma), and 3 were diagnosed after screening on the basis of family history of biallelic FH. Diet and medications alone reduced LDL-C by 32.2% (SD, 18.0%) to a mean of 510 mg/dL (SD, 201 mg/dL). In contrast, weekly or twice-weekly lipoprotein apheresis resulted in an additional reduction of 63.9% (SD, 15.5%) to a mean LDL-C of 184 mg/dL (SD, 83 mg/dL) between apheresis treatments. After apheresis was started at a mean

- Among US adults with severe dyslipidemia (LDL-cholesterol evaluation in the preceding 5 years, with 2011 to 2012 and 2017 to March 2020.⁵⁷
- In the United States, universal cholesterol screening between 9 and 11 years of age and again cascade screening of family members is recommended for children found to have moderate to severe hypercholesterolemia.^{2,58}
 - In a survey of 472 clinicians in the United States, 64.8% of pediatricians and 34.1% of family medicine physicians reported completing lipid screening of eligible pediatric-age patients within the preceding year.⁵⁹
 - In a survey of 472 clinicians in the United States, 64.8% of pediatricians and 34.1% of family medicine physicians reported completing lipid screening of eligible pediatric-age patients within the preceding year.⁵⁹

- It has been estimated that in the United States the numbers of children 10 years of age needed to universally screen to identify 1 case of severe hyperlipidemia (LDL-C ≥ 190 mg/dL or LDL-C ≥ 160 mg/dL plus family history) or any hyperlipidemia (LDL-C ≥ 130 mg/dL) were 111 and 12, respectively. These numbers were 49 and 7, respectively, for a targeted screening program based on parental dyslipidemia or early CVD in a first-degree relative. The incremental costs of detection per case for universal (versus targeted) screening were \$32 170 for severe and \$1980 for any hyperlipidemia, and the universal (versus targeted) strategy would annually detect ≈ 8000 more children with severe hyperlipidemia and 126 000 more children with any hyperlipidemia.⁶⁰
 - In a cross-sectional analysis of primary care visits from the IOVIA National Disease and Therapeutic Index, a nationally representative audit of outpatient practices in the United States, a 36.9% decrease was noted in cholesterol level measurements in the second quarter of 2020 during the COVID-19 pandemic compared with the same time frame in 2018 to 2019.⁶¹
 - Screening for lipoprotein(a) is uncommon, with region- and system-level variation. An analysis of health claims data for >9000 patients in the United States showed that only 0.6% of primary prevention and 0.7% of secondary prevention patients with laboratory data had lipoprotein(a) levels measured.⁶² Among 5 553 654 adults who received care across 6 medical centers in the University of California health system between 2012 to 2021, 0.3% had lipoprotein(a) testing done.⁶³ Those tested were more likely to be older, male, and White and to have a greater burden of CVD. Lipoprotein(a) testing was performed in 1.8% of patients who had a lipid panel checked, but lipoprotein(a) testing was still <5% even in those with a personal or family history of ASCVD, with little improvement in testing over the past decade. In comparison, among 2 412 020 patient charts in the Hartford Health network in Connecticut from 2017 to 2022, 0.25% had lipoprotein(a) measured; those who had a measurement were more likely to be younger and NH.⁶⁴ Among patients in the Optum Clinformatics database receiving lipid-lowering treatment and with lipid measures, only 0.7% of secondary prevention and 0.6% of primary prevention patients had lipoprotein(a) test results.⁶²
 - In the Mass General Brigham health care system in the Northeast United States between 2000 and 2023, lipoprotein(a) testing was done in 5.8% of 465 814 patients with CHD, with Black patients and female patients having lower rates of testing.⁶⁵ Among ≈ 65 000 adults without CHD who had a 10-year between 2010 lipoprotein(a)
- Awareness**
- According to adults report cholesterol available for adjusted have been est in Puerto and Virginia (25.1%).
 - Among 73 771 States NHIS, the cholesterol 34.1% in adults, 30.9% adults, 25.4% in Central
 - Among US the proportion levels 2005 to 2006 and 2015 to adults with dL) remained [SE, 5.5%) to 5.8%)].⁵⁷
 - In US adults in those with who were 52.1% (95% to 42.7% million people) in 40.8% (95% to 26.8% million
 - Among young 20 to 39 years dL, 23.3% NHANES
 - Among US 2016, as being told had high sexual in bisexual reported in in bisexual another sexual

Treatment

- The Healthy People 2030 target for cholesterol treatment is 54.9% of eligible adults treated. In 2013 to 2016, 44.9% of eligible adults ≥ 21 years of age received treatment for blood cholesterol.⁷ In an analysis of 5218 adults with ASCVD in NHANES 1999 to 2020, there was a significant increase in the use of lipid-lowering medications among all 1999 and 2020 (Black, 18.31%; Hispanic or Latino, 26.02%; and White, 23.50%). Compared with White individuals, the use of lipid-lowering
- In 3 232 153 patients with a history of ASCVD between 2017 and 2018 in the Cerner electronic health record database of 92 US health systems, 76.1% were on statin medications.⁷⁶ Patients with PAD (OR, 0.40 [95% CI, 0.37–0.42]) and cerebro-vascular disease (OR, 0.75 [95% CI, 0.70–0.80]) had lower odds of using high-intensity statins compared with medications between 2017 and 2020 remained significantly lower among Black individuals (–24.07%; $P < 0.001$) and Hispanic and Latino individuals (–17.56%;

- Among US adults assessed in NHANES 2007 to 2016, use of lipid-lowering medication was 7.7% in heterosexual females, 0% in lesbian females, 1.1% in bisexual females, and 5.5% in females who reported another sexual identity, as well as 9.6% in heterosexual males, 8.5% in gay males, 9.6% in bisexual males, and 0% in males who reported another sexual identity ($P=0.005$).⁷⁰
 - Within the Optum database between 2015 and 2018 among patients with ASCVD (N=1 424 893), only 43.7% had at least 1 LDL-C measurement at baseline, and during the 31-month follow-up, about one-quarter of the patients did not receive any lipid treatment; among those treated, 89.5% received statins and 10.5% received nonstatin lipid-lowering therapy.⁷¹
- Fewer than half (47.6%) of the patients were adherent to the index treatment during the 12-month follow-up.
- In a study of lipid-lowering therapy after 81 372 events in US adults in the Veterans Affairs Health System, lipid-lowering therapy intensification was most common (82.5%) among those not taking

another sexual identity.⁶⁹

- In ≈350 000 patients who were 40 to 79 years of health system with lipid information before (March–December 2021) the COVID-19 pandemic, statin
- In an analysis of adults in NHANES from 2017 to groups, the proportion not on statin therapy was and those with intermediate ASCVD risk plus with high ASCVD risk (59.4%), those with diabetes and lipid-lowering therapy before the coronary event.⁷² Having higher baseline LDL-C, having lipid levels checked, and attending a cardiology visit after the event were associated with a greater likelihood of intensification of lipid-lowering therapy.
- Among US adults with diabetes who were 40 to 75 years of age, statin use increased from 48.5% in 2011 to 2014 to 53.0% in 2015 to 2018.⁷³
- Among US adults with a 10-year predicted ASCVD risk ≥7.5%, the proportion taking a statin increased from 27.9% to 32.5% between 2005 to

age in the Kaiser Permanente Southern California 2019–March 2020) and during (December 2020–use increased from 37.7% to 42.4%.¹⁸ 2020 examining statin use in different ASCVD risk highest in those with LDL-C ≥190 mg/dL (92.8%) risk-enhancing factors (74.6%), followed by those with (54.8%), and those with established ASCVD (41.5%).⁷⁷

2006 and 2015 to 2016.¹⁶

- In US adults without a history of CVD at borderline (5%–7.5%) or intermediate (7.5%–20%) 10-year ASCVD risk, 55% and 53%, respectively, had at least 1 ASCVD risk-enhancing factor, as defined by the 2019 CVD Primary Prevention Clinical Practice Guidelines.^{3,74} Among those with any risk-enhancing factors, only 23% were on a statin for primary prevention. Compared with White adults (27.4% statin use), statin use was lower in Black adults (20.0%)

- Among 81 332 participants with diabetes in the All of Us Program, 49.8% were not on statin therapy.⁷⁸ Only 18.2% of those with diabetes and ASCVD were on high-intensity statins. Overall, 5.1% were using ezetimibe and 0.6% were using PCSK9 inhibitors. Overall, 1.9% of participants with triglycerides ≥ 150 mg/dL were on icosapent ethyl.
- In the PROMINENT trial of >10 000 patients with type 2 diabetes, mild to moderate hypertriglyceridemia (200–499 mg/dL), and HDL-C ≤ 40 mg/dL; on guideline-directed lipid-lowering therapy; or with adverse reactions to statins who were randomized to receive pemafibrate or placebo, there was no significant difference between groups in the primary outcome of MACEs (HR, 1.03 [95% CI, 0.91–1.15]). The group receiving pemafibrate showed an increase in LDL-C and apolipoprotein B levels.⁷⁹• In an open-label 4-year extension of the ORION-1 trial (ORION-3), twice-yearly inclisiran resulted in a 4-year averaged LDL-C reduction of 44% (95% CI, 41%–47%).⁸⁰
- In a patient-level analysis of 3655 patients in the ORION-9, -10, and -11 trials who had heterozygous

FH, ASCVD, or ASCVD risk tolerated statin therapy versus placebo. over 18 patients on inclisiran had a (7.1% versus 9.4% receiving [95% CI, 0.58–0.94]). significant difference in incidence MI (1.8% versus 2.3%) or (0.7% versus 0.8%).^{.81}

- In the CLEAR Outcomes trial of who had or at were high risk for CVD, who were unable to take statins, or who were statin intolerant randomized to receive bempedoic acid or placebo, the incidence of MACEs was lower among patients who received bempedoic acid (11.7%) compared with placebo (13.3%; HR, 0.87 [95% CI, 0.79– 0.96]), although no significant differences in fatal or nonfatal stroke, death resulting from cardiovascular causes, or all-cause mortality were observed.^{.82}

- In a prespecified subgroup analysis of 4206 primary prevention patients in the CLEAR Outcomes trial, participants who were randomized to receive bempedoic acid had a lower risk of MACEs (5.3%) compared with participants who received placebo (7.6%; aHR, 0.70 [95% CI, 0.55–0.89]) including MI, cardiovascular death, and all-cause mortality.^{.83}

There was no significant difference between groups in stroke or coronary revascularization.

- In the LODESTAR randomized trial of 4400 patients with CAD at 12 centers in South Korea, a treat-to- target strategy of lowering LDL-C to a goal between 50 and 70 mg/dL was not significantly different from a strategy of using high-intensity statin for the rate of a 3-year

not significantly change over 2007 to 2008 to 79.5% in lar patterns by sex.^{.14} Between 2017 to 2018, lipid control improved among Mexican to 86.5%) but did not Black adults (67.4% to to 82.0%), or Asian adults to 75.2% in 2017 to 2018).

- Among 5391 adults with composite end point of death, MI, stroke, or coronary revascularization (8.1% versus 8.7%).^{.84} In the 2×2 factorial design of this trial, there was no difference in rate of the primary outcome between participants who received rosuvastatin (8.7%) and those who received atorvastatin (8.2%; HR, 1.06 [95% CI, 0.86–1.30]).^{.85}
- In a systematic review and meta-analysis of randomized trials evaluating the effect of a fixed-dose combination polypill that included at least 1 lipid-lowering medication and 1 BP-lowering medication, studies of mostly primary prevention patients demonstrated that the polypill (versus comparator) was associated with a lower risk of all-cause mortality by 11% (5.6% versus 6.3%; RR, 0.89 [95% CI, 0.78– 1.00]) and lower risk of fatal and nonfatal ASCVD events by 29% (6.1% versus 8.4%; RR, 0.71 [95% CI, 0.63–0.79]).^{.86}

- NHANES 1999 to 2018, there was an increase in the proportion achieving non-HDL-C<100 mg/dL from 7.0% in 1999 to 2002 to 26.4% in 2015 to 2018 ($P_{\text{trend}} < 0.001$).⁸⁷ The proportion taking statins increased from 40.1% in 1999 to 2002 to 63.4% in 2011 to 2014 but plateaued thereafter ($P_{\text{trend}} < 0.001$). Ezetimibe use rose to 7.0% in 2007 to 2010 but declined to 1.6% in 2015 to 2018.
- Between 1999 and 2020 among US adults with diagnosed diabetes, non-HDL-C control (<130 mg/dL) increased from 26.6% in 1999 to 2002 to 58.6% in 2015 to 2020.⁸⁸ A trend of increasing non-HDL-C control was observed in adults with diabetes across all obesity categories (Proportion with non-HDL-C control in 2015 to 2020 was 66.5% in normal-weight adults, 58.7% in adults with overweight, 55.9% in adults with obesity class I, 58.0% in adults with obesity class II, and 56.9% in adults with obesity class III).

Mortality and Complications

- Among 18 288 healthy young and middle-aged adults in 4 US cohorts (ARIC, FHS Offspring, CARDIA, MESA) followed up for a median of 16 years, the highest quartiles of cumulative LDL-C exposure level and time-weighted average LDL-C were associated with incident CHD (aHR, 1.57 [95% CI, 1.10–2.23] for cumulative LDL-C level; aHR, 1.69 [95% CI, 1.23–2.31] for time-weighted average LDL-C) relative to the lowest quartile of each measure, adjusted for demographic and clinical risk factors and index visit LDL-C.⁸⁹
- In 589 participants in the Cardiovascular Risk in Young Finns Study with non-HDL-C measured in adolescence (12–18 years of age), young adulthood (21–30 years of age), and middle adulthood (33–45 years of age), a 38.61-mg/dL higher non-HDL-C at each life stage was associated with higher odds of CAC in middle adulthood, adjusted for cardiovascular risk factors (adolescence aOR, 1.16 [95% credible interval, 1.01–1.46]; young adulthood aOR, 1.14 [95% credible interval, 1.01–

Control

- Among US adults receiving statin therapy, age-adjusted rates of lipid control (TC ≤200 mg/dL) did

interval, 1.01–1.34]), with an accumulated aOR for CAC of 1.50 (95% credible interval, 1.14–1.92).⁹⁰

-
- In a large study of the National Health Insurance Service in Korea (N=15 860 253) starting in 2009 to 2010 that evaluated 555 802 deaths resulting from all causes during a mean of 8.4 years of follow-up through 2018, a U-shaped association of HDL-C with all-cause mortality was observed. Relative to HDL-C levels of 50 to 59 mg/dL, individuals at the lowest HDL-C levels (<20 mg/dL) had higher risk for all-cause mortality (aHR for [95% CI, 1.84–2.40]), and individuals at the highest HDL-C levels (≥ 110 mg/dL) also had
 - In >460 000 individuals from the UK Biobank, the risk of incident ASCVD per 50 nmol/L lipoprotein(a) was similar across ethnicity, with an HR of 1.11 (95% CI, 1.10–1.12) in White individuals, 1.10 (95% CI, 1.04–1.16) in South Asian individuals, and 1.07 (95% CI, 1.00–1.15) in Black individuals.¹⁰ Lipoprotein(a) ≥ 150 nmol/L was present in 12.2% of those higher risk for all-cause mortality (aHR for males, 1.30 [95% CI, 1.23–1.38]; aHR for females, 1.21 [95% CI,

for incident ASCVD, respectively.

- In an analysis among >435 000 adults in the UK Biobank, each 50–nmol/L higher lipoprotein(a) was associated with a higher risk of AF (HR, 1.03 [95% CI, 1.02–1.04]).⁹⁵ Only 39% (95% CI, 27%–73%)
- A mendelian randomization analysis of data from 654 783 participants including 91 129 cases of CHD demonstrated that triglyceride-lowering vari-

of the lipoprotein(a)-associated risk was mediated through ASCVD, suggesting that lipoprotein(a) may increase risk of AF independently of its effect on variants in the lipoprotein lipase gene and LDL-C-lowering variants in the LDL receptor gene were associated with similarly lower CHD risk when evaluated per 10-mg/dL lower apolipoprotein B level (OR, 0.771 [95% CI, 0.741–0.802] and 0.773 [95% CI, 0.747–0.801], respectively). This suggested that

ASCVD risk.
the clinical benefit of both triglyceride and LDL-C lowering might be related to the absolute reduction in apolipoprotein B-containing lipoprotein particles (very-low-density lipoprotein and LDL particles,

- In a systematic review and meta-analysis of 43 studies comprising data from 957 253 participants, lipoprotein(a) in the top (versus bottom) tertile was associated with a higher risk of all-cause mortality in the general population (HR, 1.09 [95% CI, 1.01–1.18]) and in patients with CVD (HR, 1.18 [95% CI, 1.04–1.34]).⁹⁶ There was a linear dose-response relationship indicating that each 50-mg/dL higher lipoprotein(a) was associated with a 31% higher risk of death in the general population.³⁵
- In a systematic review and trial-level meta-regression analysis that included 197 270 participants from 24 nonstatin trials and 25 statin trials, the RR of major vascular events was 0.80 (95% CI, 0.76–0.85) per 1-mmol/L reduction in LDL-C (or 0.79 per 40 mg/dL) and 0.84 (95% CI, 0.75–0.94) per

- Among 502 655 adults 40 to 69 years of age in the UK Biobank, a linear association between higher prepandemic HDL-C level and later COVID-19–related hospitalization was observed.⁹⁷ Each 0.2–mmol/L higher HDL-C level was associated with 7% lower odds of hospitalization (aOR, 0.93 [95% CI, 0.90–0.96]).
- A meta-analysis of 21 RCTs of lipid-lowering therapies, including statins, ezetimibe, and PCSK9 inhibitors, comprising 184 012 patients with mean 4.4 years of follow-up showed greater RR reduction of major vascular events with increasing duration of treatment: each 1 mmol/L of LDL-C lowered was associated with a 12% (95% CI, 8%–16%) RR reduction for year 1, 20% (95% CI, 16%–24%) reduction for year 3, 23% (95% CI, 18%–27%) reduction for year 5, and 29% (95% CI, 14%–42%) reduction for year 7.⁹³
- Among 20 490 adults who had an MI or coronary revascularization in Stockholm, Sweden, between 2012 and 2018 and initiated lipid-lowering therapy, the risk of MACEs was significantly lower for each 10% increase in 1-year adherence (HR, 0.94 [95% CI, 0.93–0.96]), intensity (HR, 0.92 [95% CI, 0.88–0.96]), and adherence-adjusted intensity (HR, 0.91 [95% CI, 0.89–0.94]).⁹⁴

from RCTs of statin therapy participating in the Cholesterol Treatment Trialists' Collaboration evaluated the risk of diabetes associated with statin treatment.⁹⁸ Compared with placebo, randomization to low- or moderate-intensity statin resulted in a 10% proportional increase in new-onset diabetes (1.3% versus 1.2% per year; rate ratio, 1.10 [95% CI, 1.04–1.16]), and randomization to high-intensity statin resulted in a 36% proportional increase in new-onset diabetes (4.8% versus 3.5% per year; rate ratio, 1.36 [95% CI, 1.25–1.48]). Among participants who had a baseline measure of glycaemia, ≈62% of new-onset diabetes cases were in the top 25% of the baseline glucose distribution (mean fourth quartile HbA1c, 6.2% in the low- to moderate-intensity statin trials and 6.1% in the high-intensity statin trials).

- In an analysis of 27 756 adults from 5 US prospective studies of CVD (ARIC, CARDIA, Framingham

Offspring, JHS, and MESA) of 21.1 years, lipoprotein(a) (averaging 53 mg/dL; centile) was associated with ASCVD events (HR, 1.46 including MI (HR, 1.66 [95% revascularization (HR, 1.69 The risk of ASCVD events higher among those with 1.92 [95% CI, 1.50–2.45]). lar by sex, race and ethnicity, levels.

- In the Copenhagen General Population study of 108 146 individuals followed up for a median of 7.4 years, those with lipoprotein(a) ≥ 99 th percentile (versus < 50 th percentile) had higher risks of developing PAD (RR, 2.99 [95% CI, 2.09–4.30]), AAA (RR, 2.22 [95% CI, 1.21–4.07]), and major adverse limb events (RR, 3.04 [95% CI, 1.55–5.98]).¹⁰⁰ Among 6086 cases of first MI and 6857 controls from the INTERHEART study, which included individuals of African, Chinese, Arab, European, Latin American, South Asian, and Southeast Asian descent, lipoprotein(a) concentrations > 50 mg/dL were associated with a higher risk of MI (OR, 1.48 [95% CI, 1.32–1.67]).¹² The association was strongest in South Asian individuals (OR, 2.14 [95% CI, 1.59–2.89]).

ambulatory care, 5.9% care facility, 0.5% ED). the conditions with the highest growth for public insurance at 9.3% (95% CI, 8.2%–spending growth for all, 4.0% for private of-pocket payments.

- Among Medicare Part D States from 2014 to 2018, for LDL-C–lowering therapy \$6.3 billion in 2014 to \$3.3

Cost

- In an analysis of 2016 US health care spending, hyperlipidemia ranked the 35th most expensive health condition, with estimated spending of \$26.4 (95% CI, \$24.3–\$29.4) billion overall.¹⁰¹ Costs were split relatively evenly between younger and older adults (51.0% for 20–64 years of age, 48.4% for ≥ 65 years of age, 0.6% for < 20 years of age), were higher for public compared with private insurance (49.1% public insurance, 43.8% private insurance, 7.1% out-of-pocket payments), and were concentrated in prescription medications and ambulatory visits (45.6% prescribed pharmaceuticals, 33.4%

Global Burden of Hypercholesterolemia

(See Chart 7-5 and Table 7-2)

- Among the GBD data, global years of life lost attributable to high LDL-C totaled 5.71 million (95% UI, 3.68–8.27) in 2019. LDL-C was the third highest contributor to CVD DALYs in 2019, after high SBP and dietary risks.¹⁰³
- Based on 204 countries and territories, among regions, age-standardized mortality rates attributable to high LDL-C were highest for eastern Europe followed by Central Asia and North Africa and the Middle East in 2021 (Chart 7-5). There were 3.65 (95% UI, 2.13–5.26) million total deaths attributable to high LDL-C in 2021. The PAF was 5.37% (95% UI, 3.12%–7.77%; Table 7-2).
- Among >10.7 million adults across 31 provinces of China between 2017 and 2020, the prevalence of dyslipidemia (TC ≥200 mg/dL, triglycerides ≥150 mg/dL, LDL-C ≥130 mg/dL, HDL-C <40 mg/dL, or use of dyslipidemia medication) was 58.4%, with mean TC of 191 mg/dL, triglycerides of 123 mg/dL, LDL-C of 109 mg/dL, and HDL-C of 52 mg/dL.¹⁰⁴
- Among Korean adults ≥20 years of age evaluated in the 2007 to 2020 Korean National Health and Nutrition Examination Survey, the prevalence of triglycerides ≥150 mg/dL was 38.5% in males and 20.5% in females. In 2020, ≈10% of Korean adults were using lipid-lowering medications.¹⁰⁵

Table 7-1. High TC and LDL-C and Low HDL-C, United States (≥20 Years of Age), 2017 to 2020

Population group	Prevalence of TC≥200 mg/dL	Prevalence of TC≥240 mg/dL	Prevalence of LDL-C≥130 mg/dL	Prevalence of HDL-C<40 mg/dL
Both sexes	86 400 000 (34.7)	24 700 000 (10.0)	63 100 000 (25.5)	41 300 000 (16.9)
Males	38 900 000 (32.8)	11 000 000 (9.5)	30 300 000 (25.6)	29 900 000 (24.9)
Females	47 500 000 (36.2)	13 700 000 (10.4)	32 800 000 (25.4)	11 400 000 (9.3)
NH White males	32.5	9.6	25.0	25.0
NH White females	37.2	10.7	24.0	8.8
NH Black males	27.5	6.9	26.4	15.3
NH Black females	29.6	9.3	22.5	7.9
Hispanic males	32.8	9.3	23.7	29.5
Hispanic females	33.6	10.0	27.5	11.8
NH Asian males	40.7	13.0	31.5	25.4
NH Asian females	37.7	8.7	25.3	6.9

Values are number (percent) or percent. Prevalence of TC ≥200 mg/dL includes people with TC ≥240 mg/dL. In adults, levels of 200 to 239 mg/dL are considered borderline high, and levels of ≥240 mg/dL are considered high. Data for TC, LDL-C, and HDL-C are age adjusted. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹⁰⁶

COVID-19 indicates coronavirus disease 2019; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES,⁵ applied to 2020 population estimates.

Table 7-2. Deaths Caused by High LDL-C Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	3.65 (2.13 to 5.26)	2.01 (1.21 to 2.85)	1.64 (0.91 to 2.46)
Percent	48.69 (40.45 to 56.94)	57.63 (46.33 to 69.75)	39.02 (30.18 to 48.20)
Percent change (%) in total	17.41 (11.77 to 22.99)	18.52 (10.86 to 26.48)	16.08 (9.59 to 23.38)
Rate per 100 000, age	43.67 (25.33 to 63.43)	53.15 (31.05 to 76.26)	35.12 (19.69 to 52.58)
Percent change (%) in rate, age	−38.06 (−41.08 to −34.70)	−33.91 (−38.25 to −28.96)	−42.36 (−45.58 to −38.40)
Percent change (%) in rate, age	−14.68 (−18.40 to −10.83)	−13.11 (−18.43 to −7.46)	−16.25 (−20.84 to −10.94)
PAF (%), all ages, 2021	5.37 (3.12 to 7.77)	5.33 (3.23 to 7.51)	5.42 (3.01 to 8.06)
Percent change (%) in PAF, all	0.98 (−3.30 to 4.92)	3.76 (−1.69 to 9.35)	−1.98 (−7.10 to 2.72)
Percent change (%) in PAF, all	−8.21 (−10.60 to −5.72)	−8.68 (−11.59 to −5.77)	−7.62 (−10.87 to −4.72)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; LDL-C, low-density lipoprotein cholesterol; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁰⁷

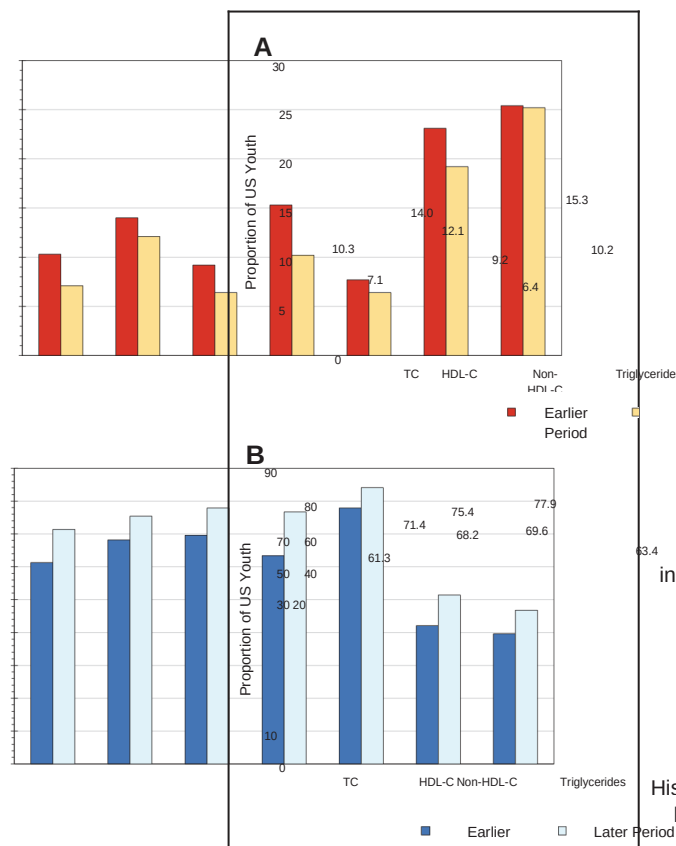


Chart 7-1. Proportions of US youths with high (or, for HDL-C, low) and acceptable lipid levels, period of 1999 to 2016, NHANES.

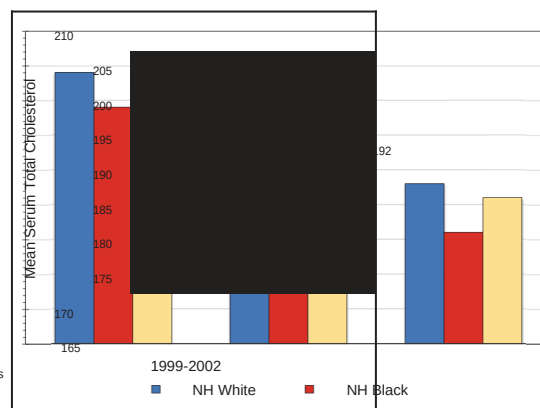
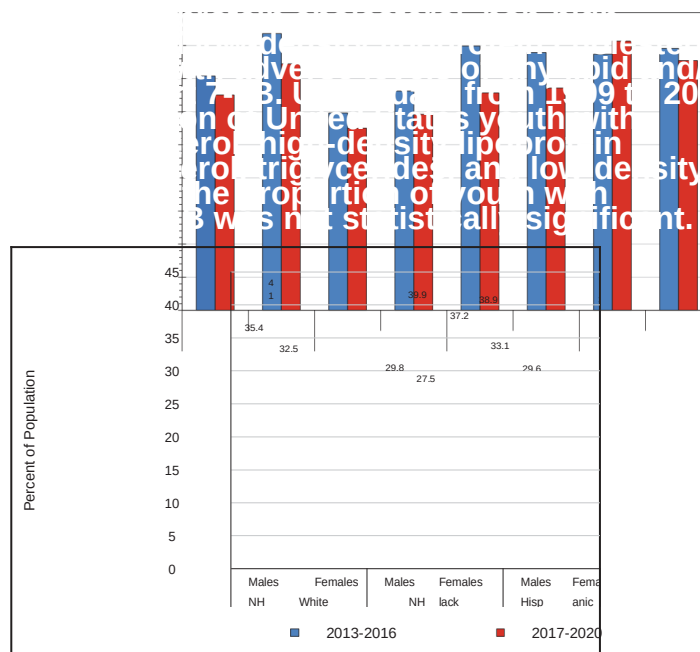


Chart 7-2. Age-adjusted trends in adults ≥ 20 years of age, by race and (NHANES 1999–2002, 2007–2010).

Values are in milligrams per deciliter. pandemic halted NHANES field in the partial 2019 to 2020 cycle are not they were combined with previously produce nationally representative COVID-19 indicates coronavirus NHANES. National Health and total cholesterol. *Data for the category of Mexican collected in all NHANES years, but the Hispanic people was used starting only in long-term trend data, the category of used.

Source: Unpublished National Heart, tabulation using NHANES.⁵

A, High (or, for HDL-C, low) lipid levels. **B**, Acceptable lipid levels. TC, HDL-C, and non-HDL-C are shown for all youths 6 to 19 years of age, and triglycerides, LDL-C, and any or all lipids plus apoB are shown for fasting adolescents 12 to 19 years of age. **A**, For high (or, for HDL-C, low) lipid levels, the earlier and later periods shown for each lipid are as follows: 1999 to 2006 and 2009 to 2016 for TC; 2007 to 2010 and 2013 to 2016 for HDL-C; 2007 to 2010 and 2013 to 2016 for non-HDL-C; 1999 to 2006 and 2007 to 2014 for triglycerides; 1999 to 2006 and 2007 to 2014 for LDL-C; 2007 to 2010 and 2013 to 2016 for any of TC, HDL-C, or non-HDL-C; and 2007 to 2010 and 2011 to 2014 for any lipid or apoB. **B**, For acceptable lipid levels, the earlier and later periods shown for each lipid are as follows: 1999 to 2000 and 2015 to 2016 for TC; 2007 to 2008 and 2015 to 2016 for TC; 2007 to 2008 and 2015 to 2016 for TC, HDL-C, and non-HDL-C; and 2007 to 2008 and 2013 to 2014 for all lipids and apoB. High (or, for HDL-C, low) and acceptable levels were defined according to the 2011 National Heart, Lung, and Blood Institute pediatric guideline⁵⁸ as follows: for TC, ≥ 200 and <170 mg/dL, respectively;



for LDL-C, ≥ 130 and <110 mg/dL; for HDL-C, <40 and >45 mg/dL; for non-HDL-C, ≥ 145 and <120 mg/dL; for triglycerides, ≥ 130 and <90 mg/dL; and for apoB, ≥ 110 and <90 mg/dL.

Chart 7-3. Age-adjusted trends in the prevalence of serum TC ≥ 200 mg/dL in US adults ≥ 20 years of age, by race and ethnicity, sex, and survey year (NHANES 2013–2016 and 2017–2020).

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹⁰⁶

apoB indicates apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.

Source: Data derived from Perak et al.⁶

COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and total cholesterol.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁵

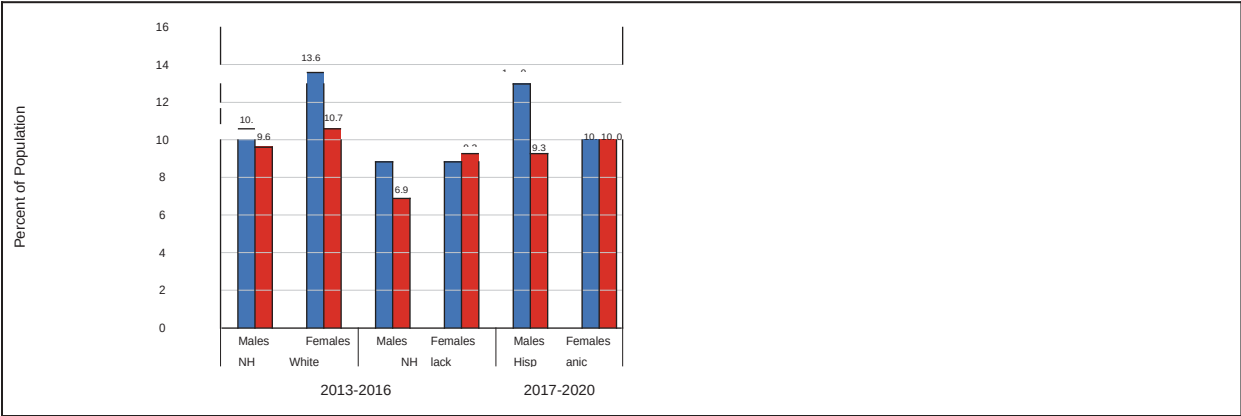


Chart 7-4. Age-adjusted trends in the prevalence of serum TC ≥ 240 mg/dL in US adults ≥ 20 years of age, by race and ethnicity, sex, and survey year (NHANES 2013–2016 and 2017–2020).

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹⁰⁶ COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁵

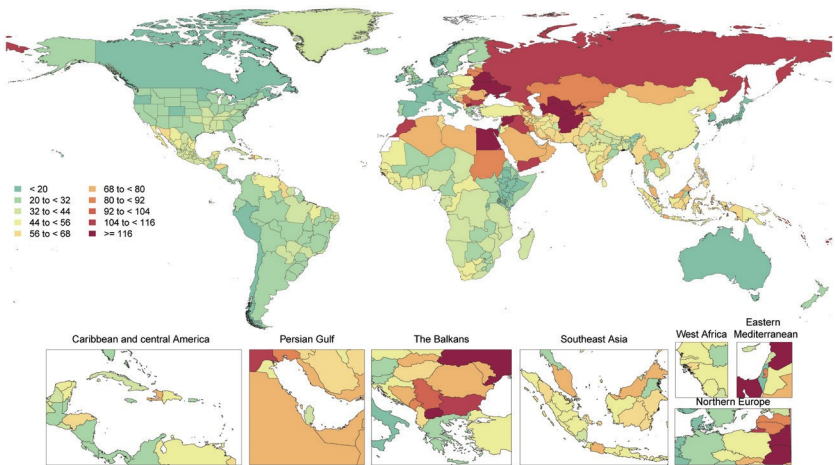


Chart 7-5. Age-standardized global mortality rates attributable to high LDL-C per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and LDL-C, low-density lipoprotein cholesterol.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁰⁷

REFERENCES

- Lloyd-Jones DM, Allen NB, Anderson CAM, RE, Grandner MA, Lavretsky H, Perak AM, the American Heart Association. Life's into the American Heart Association's a presidential advisory from the American 2022;146:e18–e43. doi:
- Grundv SM, Stone NJ, Bailey AL, Beam C, Braun LT, de Ferranti S, Faiella-Tommasino AHA/ACC/AACVPR/AAPA/ABC/ACPM/ NLA/PCNA guideline on the management of lished corrections appear in *Circulation*. *Circulation*. 2023;148:e51. *Circulation*. 10.1161/CIR.0000000000000625
- Arnett DK, Blumenthal RS, Albert MA, Buroker EJ, Himmelfarb CD, Khera A, Lloyd-Jones ACC/AHA guideline on the primary ease (published corrections appear in *Circulation*. 2020;141:e60. and *Circulation*. 2019;140:e596–e646. doi:
- Lloyd-Jones DM, Morris PB, Ballantyne CM, DePalma SM, Minissian MB, Orringer CE, Writing Committee. 2022 ACC expert role of nonstatin therapies for LDL- of atherosclerotic cardiovascular disease leage of Cardiovascular Solution Set Oversight 2022;80:1366–1418. doi:
- Centers for Disease Control and Prevention Statistics. National Health and Nutrition public use data files. Accessed April 1.
- Perak AM, Nina H, Kit BK, de Ferranti SD, Van Lloyd-Jones DM. Trends in levels of lipids youths aged 6 to 19 years. 1999–2016. doi: 10.1001/iama.2019.4984
- US Department of Health and Human cessed March 14, 2024.
- Aggarwal R, Chiu N, Libby P, Boden WE. lipoprotein cholesterol levels in adults with the US. January 2015 to March 2020. 10.1001/iama.2023.8646
- Koschinsky ML, Baij A, Boffa MB, Dixon DL, Gill EA, Jacobson TA, Michos ED, Safarova the 2019 NLA scientific statement on use of tice. *J Clin Lipidol*. 2024;18:e308–e319. doi:
- Patel AP, Wang M, Pirruccello JP, Ellnor PT, AV, Lo(a) (lipoprotein(a)) concentrations and diovascular disease: new insights from a *Thromb Vasc Biol*. 2021;41:465–474. doi:
- Joshi PH, Marcovina S, Orroth K, Lopez JAG, K, Sotres-Alvarez D, Thvaaraian B. lipoprotein(a) levels among Hispanic or *JAMA Cardiol*. 2023;8:691–696. doi:
- Pare G, Caku A, McQueen M, Anand SS, Koschinsky M, Wang X, Yusuf S: levels and the risk of myocardial infarction 2019;139:1472–1482. doi:
- Aberra T, Peterson ED, Padipati NJ, Mulder Granowitz C, Navar AM. The association cardiovascular disease: what is “optimal?” *J e3*. doi: 10.1016/j.jacl.2020.04.009
- Aggarwal R, Bhatt DL, Rodriguez F, Yeh RW. concentrations and lipid control among US 2022;328:737–745. doi:
- Carroll MD, Fryar CD. Total and high-density lipoprotein cholesterol in adults: United States, 2015–2018. *NCHS Data Brief*. 2020;1:8.
- Patel N, Bhargava A, Kalra R, Parcha V, Arora G, Muntner P, Arora P. Trends in lipid, lipoproteins, and statin use among U.S. adults: impact of 2013 cholesterol guidelines. *J Am Coll Cardiol*. 2019;74:2525–2528.
- to 44 Years, 2009 to March 2020. 10.1001/iama.2023.2307
- Lee MS, Chen A, Zhou H, Herald J. sclerotic risk factors during the COVID- *Med*. 2023;64:125–128. doi:
- Carroll MD, Kruszon-Moran D, Tolliver high-density lipoprotein cholesterol. terol for adults aged 20 and over. 2005- 2019;1:16.
- Willer CJ, Schmidt EM, Sengupta S, Ganna A, Chen J, Buchkovich ML, Consortium. Discovery and refinement *Nat Genet*. 2013;45:1274–1283. doi:
- Peloso G, Auer P, Bis J, Voorman A, Khetaroal S, Crosby J, Fornace M. coding-sequence variants with blood in 56,000 Whites and Blacks. *Am J* 10.1016/j.ajha.2014.01.009
- Dewe FE, Murray MF, Overton JD, O'Dushlaine C, Van Hout CV. Staples tribution and clinical impact of sequences from the DiscovEHR study. 10.1126/science.aaf6814
- Natarajan P, Peloso GM, Zekavat SM, Khera AV, Zhou W, Bloom JM, ids Working Group. Deep coverage blood lipids among 16,324 individuals. 10.1038/s41467-018-05747-8
- Klarin D, Damrauer SM, Cho K, Sun DR, DuVall SL, Li J, Peloso GM, et al: tium. Genetics of blood lipids among of the Million Veteran Program. *Nat* 10.1038/s41588-018-0222-9
- Graham SE, Clarke SL, Wu KH, Kanoni Ntalla I, Vedantam S, Winkler TW, et al: The power of genetic diversity in *Nature*. 2021;600:675–679. doi:
- Patel AP, Wang M, Ruan Y, Kovama S, Aorawal S, Fahed AC, Ellnor PT, et al: and the Million Veteran Program. A proves risk prediction for coronary 1803. doi: 10.1038/s41591-023-02429-
- Selvaraj MS, Li X, Li Z, Pampana A, Brody JA, Cade BE, et al; NHLBI tium. Whole genome sequence viduals. *Nat Commun*. 2022;13:5995.
- Zekavat SM, Ruotsalainen S, T, Seed C, Ernst J, Chaffin M, Engreitz Working Group. Deep coverage whole lipoprotein(a) in individuals of *mun*. 2018;9:2606. doi:
- Bolli A, Di Domenico P, Pastorino R, nary artery disease conferred by low- pendents on polygenic background. 10.1161/
- Khera AV, Chaffin M, Zekavat SM, JH, D'Onofrio G, Mattera J, Drever R. characterize monoogenic and polygenic with early-onset myocardial infarction. doi:
- Allara E, Morani G, Carter P, Gkatzionis Mason AM, Bell S, Gill D, et al: of lipids and cardiovascular disease randomization investigation. *Circ* doi: 10.1161/CIRCGEN.119.002711 doi: 10.1016/j.jacc.2019.09.026
- Aggarwal R, Yeh RW, Joynt Maddox KE, Wadhera RK. Cardiovascu- lar risk factor prevalence, treatment, and control in US adults aged 20

32. Bjornsson E, Thorleifsson G, Helgadóttir A, Guethnason T, Guethbjartsson T, Andersen K, Gretarsdóttir S, Olafsson I, Tragante V, Olafsson OH, et al. Association of genetically predicted lipid levels with the extent of coronary atherosclerosis in Icelandic adults. *JAMA Cardiol.* 2019;5:13–20. doi: 10.1001/jamacardio.2019.2946
33. Karjalainen MK, Holmes MV, Wang Q, Anufrieva O, Kahonen M, Lehtimäki T, Havulinna AS, Kristiansson K, Salomaa V, Perola M, et al. Apolipoprotein A-I concentrations and risk of coronary artery disease: a

- mendelian randomization study. *Atherosclerosis*. 2020;299:56–63. doi: 10.1016/j.atherosclerosis.2020.02.002
34. Ference BA, Bhatt DL, Catapano AL, Packard CJ, Graham I, Kaptoge S, Ference TB, Guo Q, Laufs U, Ruff CT, et al. Association of genetic variants related to combined exposure to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease. *JAMA*. 2019;322:1381–1391. doi: 10.1001/jama.2019.14120
35. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321:364–373. doi: 10.1001/jama.2018.20045
- Davey Smith G, Holmes MV. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: a multivariable mendelian randomisation analysis. *PLoS Med*. 2020;17:e1003062. doi: 10.1371/journal.pmed.1003062
37. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van der Kooij AJ, et al. Genetic variants associated with low-density lipoprotein cholesterol from eight European countries. *Atherosclerosis*. 2020;292:178–187. doi: 10.1016/j.atherosclerosis.2019.11.012
50. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. *JAMA*. 2017;318:381–382. doi: 10.1001/jama.2017.8543
51. Lee C, Rivera-Valerio M, Bangash H, Prokop L, Kullo IJ. New case detection by cascade testing in familial hypercholesterolemia: a systematic review of the literature. *Circ Genom Precis Med*. 2019;12:e002723. doi: 10.1161/CIRCGEN.119.002723
52. Wald DS, Bestwick JP. Reaching detection targets in familial hypercholesterolemia: Comparison of identification and treatment. *Leeuwen EM, Natarajan P, Emdin CA, Bick AG, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol*. 2016;67:2578–2589. doi: 10.1016/j.jacc.2016.03.520

- J, Schürfeld C, Spitthöver R, Versen A, et al. Cardiovascular outcome of pediatric patients with bi-allelic (homozygous) familial hypercholesterolemia before and after initiation of multimodal lipid lowering therapy including lipoprotein apheresis. *Am J Cardiol.* 2020;136:38–48. doi: 10.1016/j.amjcard.2020.09.015
54. Bello-Chavolla OY, Kuri-Garcia A, Rios-Rios M, Vargas-Vazquez A, CA. Familial combined hyperlipidemia: current knowledge, perspectives, and controversies. *Rev Invest Clin.* 2018;70:224–236. doi: 10.24875/RIC.18002575
38. Defesche JC, Stefanutti C, Langslet G, Hopkins PN, Seiz W, Baccara-Dinet MT, Hamon SC, Banerjee P, Kastelein JJP. Efficacy of alirocumab in 1191 patients with a wide spectrum of mutations in genes causative for familial hypercholesterolemia. *J Clin Lipidol.* 2017;11:1338–1346.e7. doi: 10.1016/j.jacl.2017.08.016
39. Banda JM, Sarraju A, Abbasi F, Parizo J, Pariani M, Ison H, Briskin E, Wand H, Dubois S, Jung K, et al. Finding missed cases of familial hypercholesterolemia in health systems using machine learning. *NPJ Digit Med.* 2019;2:23. doi: 10.1038/s41746-019-0101-5
40. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. World-wide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. *J Am Coll Cardiol.* 2020;75:2553–2566. doi:

55. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 7, 2024.
56. Gao Y, Shah LM, Ding J, Martin SS. US trends in cholesterol screening, lipid levels, and lipid-lowering medication use in US adults, 1999 to 2018. *J Am Heart Assoc*. 2023;12:e028205. doi: 10.1161/JAHA.122.028205
57. Shetty NS, Gaonkar M, Patel N, Knowles JW, Natarajan P, Arora G, Arora P. Trends of lipid concentrations, awareness, evaluation, and treatment in severe dyslipidemia in US adults. *Mayo Clin Proc*. 2024;99:271–282. doi: 10.1016/j.mayocp.2023.09.016
- 10.1016/j.jacc.2020.03.057
41. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. *Circulation*. 2016;134:9–19. doi: 10.1161/CIRCULATIONAHA.116.022335
42. Mundal LJ, Hovland A, Igland J, Veierod MB, Holven KB, Bogsrud MP, Tell GS, Leren TP, Retterstol K. Association of low-density lipoprotein cholesterol with risk of aortic valve stenosis in familial hypercholesterolemia. *JAMA Cardiol*. 2019;4:1156. doi: 10.1001/jamacardio.2019.3903
43. Trinder M, Francis GA, Brunham LR. Association of monogenic vs polygenic hypercholesterolemia with risk of atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2020;5:390–399. doi: 10.1001/jamacardio.2019.5954
44. Perez de Isla L, Alonso R, Mata N, Fernandez-Perez C, Muniz O, Diaz-Diaz JL, Saltijeral A, Fuentes-Jimenez F, de Andres R, Zambon D, et al. 58. National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128:S213–S256. doi: 10.1542/peds.2009-2107C
- Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation*. 2017;135:2133–2144. doi: 10.1161/CIRCULATIONAHA.116.024541
45. Lurink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-Year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med*. 2019;381:1547–1556. doi: 10.1056/NEJMoa1816454
46. Buchholz EM, Rodday AM, Kolor K, Khoury MJ, De Ferranti SD. Prevalence and predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia (1999–2014). *Circulation*. 2018;137:2218–2230. doi: 10.1161/CIRCULATIONAHA.117.032321
47. deGoma EM, Ahmad ZS, O'Brien EC, Kindt I, Shrader P, Newman CB, Pokharel Y, Baum SJ, Hemphill LC, Hudgins LC, et al. Treatment gaps in

59. Zhang X, DeSantes K, Dodge A, Larson M, Eickhoff J, Moreno M, Peterson A. Practices and attitudes regarding pediatric cholesterol screening recommendations differ between pediatricians and family medicine clinicians. *Pediatric Cardiol.* 2022;43:631–635. doi: 10.1007/s00246-021-02767-y 60. Smith AJ, Turner EL, Kinra S, Bodurtha JN, Chien AT. A cost analysis of universal versus targeted cholesterol screening in pediatrics. *J Pediatr.* 2018;196:201–207.e2. doi: 10.1016/j.jpeds.2018.01.027
61. Alexander GC, Tajanlangit M, Heyward J, Mansour O, Qato DM, Stafford RS. Use and content of primary care office-based vs telemedicine care visits during the COVID-19 pandemic in the US. *JAMA Netw Open.* 2020;3:e2021476. doi: 10.1001/jamanetworkopen.2020.21476
62. Hu X, Cristino J, Gautam R, Mehta R, Amari D, Heo JH, Wang S, Wong ND. Characteristics and lipid lowering treatment patterns in patients tested for lipoprotein(a): a real-world US study. *Am J Prev Cardiol.* 2023;14:100476. doi: 10.1016/j.ajpc.2023.100476
63. Bhatia HS, Hurst S, Desai P, Zhu W, Yeang C. Lipoprotein(a) testing trends in a large academic health system in the United States. *J Am Heart Assoc.* 2023;12:e031255. doi: 10.1161/JAHA.123.031255
64. Panza GA, Blazek O, Tortora J, Saucier S, Fernandez AB. Prevalence of lipoprotein(a) measurement in patients with or at risk of cardiovascular disease. *J Clin Lipidol.* 2023;17:748–755. doi: 10.1016/j.jacl.2023.09.016 65. Faaborg-Andersen CC, Cho SMJ, Natarajan P, Honigberg MC. Trends and disparities in lipoprotein(a) testing in a large integrated U.S. health system, 2000-2023. *Eur J Prev Cardiol.* 2024;31:e79–e82. doi: 10.1093/eurjpc/zwae155
- adults with heterozygous familial hypercholesterolemia in the United States: data from the CASCADE-FH Registry. *Circ Cardiovasc Genet.* 2016;9:240–249. doi: 10.1161/CIRCGENETICS.116.001381
48. de Ferranti SD, Shrader P, Linton MF, Knowles JW, Hudgins LC, Benuck I, Kindt I, O'Brien EC, Peterson AL, Ahmad ZS, et al. Children with hetero-

66. Elias S, Turkson-Ocran RA, Koirala B, Byiringiro S, Baptiste D, Himmelfarb CR, Commodore-Mensah Y. Heterogeneity in cardiovascular disease risk factors among Latino immigrant subgroups: evidence from the 2010 to 2018 National Health Interview Survey. *J Am Heart Assoc.* 2023;12:e027433. doi: 10.1161/JAHA.122.027433
- zygous familial hypercholesterolemia in the United States: data from the Cascade Screening for Awareness and Detection-FH Registry. *J Pediatr.* 2021;229:70–77. doi: 10.1016/j.jpeds.2020.09.042
49. Ramaswami U, Futema M, Bogsrud MP, Holven KB, Roeters van Lennep J, Wiegman A, Descamps OS, Vrablik M, Freiburger T, Dieplinger H, et al. Comparison of the characteristics at
67. Sayed A, Navar AM, Slipczuk L, Ballantyne CM, Samad Z, Lavie CJ, Virani SS. Prevalence, awareness, and treatment of elevated LDL cholesterol in US adults, 1999-2020. *JAMA Cardiol.* 2023;8:1185–1187. doi: 10.1001/jamacardio.2023.0000
- diagnosis and treatment of children with heterozygous familial hypercholesterolaemia (FH)

- among young adults in the US, 2003-2020. 1080. doi: 10.1001/iamacardio.2022.2641
69. Caceres BA, Sharma Y, Ravindranath R, Streed CG. Differences in ideal minority and heterosexual adults. *JAMA* 10.1001/iamacardio.2022.5660
70. Lu Y, Liu Y, Dhindra LS, Caraballo C, Sharma R, Rodriguez F, Watson KE, et al. disparities in use of recommended therapies cardiovascular disease. 1999-2020. *JAMA* doi: 10.1001/iamanetworkopen.2023.45964
71. Lahoz R, Seshaniri D, Electricwala B, Sturder R. Clinical characteristics and atherosclerotic cardiovascular disease with hypercholesterolemia: a retrospective analysis of a large US real-world database cohort. *Curr Med Res Opin*. 2024;40:15–25. doi: 10.1080/03007995.2023.2270901
72. Zheutlin AR, Derington CG, Herrick JS, Rosenson RS, Poudel B, Safford MM, Brown TM, Jackson EA, Woodward M, Reading S, et al. Lipid-lowering therapy use and intensification among United States veterans following myocardial infarction or coronary revascularization between 2015 and 2019. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008861. doi: 10.1161/CIRCOUTCOMES.121.008861
73. Leino AD, Dorsch MP, Lester CA. Changes in statin use among U.S. adults with diabetes: a population-based analysis of NHANES 2011-2018. *Diabetes Care*. 2020;43:3110–3112. doi: 10.2337/dc20-1481
84. Hong SJ, Lee YJ, Lee SJ, Hong BK, Yoon J, Ahn CM, et al: LODESTAR intensify statin in patients with coronary trial. *JAMA*. 2023;329:1078–1087. doi: 10.1136/bmi-2023-075837
85. Lee YJ, Hong SJ, Kang WC, Hong BK, J, Lee SJ, Ahn CM, et al: LODESTAR atorvastatin treatment in adults with analysis of the randomised
86. Anarwal A, Mehta PM, Jacobson T, Bahiru E, de Cates AN, Ebrahim S, et al: nv for the prevention of atherosclerotic
74. Hammond MM, Cameron NA, Ning H, Bah I, Beltrame K, Khan SS, Shah NS. Statin use and eligibility for primary prevention of atherosclerotic cardiovascular disease among adults at borderline or intermediate risk in the United States. *J Am Heart Assoc*. 2023;12:e029263. doi: 10.1161/JAHA.122.029263
75. Jacobs JA, Addo DK, Zheutlin AR, Derington CG, Essien UR, Navar AM, Hernandez I, Lloyd-Jones DM, King JB, Rao S, et al. Prevalence of statin use for primary prevention of atherosclerotic cardiovascular disease by race, ethnicity, and 10-year disease risk in the US: National Health and Nutrition

87. Zhang X, Chen Z, Fang A, Kang L, Xu W, Xu B, Chen J, Zhang X. Trends in prevalence, risk factor control and medications in atherosclerotic car-diovascular disease among US adults, 1999-2018. *Am J Prev Cardiol.* 2024;17:100634. doi: 10.1016/j.ajpc.2024.100634
88. Hu G, Ding J, Ryan DH. Trends in obesity prevalence and cardiometabolic risk factor control in US adults with diabetes, 1999-2020. *Obesity (Silver Spring).* 2023;31:841–851. doi: 10.1002/oby.23652
89. Zhang Y, Pletcher MJ, Vittinghoff E, Clemons AM, Jacobs DR Jr, Allen NB, Alonso A, Bellows BK, Oelsner EC, Zeki A, et al. Association between cumulative low-density lipoprotein cholesterol exposure during young adulthood and middle age and risk of cardiovascular events. *JAMA Cardiol.* 2021;6:1406–1413. doi: 10.1001/jamacardio.2021.3508
90. Armstrong MK, Fraser BJ, Hartiala O, Buscot MJ, Juonala M, Wu F, Koskinen J, Hutri-Kahonen N, Kahonen M, Laitinen TP, et al. Association of non-high-density lipoprotein cholesterol measured in adolescence, young adulthood, and mid-adulthood with coronary artery calcification measured in mid-adulthood. *JAMA Cardiol.* 2021;6:661–668. doi: 10.1001/jamacardio.2020.7238
91. Yi SW, Park SJ, Yi JJ, Ohrr H, Kim H. High-density lipoprotein cholesterol and all-cause mortality by sex and age: a prospective cohort study among 15.8 million adults. *Int J Epidemiol.* 2021;50:902–913. doi: 10.1093/ije/dyaa243
- Examination Surveys, 2013 to March 2020. *JAMA Cardiol.* 2023;8:443–452. doi: 10.1001/jamacardio.2023.0228
76. Navar AM, Kolkailah AA, Gupta A, Gillard KK, Israel MK, Wang Y, Peterson ED. Gaps in guideline-based lipid-lowering therapy for secondary prevention in the United States: a retrospective cohort study of 322 153 patients. *Circ Cardiovasc Qual Outcomes.* 2023;16:533–543. doi: 10.1161/CIRCOUTCOMES.122.009787
77. Chobufo MD, Regner SR, Zeb I, Lacoste JL, Virani SS, Balla S. Burden and predictors of statin use in primary and secondary prevention of atherosclerotic vascular disease in the US: from the National Health and Nutrition Examination Survey 2017-2020. *Eur J Prev Cardiol.* 2022;29:1830–1838. doi: 10.1093/eurjpc/zwac103
78. Akbarpour M, Devineni D, Gong Y, Wong ND. Dyslipidemia treatment and lipid control in US adults with diabetes by sociodemographic and cardiovascular risk groups in the NIH Precision Medicine Initiative All of Us research program. *J Clin Med.* 2023;12:1668. doi: 10.3390/jcm12041668
79. Das Pradhan A, Glynn RJ, Fruchart JC, MacFadyen JG, Zaharris ES, Everett BM, Campbell SE, Oshima R, Amarenco P, Blom DJ, et al; PROMINENT Investigators. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. *N Engl J Med.* 2022;387:1923–1934. doi: 10.1056/NEJMoa2210645
80. Ray KK, Troquay RPT, Visseren FLJ, Leiter LA, Scott Wright R, Vikarunnessa S, Tallosy Z, Zang X, Maheux P, Lesogor A, et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. *Lancet Diabetes Endocrinol.* 2023;11:109–119. doi: 10.1016/S2213-8588(23)00010-1

92. Marston NA, Giugliano RP, Im K, Silverman MG, O'Donoghue ML, Wiviott SD, Ference BA, Sabatine MS. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-regression analysis of randomized controlled trials. *Circulation*. 2019;140:1308–1317. doi: 10.1161/CIRCULATIONAHA.119.041998
93. Wang N, Woodward M, Huffman MD, Rodgers A. Compound- ing benefits of cholesterol-lowering therapy for the reduction of major cardiovascular events: systematic review and meta- analysis. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008552. doi: 10.1161/CIRCOUTCOMES.121.008552
94. Mazhar F, Hjemdahl P, Clase CM, Johnell K, Jernberg T, Sjölander A, Carrero JJ. Intensity of and adherence to lipid-lowering therapy as predictors of major adverse cardiovascular outcomes in patients with coronary heart disease. *J Am Heart Assoc*. 2022;11:e025813. doi: 10.1161/JAHA.122.025813
95. Mohammadi-Shemirani P, Chong M, Narula S, Perrot N, Conen D, Roberts JD, Thériault S, Bossé Y, Lanktree MB, Pigeys M, et al. Elevated lipoprotein(a) and risk of atrial fibrillation: an observational and mendelian randomization study. *J Am Coll Cardiol*. 2022;79:1579–1590. doi: 10.1016/j.jacc.2022.02.018
96. Amiri M, Raeisi-Dehkordi H, Verkaar A, Wu Y, van Westing AC, Berk KA, Bramer WM, Aune D, Voortman T. Circulating lipoprotein (a) and all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis. *Eur J Epidemiol*. 2023;38:485–499. doi: 10.1016/S2213-8587(22)00353-9 10.1007/s10654-022-00956-4
81. Ray KK, Raal FJ, Kallend DG, Jaros MJ, Koenig W, Leiter LA, Landmesser U, Schwartz GG, Lawrence D, Friedman A, et al; ORION Phase III Investigators. Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. *Eur Heart J*. 2023;44:129–138. doi: 10.1093/eurheartj/ehac594
82. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, Thompson PD, Libby P, Cho L, Plutzky J, et al; CLEAR Outcomes Investigators. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med*. 2023;388:1353–1364. doi: 10.1056/NEJMoa2215024
83. Nissen SE, Menon V, Nicholls SJ, Brennan D, Laffin L, Ridker P, Ray KK, Mason D, Kastelein JJP, Cho L, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. *JAMA*. 2023;330:131–

97. Lassale C, Hamer M, Hernaez A, Gale CR, Batty GD. Association of pre-pandemic high-density lipoprotein cholesterol with risk of COVID-19 hospitalisation and death: the UK Biobank cohort study. *Prev Med Rep.* 2021;23:101461. doi: 10.1016/j.pmedr.2021.101461

98. Cholesterol Treatment Trialists' Collaboration. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis. *Lancet Diabetes Endocrinol.* 2024;12:306–319. doi: 10.1016/S2213-8587(24)00040-8

99. Wong ND, Fan W, Hu X, Ballantyne C, Hodgevee RC, Tsai MY, Browne A, Budoff MJ. Lipoprotein(a) and long-term cardiovascular risk in a multi-ethnic pooled prospective cohort. *J Am Coll Cardiol.* 2024;83:1511–1525. doi: 10.1001/jama.2023.9696

doi: 10.1016/j.jacc.2024.02.031

100. Thomas PE, Vedel-Krogh S, Nielsen SF, Nordestgaard BG, Kamstrup PR. Lipoprotein(a) and risks of peripheral artery disease, abdominal aortic aneurysm, and major adverse limb events. *J Am Coll Cardiol*. 2023;82:2265–2276. doi: 10.1016/j.jacc.2023.10.009
101. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyas T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA*. 2020;323:863–884. doi: 10.1001/jama.2020.0734
102. Sumarsono A, Lalani HS, Vaduganathan M, Navar AM, Fonarow GC, Das SR, Pandey A. Trends in utilization and cost of low-density lipoprotein cholesterol-lowering therapies among Medicare beneficiaries: an analysis from the Medicare Part D database. *JAMA Cardiol*. 2023;12:201–212. doi: 10.12997/jla.2023.12.2.201
103. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. Global burden of cardiovascular diseases: from the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
104. Fu J, Deng Y, Ma Y, Man S, Yang X, Yu C, Lv J, Wang B, Li L. National and provincial-level prevalence and risk factors of carotid atherosclerosis in Chinese adults. *JAMA Netw Open*. 2024;7:e2351225. doi: 10.1001/jamanetworkopen.2023.51225
105. Park KY, Hong S, Kim KS, Han K, Park CY. Trends in prevalence of hypertriglyceridemia and related factors in Korean adults: a serial cross-sectional study. *J Lipid Atheroscler*. 2023;12:201–212. doi: 10.12997/jla.2023.12.2.201
106. Stierman B, Afful J, Carroll MD, Chen TC, Davv O, Fink S, Frvar CD, Gu S, Hales CM, al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global

8. HIGH BLOOD

BLOOD PRESSURE

*ICD-9 401 to 404; ICD-10 I10 to
through 8-3 and Charts 8-1
through 8-6*

[Click here to return to the Table](#)

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HBP is a major risk factor for CHD, AHA has identified untreated BP (children) and $<120/80$ mm Hg (age) as 1 of the 8 components of ideal CVH.

Prevalence

(See Table 8-1 and Charts 8-1 and 8-2)

- Although surveillance definitions vary widely in the published literature, including for the CDC and NHLBI, as of the 2017 Hypertension Clinical Practice Guidelines, the following definition of hypertension has been proposed for surveillance⁴:
 - SBP ≥ 130 mm Hg, DBP ≥ 80 mm Hg, self-reported antihypertensive medicine use, or having been told previously, at least twice, by a physician or other health professional that one has HBP.
- Other important BP classifications, or phenotypes, assessed by 24-hour ambulatory BP monitoring include the following:
 - Sustained hypertension, defined as elevated clinic BP with elevated 24-hour ambulatory BP
 - White-coat hypertension, defined as elevated clinic BP with normal 24-hour ambulatory BP
 - Masked hypertension, defined as normal clinic BP with elevated 24-hour ambulatory BP
- With the use of the most recent 2017 definition, the age-adjusted prevalence of hypertension

- In NHANES 2017 to 2020,⁵ the hypertension was 28.5% the years of age. 58.6% among of age. and 76.5% among (unpublished NHLBI
- In NHANES 2017 to 2020,⁵ a males than females had of age. For those ≥ 65 years of of females with hypertension males (unpublished NHLBI
- The prevalence of of age is presented by both 8-1.
- Data from NHANES 2017 to 38.0% of US adults with among US adults ≥ 20 years of age was estimated to be 46.7% in NHANES in 2017 to 2020 (50.4% for males and 43.0% for females). This equates to an estimated 122.4 million adults ≥ 20 years of age who have hypertension (62.8 million males and 59.6 million females; Table 8-1).

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- that they have it (unpublished NHLBI tabulation).• The age-adjusted prevalence of hypertension in 1999 to 2002, 2007 to 2010, and 2017 to 2020 is shown in race and ethnicity and sex subgroups in Chart 8-2.
- In 2022, the prevalence of HBP in US adults was highest in Mississippi (40.2%) and lowest in Colorado (24.6%; unpublished NHLBI tabulation using BRFSS₆).
 - In a meta-analysis of 42 studies and 71 353 patients with apparent treatment-resistant hypertension, the overall pooled prevalence of nonadherence was 37% (95% CI, 27%–47%).⁷ The prevalence was higher with direct methods of assessment (eg, direct observed therapy test or therapeutic drug monitoring) at 46% (95% CI, 40%–52%) than with indirect methods (pill counts or questionnaires) at 20% (95% CI, 11%–35%).

Children and Adolescents

- According to the 2017 guidelines from the American Academy of Pediatrics,⁸ hypertension in children and adolescents is defined as follows:
 - 120/80 mm Hg to <95th percentile (whichever is lower) for children 1 to <13 years of age and 120/<80 to 129/<80 mm Hg for those ≥13 years of age
 - Stage 1 hypertension as ≥95th to <95th percentile+12 mm Hg or 130/80 to 139/89 mm Hg for those ≥13 years of age
 - Stage 2 hypertension as ≥95th percentile+12 mm Hg or ≥140/90 mm Hg (whichever is lower) for children 1 to <13 years of age and ≥140/90 mm Hg for those ≥13 years of age
- In NHANES 2015 to 2016, 13.3% (SE, 1.3%) of children and adolescents 8 to 17 years of age had elevated BP, and 4.9% (SE, 0.7%) had hypertension (defined according to the 2017 guidelines from the

American Academy of Pediatrics⁸). Rates of elevated BP were higher among youths 13 to 17 years of age compared with those 8 to 12 years of age (15.6% and 10.8%, respectively). However, rates of hypertension were slightly higher among youths at younger ages, with a prevalence of 4.4% among youths 13 to 17 years of age and 5.3% in youths 8 to 12 years of age.⁹

- In NHANES 2015 to 2016, among youths 8 to the 2017 guidelines from the American Academy of Pediatrics⁸) was more common among males (5.9%) than females (3.8%) and among Mexican American youths (9.0%) compared with NH Black youths (4.7%) and NH White youths (2.7%). Having elevated BP was more common among males (16.9%) than females (9.8%). In addition, Mexican American youths (16.9%) and NH Black youths (16.4%) were more likely to have elevated BP than NH White youths (10.7%).⁹

- In a systematic review of 60 studies of pediatric patients (defined as individuals ≤ 18 years of age) with type 2 diabetes, the prevalence of hypertension among 3463 participants was 25.3% (95% CI, 19.6%–31.5%).¹⁰ Male participants had higher hypertension risk than female participants (OR, 1.42 [95% CI, 1.10–1.83]), with Pacific Islander youths and Indigenous youths (referring to the indigenous populations of North America) having the highest prevalence of all racial and ethnic groups (Pacific Islander youths, 26.7% [95% CI,

- A meta-analysis from 2022 of secondary hyper-tension in children included 19 prospective studies and 7 retrospective studies with 2575 children with hypertension.¹³ The overall pooled prevalence of secondary hypertension was 8.0% (95% CI, 4.0%–13.0%) among otherwise healthy youths with hypertension. Studies conducted in

14.5%–40.7%]; Indigenous youths, 26.5% [95% CI, 17.3%–36.7%]; White youths, 21.0% [95% CI, 12.7%–30.6%]; Black youths, 19.0% [95% CI, 12.0%–27.2%]; Hispanic/Latino youths, 15.1% [95% CI, 6.6%–26.3%]; Asian youths, 18.4% [95% CI, 9.5%–29.2%]).

- In an analysis from SHIP AHOY, a cross-sectional cohort study of 397 adolescents 11 to 19 years of age, the prevalence of hypertension with awake ambulatory BP using the 95th percentile was 17% and 11% for SBP and DBP, respectively.¹¹ With the use of the 2017 ACC/AHA adult thresholds of $\geq 130/80$ mm Hg, the prevalence was higher at 27% and 13% for SBP and DBP, respectively.

- In a 2022 systematic review of 53 studies of pediatric populations from Africa, hypertension prevalence ranged from 0.2% to 38.9%.¹² In the meta-analysis, which included 41 studies and 52 918 participants 3 to 19 years of age from 10 countries, the pooled prevalence for hypertension (SBP or DBP ≥ 95 th percentile) was 7.5% (95% CI, 5.3%–9.9%) and elevated BP (SBP or DBP ≥ 90 th and < 95 th percentile) was 11.4% (95% CI, 8.0–15.3) with a high degree of statistical heterogeneity ($I^2 > 99$).

ducted in referral clinics (pooled prevalence, 20.1% [95% CI, 11.5%–30.3%]).

- A retrospective analysis of medical records from 9 tertiary children's hospitals in China during 2010 to 2020 included 5847 pediatric inpatients (<18 years of age) with a diagnosis of hypertension.¹⁴ The proportion of those with diagnosed secondary hypertension increased from 51.2% during the period of 2010 to 2015 to 59.8% during the period of 2016 to 2020. Compared with primary hypertension, secondary hypertension was more common in girls (43.1% versus 23.3%) and children <5 years of age (32.2% versus 2.1%). Among those with primary hypertension, obesity and obesity-related comorbidities were noted in 85.2% of individuals.
- A systematic review and meta-analysis of 136 studies with 28 612 individuals (4–25 years of age) to estimate the prevalence and complications of masked hypertension showed that the pooled prevalence of masked hypertension was 10.4% (95% CI, 8.0%–12.8%).¹⁵ Compared with the general pediatric population, the prevalence of masked hypertension was higher in the presence of coarctation of the aorta (RR, 1.91 [95% CI, 1.53–2.38]), solid-organ or stem-cell transplantation (RR, 2.34 [95% CI, 2.16–2.54]), CKD (RR, 2.44 [95% CI, 2.29–2.59]), and sickle cell disease (RR, 1.33 [95% CI, 1.06–1.69]). Masked hypertension was associated with greater subclinical cardiovascular outcomes compared with normotension, including higher LVH (OR, 2.44 [95% CI, 1.50–3.96]) and higher pulse wave velocity (WMD, 0.30 m/s [95% CI, 0.14–0.45 m/s]).

Race and Ethnicity

(See Table 8-1 and Chart 8-2)

- Table 8-1 includes statistics on prevalence of HBP, mortality resulting from HBP, hospital discharges for HBP, and cost of HBP for different race, ethnicity, and sex groups.
- The prevalence of hypertension in Black people in the United States is among the highest in the world. According to NHANES 2017 to 2020 data,⁵ the age-adjusted prevalence of hypertension among NH Black people was 55.8% among males and 56.9% among females (Chart 8-2).

- Data from the NHIS 2018 showed ≥ 18 years of age were more been told on ≥ 2 occasions than American (27.2%), White adults (23.7%), or Asian
- Data from the National Adolescent to Adult Health years of age: 2007–2008, 24– show that older age, being male sex, BMI, and current
- With the use of the 2017 American Academy of for children and adolescents 8 (N=12 249) from NHANES NHANES 2015 to 2016 found of either elevated BP or significantly declined from to 13.3% in 2015 to 2016 ($P_{\text{trend}} < 0.001$) and the 4.5% ($P_{\text{trend}} = 0.005$).⁹
- In NHANES, among youths

ated with higher incidence of hypertension (defined as SBP ≥ 140 or DBP ≥ 90 mm Hg).¹⁷ At the individual level, compared with NH White students, NH Black students (OR, 1.21 [95% CI, 1.03–1.42]) and Asian students (OR, 1.28 [95% CI, 1.02–1.62]) had higher odds of hypertension. At the school level, however, hypertension was associated with the percentage of NH White students (OR for 10% higher, 1.06 [95% CI, 1.01–1.09]). Parental education and neighborhood-level fixed effects were not associated with hypertension.

- Data from 13 160 participants in cohorts in the Cardiovascular Lifetime Risk Pooling Project (ie, the Framingham Offspring Study, CARDIA, and ARIC) showed that the lifetime risk of hypertension from 20 to 85 years of age according to the 2017 Hypertension Clinical Practice Guidelines was 86.1% (95% CI, 84.1%–88.1%) for Black males, 85.7% (95% CI, 84.0%–87.5%) for Black females, 83.8% (95% CI, 82.5%–85.0%) for White males, and 69.3% (95% CI, 67.8%–70.7%) for White

Incidence and Lifetime Risk

normal weight (8–17 years of age), there was a statistically significant decline in the prevalence of elevated BP/hypertension and hypertension (defined according to the 2017 guidelines from the American Academy of Pediatrics⁸) between 2003 to 2004 and 2015 to 2016. There were no changes in the prevalence of elevated BP/hypertension or hypertension among youths with overweight during this time period; among youths with obesity, there was a decline in the prevalence of elevated BP/hypertension ($P_{\text{trend}}=0.03$) but not hypertension. Among adolescents with underweight or normal weight, the unadjusted prevalence of elevated BP/hypertension was 12.9% (SE, 1.6%) and the prevalence of hypertension was 4.9% (SE, 0.9%) in 2003 to 2004; the prevalence of elevated BP/hypertension was 8.7% (SE, 1.7%) and of hypertension was 2.7% (SE, 1%) in 2015 to 2016 ($P_{\text{trend}}=0.001$ and 0.002). Among youths with obesity, the unadjusted prevalence of elevated BP/hypertension was 30.1% (SE, 5.0%) and that of hypertension was 12.4% (SE, 3.3%) in 2003 to 2004; the unadjusted prevalence of prehypertension was 25.5% (SE, 2.4%) and that of hypertension was 11.6% (SE, 2.1%) in 2015 to 2016.⁹

females.¹⁸

Secular Trends

- In 51 761 participants from NHANES, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure definition of hypertension ($\geq 140/90$ mm Hg), the age-adjusted estimated prevalence of hypertension in US adults >18 years of age (weighted to the US population) increased from 30.0% (95% CI, 27.1%–32.9%) in 1999 to 2000 to 32% (95% CI,

29.3%–34.6%) in 2017 to 2018. However, with the use of the 2017 Hypertension Clinical Practice Guidelines definition of hypertension ($\geq 130/80$ mm Hg), the age-adjusted estimated prevalence of hypertension in US adults >18 years of age was 48.6% (95% CI, 45.7%–51.5%) in 1999 to 2000 and 46.5% (95% CI, 44.0%–49.0%) in 2017 to 2018.¹⁹

- In NHDS data compiled by the CDC, chronic hypertension in pregnancy (defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg either before pregnancy or up to the first 20 weeks during pregnancy) increased >13-fold between 1970 and 2010. Black females had a persistent 2-fold higher rate of chronic hypertension compared with White females over the 40-year period.²⁰
- In an observational study of 11 million Veterans Affairs patients between 2010 and 2019 who were 18 to 50 years of age with a diagnosis of chronic hypertension before a documented pregnancy, 8% had maternal chronic hypertension.²¹ Of these, 60% had uncontrolled BP on at least 1 BP reading and 31% had uncontrolled BP on at least 2 BP readings in the year before pregnancy. The use of nonrecommended BP-lowering medications in pregnancy was observed in 16% of the veterans. CKD (OR, 3.2 [95% CI, 1.6–6.4]) and diabetes (OR, 2.3 [95% CI, 1.7–3.0]) were associated with a higher likelihood

of using nonrecommended BP-lowering medication during pregnancy.

Risk Factors

- In NHANES 2015 to 2016, the prevalence of hypertension (defined according to the 2017 guide-lines from the American Academy of Pediatrics⁸) was 11.6% among US adolescents with obesity (BMI $\geq 120\%$ of 95th percentile of sex-specific BMI for age among children with normal weight or underweight). The prevalence of elevated BP among youths with obesity compared with youths with normal weight or underweight was 16.2% compared with 8.7%.⁹• In an analysis of the Australian Longitudinal Study on Women's Health, 9508 females were followed up for 145 159 PY, and 1556 females (16.4%) developed hypertension during follow-up.²² The incidence of hypertension was higher among females with polycystic ovarian syndrome (17 per 1000 PY) compared with females without (10 per 1000 PY). The incidence rate difference of hypertension was 4-fold higher (15.8 per 1000 PY versus 4.3 per 1000 PY) among females with obesity with polycystic ovarian syndrome compared with age-matched lean females with polycystic ovarian syndrome. Polycystic ovarian syndrome was independently associated with 37% greater risk of hypertension (HR, 1.37 [95% CI, 1.14–1.65]) after adjustment for BMI, family history of hypertension, occupation, and comorbidity with type 2 diabetes.
- In a meta-analysis of 133 studies with 12 197 participants, each 50-mmol sodium excretion (a marker of sodium consumption) was associated with a 1.10-mm Hg (95% CI, 0.66–1.54) reduction in SBP and a 0.33-mm Hg (95% CI, 0.04–0.63) reduction in DBP.²⁶ Greater SBP and DBP lowering from the same amount of sodium reduction was seen in populations with older age (–3.33/–1.23 mm Hg in those >65 years of age compared with –0.39/–0.18 mm Hg in younger age).
- In a systematic review of 11 cohort studies including 224 829 individuals, living or working in environments with noise exposure was significantly associated with increased risk of hypertension (RR, 1.18 [95% CI, 1.06–1.32]), and a linear dose-response was noted, with an RR of hypertension of 1.13 (95% CI, 0.99–1.28) per 10-dB higher ambient noise level.

baseline SBP (−2.97/−1.41 mm Hg in those with SBP >160 mm Hg compared with −0.39/−0.07 mm Hg in those with SBP <120 mm Hg), and Black individuals (−4.07/−2.37 mm Hg compared with −1.60/−0.82 mm Hg in White individuals).

- In an open-label, cluster-randomized trial involving 20 995 people from 600 villages in rural China, the use of a salt substitute (75% sodium chloride and 25% potassium chloride by mass) compared with the use of regular salt (100% sodium chloride) resulted in a lower incidence of stroke (RR, 0.86 [95% CI, 0.77–0.96]), all-cause mortality (RR, 0.88 [95% CI, 0.82–0.95]), and MACEs (RR, 0.87 [95% CI, 0.80–0.94]).²⁷ There was no increase in rates of hyperkalemia with the use of the salt substitute (RR, 1.04 [95% CI, 0.80–1.37]).
- In a population-based study from the Australian Longitudinal Study on Women's Health, which included 6599 middle-aged females and 6099 females of reproductive age, higher intakes of fla-vones (RR for highest versus lowest quintile of con-sumption, 0.82 [95% CI, 0.70–0.97]), isoflavones (RR, 0.86 [95% CI, 0.75–0.99]), and flavanones (RR, 0.83 [95% CI, 0.69–1.00]) were associated with a lower risk of hypertension in the middle-aged cohort.²⁸ In the cohort of reproductive age, higher intakes of flavanols (RR, 0.70 [95% CI, 0.49–0.99]) were associated with a lower risk of hypertension.
- ent noise.²³
- In an analysis from DEBATS of 1244 adults living near 3 major French airports, a 10-dB increase in aircraft noise levels was associated with a higher
- In an analysis of the electronic FHS participants, incidence of hypertension (RR, 1.36 [95% CI, 1.02–1.82]).²⁴ Noise annoyance, or noise sensitivity, was not associated with higher incident hypertension.

higher daily habitual PA as measured by a smart-watch was associated with lower home BP. Every 1000-step increase in the average daily step count was associated with a 0.49-mm Hg lower home SBP ($P=0.004$) and 0.36-mm Hg lower home DBP ($P=0.003$) with no difference between males and

- In a study from the China Health and Nutrition Survey of 12 080 adults 18 to 65 years of age who were enrolled from 1989 and 2011, compared with the referent group of those who worked 35 to 49 h/wk, participants who worked no more than 34 h/ wk (HR, 1.21 [95% CI, 1.03–1.41]) and at least 56 h/wk (HR, 1.38 [95% CI, 1.19–1.59]) had a higher risk of developing hypertension during follow-up after adjustment for sociodemographics, lifestyle factors, and occupation type.²⁵

- A systematic review of the relationship between screen time and hypertension in children and adolescents included 20 studies and 151 763 participants.³⁰ Screen time was defined on the basis of the use of digital video disks, tablets, smartphones, personal computers, and video games. Screen time in the highest category compared with the lowest category was associated with a higher odds of hypertension (OR, 1.15 [95% CI, 1.08–1.23];

$P < 0.001$) although with ($I^2 = 83.20\%$). High screened with higher SBP (WMD, 0.18–3.62; $P = 0.03$), againogeneity ($I^2 = 83.4$). Moreover, and adolescents with in normotensive children and 0.79 hours [95% CI, 0.02– significant heterogeneity (I

- In the JHS ancillary sleep study conducted from 2012 to 2016 among 913 participants, those with moderate or severe OSA had 2-fold higher odds (95% CI, 1.14–3.67) of resistant hypertension than participants without sleep apnea.³¹
- In a double-blind, placebo-controlled, crossover RCT, 110 individuals were randomized to receive 1 g acetaminophen 4 times daily or matched placebo for 2 weeks.³² Use of acetaminophen resulted in a significant increase in mean daytime SBP with a placebo-corrected increase of 4.7 mm Hg (95% CI, 2.9–6.6) and mean daytime DBP with a

India (95% CI, 19.0%–wives married to husbands reference. wives married to tension were more likely to the United States (PR, 1.09 England (PR, 1.09 [95% CI, (PR, 1.26 [95% CI, 1.17– [95% CI, 1.15–1.24]). Within associations were also observed

placebo- corrected increase of 1.6 mm Hg (95% CI, 0.5–2.7).• In a meta-analysis of 7 studies including 102 152 patients and 636 645 healthy individuals, male infertility was significantly associated with a slightly higher incidence of subsequent hypertension (RR, 1.08 [95% CI, 1.02–1.14]).³³ This risk persisted when only studies that adjusted for potential confounders were included (RR, 1.06 [95% CI,

Social Determinants/Health Equity

- In 1845 Black participants from the JHS with- out hypertension at baseline, medium (HR, 1.49 [95% CI, 1.18–1.89]) and high (HR, 1.34 [95% CI, 1.07–1.68]) exposure compared with low exposure to discrimination over the course of a lifetime was associated with a higher risk of incident hyperten- sion after adjustment for demographics and hyper- tension risk factors.³⁶
- In an analysis of the JHS cohort study of NH Black people, high (versus low) adult SES measures were associated with a lower prevalence of hyperten- sion, with the exception of having a college degree (PR, 1.04 [95% CI, 1.01–1.07]) and upper-middle income (PR, 1.05 [95% CI, 1.01–1.09]).³⁷ Higher childhood SES was associated with a lower preva- lence (PR, 0.83 [95% CI, 0.75–0.91]) and risk (HR, 0.76 [95% CI, 0.65–0.89]) of hypertension.
 - 1.03–1.09]).
- In the BWHS of 59 000 self-identified Black females from across the United States, a validated predicted vitamin D score relation to incident hyper-tension was reported.³⁴ Of the 42 239 participants who were free of CVD and cancer from 1995 to 2019, 19 505 incident cases of hypertension were identified during follow-up. An inverse dose-response association between predicted vitamin D score and hypertension risk was reported (HR, 0.66 [95% CI, 0.63–0.68]) for the highest quartile of pre-dicted vitamin D relative to the lowest. This trend was mostly attenuated after controlling for potential
- In a cohort of 3547 white collar workers from confounders, including BMI, PA, and smoking status (HR, 0.91 [95% CI, 0.87–0.95]).
- A study including cross-sectional data on hetero-sexual couples from contemporaneous waves of the HRS (2016–2017, n=3989 couples), ELSA (2016–2017, n=1086), CHARLS (2015–2016, n=6514), and LASI (2017/2019, n=22 389) ana- lyzed rates of concordant hypertension, defined as

Quebec, in models adjusted for demographics and a range of other risk factors, the prevalence of masked hypertension was higher among individuals working 41 to 48 h/wk (PR, 1.51 [95% CI, 1.06–2.14]) and ≥ 49 h/wk (1.70 [95% CI, 1.09–2.64]) compared with those working ≤ 40 h/wk. Similarly, the prevalence of sustained hypertension was higher among those working 41 to 48 h/wk (PR, 1.33 [95% CI, 0.99–1.76]) and ≥ 49 h/wk (1.66 [95% CI, 1.15–2.50]) compared with those working ≤ 40 h/wk.³⁸ In a systematic review including 45 studies and involving 117 252 workers, an increase in both SBP and DBP among permanent night workers (2.52 mm Hg [95% CI, 0.75–4.29] and 1.76 mm Hg [95% CI, 0.41–3.12], respectively) compared with day workers was noted.³⁹ For rotational shift workers, both with and without night work, compared with day workers without rotations, an increase was noted only for SBP (0.65 mm Hg [95% CI, 0.07–1.22] and 1.28 mm Hg [95% CI, 0.18–2.39],

both husband and wife in a couple having hypertension.³⁵ The prevalence of concordant hypertension within couples was common across all countries, at 37.9% in the United States (95% CI, 35.8%–40.0%), 47.1% in England (95% CI, 43.2%–50.9%), 20.8% in China (95% CI, 19.6%–21.9%), and 19.8% in

- In an analysis from NHANES 1999 to March 2020, of 20 761 middle-aged adults (40–64 years of age), adults with low income had an increase in hypertension over the study period (37.2% [95% CI, 33.5%–40.9%] to 44.7% [95% CI, 39.8%–49.5%]).⁴⁰

However, adults with higher income did not have a change in hypertension. The treatment and control rates for hypertension were unchanged in both groups (>80%). Income-based disparities in hypertension persisted in more recent years even after adjustment for insurance coverage, health

Genetics/Family History

- Several large-scale GWASs and whole-exome and whole-genome sequencing studies in primarily European ancestry populations, with the interrogation of common and rare variants in >1.3 million individuals, have established >300 well-replicated hypertension loci, with several hundred additional suggestive loci.^{41–51}
- Nine genetic loci have been identified for BP traits in African-ancestry populations.⁵² Large-scale genomic discovery effort in non-European ancestry populations is needed to comprehensively understand the genetic architecture of hypertension.
- Mendelian randomization analysis suggests a causal role for higher BP in 14 cardiovascular conditions, including IHD (SBP per 10 mm Hg: OR, 1.33 [95% CI, 1.24–1.41]; DBP per 5 mm Hg: OR, 1.20 [95% CI, 1.14–1.27]) and stroke (SBP per 10 mm Hg: OR, 1.35 [95% CI, 1.24–1.48]; DBP per 5 mm Hg: OR, 1.20 [95% CI, 1.12–1.28]).⁵³
- In a recent study, the multiancestry SBP PRS was constructed with 1.08 million variants identified from SBP GWAS data from >400 individuals who underwent whole-genome sequencing. The SBP PRS was associated with increased 10-year risk of incident cardiovascular events by 7% after

in multiancestry populations have not yet been conducted.

- A multistage analysis including 52 436 individuals of diverse ancestral backgrounds developed a hypertension PRS that combined 3 individual PRSs (SBP, DBP, and (OR, 2.10 [95% CI, 1.99–2.21]; $P<1\times10^{-100}$), incident hypertension (OR, 2.10 [95% CI, 1.99–2.21]; $P<1\times10^{-100}$), CAD (OR, 1.13 [95% CI, 1.07–1.18]; $P<3.2\times10^{-6}$), ischemic stroke (OR, 1.15 [95% CI, 1.04–1.28]; $P<6.94\times10^{-3}$), and type 2 diabetes (OR, 1.19 [95% CI, 1.14–1.24]; $P<8.46\times10^{-15}$).
- A GWAS for preeclampsia and gestational hypertension including 20 064 cases and 703 117 controls with preeclampsia and 11 027 cases and 412 788 controls with gestational hypertension identified 18 genomic loci.⁶⁴ Among these 18 loci, novel loci included *MTHFR–CLCN6*, *WNT3A*, *NPR3*, *PGR*, *RGL3*, *PLCE1*, and *FURIN*. An independent GWAS including 16 743 women with prior preeclampsia and 15 200 with preeclampsia or other maternal hypertension during pregnancy reported 19 loci, of which 13 loci were novel.⁶⁵ Novel loci reported in the study included *NPPA*, *NPPB*, *NPR3*, *PLCE1*, *TNS2*, *FURIN*, *RGL3*, *PREX1*, *PGR*, *TRPC6*, *ACTN4*, *PZP*, and *FLT1*.⁶⁵
- The clinical implications and utility of hypertension genes remain unclear, although some genetic variants have been shown to influence response to anti-hypertensive treatment accounting for traditional cardiovascular risk factors. These associations were seen across all racial and ethnic

Prevention

Awareness, Treatment, and Control

(See Table 8-2 and Charts 8-3 through 8-5)

- Based on NHANES 2017 to 2020 data,⁵ the groups.⁵⁴
- GWASs for BP variability and longitudinal BP traits have led to the discovery of novel loci.^{55,56} Furthermore, females were noted to have rapid progression of BP measures over a lifetime,

extent of awareness, treatment, and control of HBP which may indicate a sex-specific genetic burden for hypertension.^{57,58}

- Given the strong effects of environmental factors

is provided by race and ethnicity in Chart 8-3, by age in Chart 8-4, and by race and ethnicity and sex in Chart 8-5. Awareness, treatment, and control of hypertension were higher at older ages (Chart 8-4). In all race and ethnicity groups, females were more likely than males to be aware of their condition, under treatment, or in control of their hypertension

on hypertension, gene-environment interactions are important in the pathophysiology of hypertension. Studies of several hundred thousand people have to date revealed several loci of interest that interact with smoking^{59,60} and sodium.^{61,62} In individuals of

(Chart 8-5).

European ancestry, a high genetic risk for hyper-tension and CVD is offset by a favorable lifestyle. Large-scale gene-environment interaction studies

- Analysis of NHANES 1999 to 2002, 2007 to 2010, and 2017 to 2020⁵ found that hypertension awareness, treatment, and control increased in all racial and ethnic groups between 1999 to 2002 and 2007 to 2010. Changes in hypertension awareness, treatment, and control were more modest between 2007 to 2010 and 2017 to 2020,

with some racial and ethnic declines (Table 8-2).

- In an analysis of 18 262 adults with hypertension (defined as NHANES, the estimated age-adjusted prevalence of controlled BP increased 26.9%–36.7% in 1999 to 45.5%–51.5% in 2007 to relatively stable at 53.8% in 2013 to 2014, but declined

CI, 40.2%–47.2%) in 2017 to 2018.¹⁹ Controlled BP was less prevalent among NH Black individuals (41.5%) compared with NH White individuals (48.2%). In addition, compared with adults 18 to

(95% CI, 1.88–4.33). This association between baseline over time in SBP and DBP, effect threshold.

- In an analysis of 269 010 US adult treatment-resistant 2017, 4277 (1.6%) were on treatment.⁷¹ Testing was higher likelihood of initiating antihypertensive therapy (HR, 4.10

44 years of age, controlled BP was more common in adults 45 to 64 years of age (36.7% and 49.7%,

After adjustment for patient-, health care professional-, and center-level covariates (including baseline BP), compared with no testing, testing for primary aldosteronism was associated with an average 1.47-mm Hg (95% CI, -1.64 to -1.29 mm Hg) lower SBP over time.

respectively).

- In the UK Biobank, among 99 468 previously diagnosed, treated individuals with hypertension, 60 to 69 years of age (OR, 0.61 [95% CI, 0.58–0.64] compared with 40–50 years of age), alcohol consumption >30 units/wk (OR, 0.61 [95% CI, 0.58–0.64] compared with no alcohol use), Black ethnicity (OR, 0.73 [95% CI, 0.65–0.82] compared with White ethnicity), and obesity (OR, 0.73 [95% CI, 0.71–0.76] compared with normal BMI) were associated with lack of hypertension control.⁶⁸

- In a meta-analysis of 15 RCTs and 7415 patients Comorbidities associated with lack of BP control included CVD (OR, 2.11 [95% CI, 2.04–2.19]), migraines (OR, 1.68 [95% CI, 1.56–1.81]), diabetes (OR, 1.32 [95% CI, 1.27–1.36]), and depression (OR, 1.27 [95% CI, 1.20–1.34]).
- A longitudinal analysis of prospectively collected data from the UK Avon Longitudinal Study of

with hypertension of app-based behavioral self-monitoring interventions, a small but significant reduction in SBP was reported (WMD, 1.6 mm Hg [95% CI, 2.7–0.6]). App-based interventions were also associated with an increase in adherence behavior (SMD, 0.78 [95% CI, 0.22–1.34]) compared with usual care or minimal intervention.

- A meta-analysis of 16 cohort studies with 2 769 700 participants analyzed the association of adherence to BP-lowering medications and subsequent CVD events.⁷² The pooled RR of CVD events was 0.66 (95% CI, 0.56–0.78) for the highest versus lowest BP-lowering drug adherence categories. A linear dose-response association of adherence and CVD events was also reported ($P_{\text{nonlinearity}}=0.89$), and each 20% increase in adherence was associated with a 13% lower risk of CVD events (RR, 0.87 [95% CI,

Parents and Children cohort reported the association of self-reported alcohol intake and presence of hypertensive disorders in pregnancy.⁶⁹ Of the 8999 females in the study, 1490 (17%) had developed hypertensive disorders in pregnancy. Both maternal drinking and partner drinking were associated with decreased odds of hypertensive disorders in pregnancy (OR, 0.86 [95% CI, 0.77–0.96] and OR, 0.82 [95% CI, 0.70–0.97], respectively).

- A systematic review of longitudinal studies in healthy adults that reported the association between alcohol intake and BP included 7 studies with 19 548 participants and a median follow-up of 5.3 years.⁷⁰ Usual SBP and DBP were

0.83–0.92]).⁷³

1.25 mm Hg (95% CI, 0.49–2.01) and 1.14 mm Hg (95% CI, 0.60–1.68) higher, respectively, for a 12–g/d greater daily consumption of alcohol compared with no alcohol consumption. The corresponding SBP and DBP differences for daily alcohol consumption of 24 g/d were 2.48 mm Hg (95% CI, 1.40–3.56) and 2.03 mm Hg (95% CI, 1.19–2.86) and for 48 g/d were 4.90 mm Hg (95% CI, 3.71–6.08) and 3.10 mm Hg

- A meta-analysis of 14 RCTs of renin-angiotensin system inhibitor continuation or initiation compared with no renin-angiotensin system inhibitor therapy included 11 trials and 1838 participants with a mean follow-up of 26 days.⁷⁴ There was no effect of renin-angiotensin system inhibitors compared with control on all-cause mortality (RR, 0.95 [95% CI, 0.69–1.30]) overall or in subgroups defined by COVID-19 severity or trial type. In a network meta-analysis, renin-angiotensin system inhibitor use was associated with a nonsignificant reduction in AMI (RR, 0.59 [95% CI, 0.33–1.06]) and a higher risk of acute kidney injury (RR, 1.82 [95% CI, 1.05–3.16]) in trials that initiated and continued renin-angiotensin system inhibitors.
- In a prospective RCT of 21 104 participants who were enrolled to take all of their usual antihypertensive medications in either the morning (6–10 _{am}) or the evening (8 _{pm}–midnight), the primary cardiovascular end-point event of vascular death or hospitalization for nonfatal MI or nonfatal stroke occurred in

362 participants (3.4%) assigned to evening treatment and 390 (3.7%) assigned to morning treatment (HR, 0.95 [95% CI, 0.83–1.10]), suggesting no benefit with taking antihypertensive medications in the evening.⁷⁵

- A systematic review and meta-analysis of studies from January 2000 until April 2022 included 6 RCTs with 1550 participants comparing studies on pharmacist-led home BP telemonitoring with usual care.⁷⁶ Switching to usual care was associated with a significant decrease in SBP (WMD, -8.09 [95% CI, -11.15 to -5.04 ; $P < 0.001$]) and in DBP (WMD, -4.19 [95% CI, -5.58 to -2.81]) compared with usual care.
- A meta-analysis of RCTs to estimate the SBP reduction for team-based care strategies compared with usual care included 19 studies comprising 5993 participants.⁷⁷ Team-based care was defined as a team of ≥ 2 health care

whereas the actual number of deaths attributable to HBP increased 39.7%. In NH Black people, the HBP death rate increased 17.9%, and the actual number of deaths attributable to HBP increased 25.8%. In Hispanic people, the HBP death rate increased 21.3%, and the actual number of deaths attributable to HBP increased 37.7% (unpublished professionals working collaboratively toward a shared clinical goal. Team-based care strategies were stratified by the inclusion of a physician or a nonphysician team member who could titrate antihypertensive medications. The pooled analysis reported that the 12-month SBP change compared with usual care was -5.0 mm Hg (95% CI, -7.9 to -2.2) for team-based care with physician titration and -10.5 mm Hg (-16.2 to -4.8) for team-based care with nonphysician

100 000. Death rates were 188.6 for NH White males, 299.8 for NH Black males, 111.9 for NH Asian males, 192.3 for Native Hawaiian or Other Pacific Islander males, 205.8 for NH American Indian or Alaska Native males (underestimated because of underreporting), and 160.0 for Hispanic males. In females, rates were 135.9 for NH White females, 198.7 for NH Black females, 81.2 for NH Asian females, 156.2 for NH Native Hawaiian or Other Pacific Islander females, 159.9 for NH American Indian or Alaska Native females (under-estimated because of underreporting), and 111.8 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER⁸⁰).

- In 3394 participants from the CARDIA study cohort, greater long-term visit-to-visit variability in SBP (eg, variability independent of the mean) from young adulthood through midlife was associated with titration. greater all-cause mortality (HR, 1.24 [95% CI, 1.09–20.6 mm Hg for a polypill compared with –0.9 to –5.2 mm Hg for placebo and –9.0 to –29.3 mm Hg for a polypill compared with –2.0 to –20.6 mm Hg for monotherapy or usual care. All trials reported similar rates of
- A systematic review of the efficacy of polypills combining 3 or 4 BP-lowering medications included 18 trials and 14 307 participants.⁷⁸ The mean difference in SBP ranged from –9.8 to

1.41]) during a median follow-up of 20 years.⁸¹

- In a meta-analysis of 64 000 participants from 27 studies, untreated white-coat hypertension was associated with an increased risk of all-cause (HR, 1.33 [95% CI, 1.07–1.67]) and cardiovascular (HR, 2.09 [95% CI, 1.23–4.48]) mortality compared with normotension.⁸² There was no evidence of increased risk among those with treated white-coat hypertension. Medication adherence was high (6 trials reported >95% adherence) but was similar for polypills compared with controls.

studies, untreated white-coat hypertension was associated with an increased risk of all-cause (HR, 1.33 [95% CI, 1.07–1.67]) and cardiovascular (HR, 2.09 [95% CI, 1.23–4.48]) mortality compared with normotension.⁸² There was no evidence of increased risk among those with treated white-coat hypertension.

(See Table 8-1)

- According to data from the NVSS, in 2022,⁷⁹ 131 454 deaths were attributable primarily to HBP

Mortality

- In 1034 participants from the JHS completing ambulatory BP monitoring, each 1-SD higher level of mean nighttime SBP (15.5 mm Hg) was associated with all-cause mortality (HR, 1.24 [95% CI, 1.06–1.45]) after multivariable adjustment including clinic BP; however, there were no associations between daytime SBP, daytime DBP, or nighttime DBP and all-cause mortality.⁸³

(Table 8-1). The 2022 age-adjusted death rate attributable primarily to HBP was 31.5 per 100

Complications

Death rates by sex, race, and ethnicity for 2022 are given in Table 8-1.

- From 2012 to 2022, the age-adjusted death rate attributable to HBP increased 63.2%, and the

actual number of deaths attributable to HBP rose 93.0%. From 2018 to 2022, in NH White people, the HBP age-adjusted death rate increased 36.8%,

- In the Blood Pressure Lowering Treatment Trialists Collaboration individual patient–level meta-analysis of 48 RCTs and 344 716 participants, a 5–mm Hg reduction of SBP reduced the risk of major cardio-vascular events by $\approx 10\%$, regardless of previous diagnoses of CVD.⁸⁴ This effect was also seen at normal and high-normal BP values.

- In a cross-sectional analysis from 397 adolescents 11 to 19 mean systolic ambulatory BP mm Hg during wake hours, and 120 mm Hg over 24 have a balance of sensitivity (60%) for predicting LVH.¹¹
- Among 27 078 Black adults in the Southern hypertension was associated with in the full cohort (HR, 1.69 [95% CI, 1.56–1.84]) with a PAR of 31.8% (95% CI, 27.3%–36.0%).⁸⁵
- In an RCT of 8511 older Chinese patients with hypertension (60–80 years of age), randomizing to a BP target of 110 to <130 mm Hg (intensive treatment) compared with a target of 130 to <150 mm Hg (standard treatment) reduced MACEs (HR, 0.74 [95% CI, 0.60–0.92]).⁸⁶
- In a pooled cohort of 12 497 NH Black individuals nighttime DBP (HR, 1.30 per 9.5 mm Hg).⁸³
- In an analysis from the CRIC participants, 180 participants hypotension and 81 (2.1%) tension.⁸⁸ Orthostatic with high risk for in HF, MI, stroke, or PAD 1.03–1.21). but not kidney Orthostatic hypertension was als from the JHS and REGARDS, over a maximum 14.3 years of follow-up, the multivariable-adjusted HR associated with hypertension (defined as $\geq 130/80$ per the 2017 Hypertension Clinical Practice Guidelines⁴ compared with normotension) was almost 2-fold higher (HR, 1.91 [95% CI,

ated with high risk for kidney outcomes, including incident ESKD or 50% decline in eGFR (HR, 1.51 [95% CI, 1.14–1.97]), but not cardiovascular out-comes or mortality.

- Among 3319 adults ≥65 years of age from the S.AGES cohort in France, higher SBP variability (assessed in 6-month intervals over the course of 3 years) was associated with poorer global cognition independently of baseline SBP (adjusted 1-SD increase of coefficient of variation: $\beta = -0.12$ [SE, 0.06]; $P = 0.04$).⁸⁹ Similar results were observed for DBP variability ($\beta = -0.20$ [SE, 0.06]; $P < 0.001$).

Higher SBP variability was also associated with greater dementia risk (adjusted 1-SD increase in coefficient of variation: HR, 1.23 [95% CI, 1.01–

1.48–2.46]) for composite incident CVD and was 2.41 (95% CI, 1.59–3.66) for incident CHD, 2.20 (95% CI, 1.44–3.36) for incident stroke, and 1.52 (95% CI, 1.01–2.30) for incident HF.¹ The PAR

1.50]; $P = 0.04$).

associated with hypertension was 32.5% (95% CI, 20.5%–43.6%) for composite incident CVD, 42.7%

- In a subsample of 191 participants from CARDIA, higher cumulative SBP from baseline through year 30 was associated with slower walking speed ($P=0.010$), smaller step length ($P=0.011$), and worse cognitive function in the executive ($P=0.021$),

(95% CI, memory ($P=0.015$), and global ($P=0.010$))

(95% CI, 19.4%–55.6%) for incident stroke, and 21.6% (95% CI, 0.6%–40.8%) for incident HF.

For composite CVD, the PAR for hypertension was 54.6% (95% CI, 37.2%–68.7%) among NH people <60 years of age but was significantly lower, at 32% (95% CI, 11.9%–48.1%), among NH Black people ≥60 years of age.

- In 8022 individuals from SPRINT with hypertension but without AF at baseline, those in the intensive BP-lowering arm (target SBP <120 mm Hg) had a 26% lower risk of developing AF over the 5.2 years of follow-up (28 322 PY) than those in the standard BP-lowering arm (target SBP <140 mm Hg; HR, 0.74 [95% CI, 0.56–0.98]; $P=0.037$).⁸⁷

- In 1034 adults from the JHS cohort of NH Black participants completing ambulatory BP monitoring, each 1-SD higher level of mean daytime SBP (13.5 mm Hg) was also associated with an increased incidence of CVD events (HR, 1.53 [95% CI, 1.24–1.88]) after multivariable adjustment that included clinic BP. Adjusted findings were similar for nighttime SBP (HR, 1.48 [95% CI, 1.22–1.80]) per 15.5 mm Hg, daytime DBP (HR, 1.25 [95% CI, 1.02–1.51]) per 9.3 mm Hg, and

domains.⁹⁰ Associations between cumulative BP and both walking speed and step length were mod-erated by cerebral WMH burden ($P_{\text{interaction}} < 0.05$).

- In a meta-analysis of 20 studies and 7 899 697 participants, higher SBP variability (OR, 1.25 [95% CI, 1.16–1.35]), mean SBP (OR, 1.12 [95% CI, 1.02–1.29]), DBP variability (OR, 1.20 [95% CI, 1.12–1.29]), and mean DBP (OR, 1.16 [95% CI, 1.04–1.29]) were associated with dementia and cognitive impairment.⁹¹
- A pooled individual participant data analysis of 5 RCTs from the Dementia Risk Reduction collabora- tion included 28 008 individuals recruited from 20 countries.⁹² After a median follow-up of 4.3 years, there were 861 cases of incident dementia. The pooled mean BP difference between the antihyper- tensive and control arms was 9.6 mm Hg for SBP and 3.7 mm Hg for DBP. With multilevel logistic regression, BP-lowering treatment was associated with a lower risk of subsequent dementia (OR, 0.87 [95% CI, 0.75–0.99]).
- An analysis from the CRIC study examined the link between BP and incident cognitive impair-ment defined as a decline in modified MMSE score

to >1 SD below the cohort mean.⁹³ The analysis included 3048 participants who did not have cognitive impairment at baseline and with at least 1 follow-up modified MMSE score.

Spline analyses showed that the relationship between baseline SBP and incident cognitive impairment was J shaped and significant only in those participants with eGFR >45 mL·min⁻¹·1.73 m⁻² ($P=0.02$). The aHR was 1.13 (95% CI, 1.05–1.22) per 10-mm Hg higher

(707 events overall) was seen at an achieved SBP of 120 to <140 mm Hg; risk increased with higher (HR, 3.06 [95% CI, 1.90–3.32]) and lower (HR, 1.97 [95% CI, 1.7–3.32]) SBP, with similar RRs reported with or without diabetes.⁹⁶

- In an analysis from the CKiD cohort, high mean arterial pressure >90th percentile was associated with eGFR >45 mL·min⁻¹·1.73 m⁻². Baseline DBP was not associated with incident cognitive impairment in

4 years of follow-up.⁹⁷ Among those with glomerular CKD, higher risk for progression was noted from any analyses.

- A meta-analysis included 5 cohort studies with a total of 183 874 females with and 2 309 705 females without HDP to study the risk of subsequent dementia.⁹⁴ Any type of HDP was associated with a higher risk of subsequent dementia (HR, 1.38 [95% CI, 1.18–1.61]). For dementia subtypes, any HDP was associated with higher risk of vascular dementia (HR, 3.14 [95% CI, 2.32–4.24]).
- In a population-based cohort study, the Netherlands Perinatal Registry and the national death registry at the Dutch Central Bureau for Statistics were linked to analyze the association between cardiovascular mortality and HDP for women with a first birth during 1995 and 2015.⁹⁵ The registry included 2 462 931 deliveries and 1 625 246 women with a median follow-up time of 11.2 years, of whom 259 177 women (20.8%) had

baseline with the highest risk in those with mean arterial pressure >90th percentile (HR, 3.23 [95% CI, 1.34–7.79]).

HDP. Of these, 45 482 women (3.7%) had preeclampsia, and 213 695 women (17.2%) had gestational hypertension; 984 713 women (79.2%) did not develop hypertension in their first pregnancy (reference group). Compared with the reference group, the risk of all-cause mortality was higher in women who had HDP (HR, 1.30 [95% CI, 1.23–1.37]; $P<0.001$), preeclampsia (HR, 1.65 [95% CI, 1.48–1.83]; $P<0.0001$), and gestational hypertension (HR, 1.23 [95% CI, 1.16–1.30]; $P<0.0001$). Compared with the reference group, women with preeclampsia (aHR, 3.39 [95% CI, 2.67–4.29]) and gestational hypertension (aHR, 2.22 [95% CI, 1.91–2.57]) had higher risk for subsequent cardiovascular mortality. For women with a history of HDP who also had PTB (gestational age <37 weeks) and birth weight ≤10th percentile,

- In an individual patient meta-analysis of 33 trials including 260 447 participants with 15 012 cancer events, no associations were identified between any antihypertensive drug class and risk of any cancer (HR, 0.99 [95% CI, 0.95–1.04] for ACE inhibitors; HR, 0.96 [95% CI, 0.92–1.01] for ARBs; HR, 0.98 [95% CI, 0.89–1.07] for β -blockers; HR, 1.01 [95% CI, 0.95–1.07] for thiazides) except for calcium channel blockers (HR, 1.06 [95% CI, 1.01–1.11]).⁹⁸ In a network meta-analysis comparing each drug class with placebo, no drug class was associated with an excess cancer risk (HR, 1.00 [95% CI, 0.93–1.09] for ACE inhibitors; HR, 0.99 [95% CI, 0.92–1.06] for ARBs; HR, 0.99 [95% CI, 0.89–1.11] for β -blockers; HR, 1.04 [95% CI, 0.96–1.13] for calcium channel blockers; HR, 1.00 [95% CI, 0.90–1.10] for thiazides).
- A prospective observational cohort study of 906 patients from Italy with hypertension and CKD reported outcomes associated with baseline ambulatory BP patterns.⁹⁹ The absence of nocturnal dipping (defined as nighttime:daytime SBP ratio of <0.9) was associated with higher rates of cardiovascular events (HR, 2.79 [95% CI, 1.64–4.75]) and kidney disease progression (HR, 2.40 [95% CI, 1.58–3.65]) in participants whose daytime ambulatory SBP was not at goal (SBP >135 mm Hg).

Similar results were also noted in those whose ambulatory daytime SBP was at goal (HR for cardiovascular events, 2.06 [95% CI, 1.15–3.68]; HR for kidney disease progression, 1.82 [95% CI, 1.17–2.82]). association with cardiovascular mortality was even higher (HR, 6.43 [95% CI, 4.36–9.47]) compared with the reference group. The highest DBP measured during pregnancy was strongly associated with cardiovascular mortality (for 80–89 mm Hg: aHR, 1.47 [95% CI, 1.00–2.17]; for ≥ 130 mm Hg: HR, 14.70 [95% CI, 7.31–29.52]) with reference group having DBP <70 mm Hg.

- In an analysis of the ONTARGET study, the lowest risk of ESKD or doubling of serum creatinine

- In an analysis of the FHS including 8198 participants with hypertension subtypes, the prevalence of nonhypertension (SBP <140 mm Hg and DBP <90 mm Hg) was 79%, isolated systolic hypertension (SBP ≥140 mm Hg and DBP <90 mm Hg) was 8%, isolated diastolic hypertension (SBP <140 mm Hg and DBP ≥90 mm Hg) was 4%, and systolic-diastolic hypertension (SBP ≥140 mm Hg and DBP ≥90 mm Hg) was 9%.¹⁰⁰ Over the median

5.5-year follow-up, compared sion (referent), isolated not associated with increased [95% CI, 0.68–1.57] in hypertension [HR, 1.57 (95% systolic-diastolic hypertension 1.36–2.01)].

- In an individual participant data 23 cohorts and 53 172 compared with lower arm BP

participants at either 130– or 140–mm Hg SBP thresholds (both $P < 0.001$).¹⁰¹ Higher arm BP models fitted better using Akaike information criteria for all-cause mortality, cardiovascular mortality, and cardiovascular events (all $P < 0.001$).

- In an analysis of data from 2 waves of the National Longitudinal Study of Adolescent to Adult Health, including participants who had measured BP at wave IV (2008–09) and a pregnancy that resulted in a singleton live birth between waves IV and V (2016–2018; $n = 2038$), the prevalence of PTB was 12.6%.¹⁰² A 1-SD increment in SBP (SD, 12.2 mm Hg) and DBP (SD, 9.3 mm Hg) was associated

with the difference between cally significant ($P = 0.04$).

- A systematic review and meta-studies published through the relationship between defined as a rise in SBP or subsequent cardiovascular sis included 20 studies with and a median follow-up of 7.9 hypertension was associated with a 14% (95% CI, 2%–27%) and 20% (95% CI, 4%–37%) higher risk of preterm delivery. Compared with normotension, stage I hypertension (defined as SBP 130–139 mm Hg or DBP 80–89 mm Hg; RR, 1.33 [95% CI, 1.01–1.74]) and stage II hypertension (defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg; RR, 1.34 [95% CI, 0.89–2.00]) were also associated with increased subsequent risk of pre-

- In a study of the association between invasive aortic BP and outcomes, data on all patients undergoing cardiac catheterization in Western Denmark from 2003 to 2016 who were registered in the Western Denmark Heart Registry were linked to outcome data in the Danish National Patient Registry, the Danish National Prescription Registry, and the Danish Civil Registration System with a median follow-up of 7.2 years.¹⁰⁶ The mean difference between cuff-based brachial SBP and invasive aortic BP was -1.6 mm Hg (95% CI, -1.8 to -1.3) for patients without CKD and -2.4 mm Hg (95% CI, -2.9 to -1.8) for patients with CKD. Office SBP and aortic SBP were associated with stroke in patients without CKD (HR per 10 mm Hg, 1.08 [95% CI, 1.05–1.12] and 1.06 [95% CI, 1.03–1.09], respectively) and with MI in patients with CKD (aHR,

1.08 [95% CI, 1.03–1.13] and 1.08 [95% CI,

difference of ≥ 15 mm Hg compared with an interarm SBP difference < 15 mm Hg was associated with higher all-cause mortality (pooled HR, 1.28 [95% CI, 1.02–1.61]) and higher cardiovascular mortality (pooled HR, 1.93 [95% CI, 1.24–2.99]). In a subgroup analysis, the association with cardiovascular mortality was stronger in studies of younger patients (pooled HR, 9.03 [95% CI, 2.00–40.82]) than in studies of older patients (pooled HR, 1.67 [95% CI, 1.06–2.64]),

- In a meta-analysis of 86 articles with 18 775 387 patients with COVID-19 from 18 countries, hypertension was associated with in-hospital mortality (OR, 1.36 [95% CI, 1.28–1.45]) and other adverse outcomes (OR, 1.32 [95% CI, 1.24–1.41]).¹⁰³ The analysis by mean age at a study level reported that in-hospital mortality was higher in studies with mean age <49 or >70 years compared with a mean age of 50 to 59 and 60 to 69 years ($P<0.001$).
- A systematic review and meta-analysis analyzed the association of a simultaneously measured interarm SBP difference and all-cause mortality and cardio-vascular mortality. The study included 10 cohort studies with 15 320 individuals published before April 2023.¹⁰⁴ An interarm SBP

1.12], respectively). However, office SBP and aortic SBP were similar for prediction of outcomes when adjusted models were compared by C statistics.

- An observational study of all males in late adolescence who were conscripted into the military in Sweden from 1969 to 1997 included 1 366 519 males with a mean age of 18.3 years and a median follow-up of 35.9 years.¹⁰⁷ The baseline BP at the time of conscription was classified as elevated (defined as SBP 120–129 mm Hg and DBP <80 mm Hg) for 28.8% of participants and hypertensive ($\geq$ 130/80 mm Hg) for 53.7%. Elevated BP was associated with a higher risk of the composite outcome of cardiovascular death or first hospitalization for MI, HF, ischemic stroke, or ICH (aHR, 1.10 [95% CI, 1.07–1.13]) during follow-up.
- A reanalysis from the Spanish Ambulatory Blood Pressure Registry included clinic and ambulatory BP data obtained from 2004 to 2014 from 223 primary care centers from the Spanish National Health System in all 17 regions of Spain.¹⁰⁸ Over a median follow-up of 9.7 years, these records were linked to the vital registry of the Spanish National Institute of Statistics for outcome data. Overall, 24-hour

SBP was more strongly associated with all-cause mortality (HR, 1.41 per 1-SD increment [95% CI, 1.36–1.47]) than clinic SBP (HR, 1.18 [95% CI, 1.13–1.23]). Twenty-four-hour BP was associated with all-cause mortality after adjustment for clinic BP (HR, 1.43 [95% CI, 1.37–1.49]); however, the association between clinic BP and all-cause mortality was attenuated when adjusted for 24-hour BP (HR, 1.04 [95% CI, 1.00–1.09]). Relative to normal BP, elevated all-cause mortality risks were 1.12–1.37]) and sustained hypertension (HR, 1.24 [95% CI, 1.15–1.32]) but not white-coat hypertension. Similarly, higher cardiovascular mortality were observed for masked hypertension (HR, 1.37 [95% CI, 1.15–1.63]) and sustained hypertension (HR, 1.38 [95% CI, 1.22–1.55]) but not white-coat hypertension.

Health Care Use: Hospital Discharges/ Ambulatory Care Visits

- Beginning in 2016, a code for hypertensive crisis (*ICD-10-CM* I16) was added to the HCUP inpatient database. For 2016, hypertensive crisis is included in the total number of inpatient hospital stays for HBP. From 2011 to 2021, the number of inpatient discharges from short-stay hospitals with HBP as the principal diagnosis increased from 296 253 to 1 311 528. The number of discharges with any listing of HBP increased from 16 112 764 to 17 160 070 in that same time period.

practices, patients with hypertension at high remote patient monitoring practices had a 3.3% (95% CI, 1.9%–4.8%) increase in hypertension medication fills, a 1.6% (95% CI, 0.7%–2.5%) increase in days' supply of medication, and a 1.3% (95% CI, 0.2%–2.4%) increase in unique medications received. However, these patients also saw increases in primary care physician outpatient

Cost

- In 2021, there were 7090 principal diagnosis discharges for essential hypertension (HCUP,¹⁰⁹ unpublished NHLBI tabulation).
- In 2021, there were 8 827 938 all-listed discharges for essential hypertension (HCUP,¹⁰⁹ unpublished NHLBI tabulation).
- In 2019, 56 795 000 of 1 036 484 000 physician office visits had a primary diagnosis of essential hypertension (*ICD-9-CM* 401; NAMCS,¹¹⁰ unpublished NHLBI tabulation). There were 779 438 ED discharges with a principal diagnosis of essential hypertension in 2021 (HCUP,¹⁰⁹ unpublished NHLBI tabulation).
- A matched observational study emulating a cluster RCT design compared changes in outcomes from 2019 to 2021 for patients with hypertension at high remote patient monitoring practices with those at matched control practices with little remote patient monitoring.¹¹¹ The study matched 192 high remote patient monitoring practices including 19 978 patients with hypertension to 942 low remote patient monitoring control practices including 95 029 patients with hypertension. Compared with patients with hypertension at matched control

- The estimated direct and indirect cost of HBP for 2020 to 2021 (annual average) was \$49.0 billion (unpublished NHLBI tabulation using MEPS¹¹²).
- Estimated US health care expenditures for hypertension in 2016 were \$79 (95% CI, \$72.6–\$86.8) billion. Of 154 health conditions, hypertension ranked 10th in health care expenditures.¹¹³
- In a systematic review of 33 studies reporting cost of care with hypertension from sub-Saharan Africa, only 25% of the countries were represented.¹¹⁴ The included studies reported costs from the public sector or used a mixed approach including private, nongovernmental, or missionary facilities. Medication costs were accountable for most of the monthly expenditures with a range from \$1.7 to \$97.1 from a patient perspective and \$0.1 to \$193.6 from a health care professional perspective (per patient per month). Other patient costs reported included transportation, time, and wages lost as a result of hypertension treatment and laboratory costs. At a geographic level, macroeconomic costs ranged from \$1.6 million annually for the full population of patients ≥ 25 years of age living with hypertension on the Seychelles to \$397.6 million for direct costs for hypertensive treatment in the sub-Saharan population with SBP ≥ 115 mm Hg.
- A meta-analysis of RCTs to estimate the SBP reduction for team-based care strategies compared with usual care included 19 studies comprising 5993 participants.⁷⁷ The validated BP Control Model–Cardiovascular Disease Policy Model was used to project the expected BP reductions out to 10 years and to simulate CVD events, direct health care costs, QALYs, and cost-effectiveness of team-based care with physician and nonphysician titration. Relative to usual care at 10 years, team-based care with nonphysician titration was estimated to cost \$95 (95% UI, –\$563 to \$664) more per patient and gain 0.022 (95% UI, 0.003–0.042) QALYs, costing \$4400 per QALY gained. Team-based care with physician titration was

estimated to cost more and gain fewer QALYs and was dominated by team-based care with nonphysician titration.

and 31.7% (95% CI, 31.0%–32.4%) achieved BP control.

Global Burden

(See Chart 8-6 and Table 8-3)

- In 2019, HBP was 1 of the 5 leading risk factors for the burden of disease (YLL and DALYs) in all regions except Oceania and eastern, central, and western sub-Saharan Africa.¹¹⁵
- Based on 204 countries and territories in 2021, age-standardized mortality rates attributable to high SBP among regions were highest for central Asia, followed by eastern Europe, central sub-Saharan Africa, and North Africa and the Middle East (Chart 8-6). High SBP was attributed to 10.85 (95% UI, 9.22–12.54) million total deaths in 2021. The PAF was 15.99% (95% UI, 13.52%–18.19%; Table 8-3).¹¹⁶
- It has been estimated that 7.834 million deaths and 143.037 million DALYs in 2015 could be attributed to SBP ≥ 140 mm Hg.¹¹⁷ In addition, 10.7 million deaths and 211 million DALYs in 2015 could be attributed to SBP of ≥ 110 mm Hg.
- Between 1990 and 2015, the number of deaths related to SBP ≥ 140 mm Hg did not increase in high-income countries (from 2.197 to 1.956 million deaths) but did increase in high- and middle-income (from 1.288 to 2.176 million deaths), middle-income (from 1.044 to 2.253 million deaths), low- and middle-income (from 0.512 to 1.151 million deaths), and low-income (from 0.146 to 0.293 million deaths) countries.¹¹⁷
- In a cross-sectional study of 12 926 individuals from the Bangladesh Demographic and Health Survey conducted over 2017 to 2018, the overall prevalence of hypertension was 27.4%, being higher in females (28.4%) than males (26.2%). Of those with hypertension, 42.4% (n=1508) of people were aware of being hypertensive.¹¹⁸
- In a 2021 systematic review of 15 cross-sectional studies from the United Arab Emirates involving 139 907 adults, the pooled prevalence of hypertension was 31% (95% CI, 27%–36%).¹¹⁹ Among those with hypertension, the level of awareness was 29% (95% CI, 17%–42%). The pooled proportion being treated was 31% (95% CI, 18%–44%); among those taking antihypertensive medications, 38% (95% CI, 19%–57%) had controlled BP (defined as $<140/90$ mm Hg).
- In an analysis of LASI data from the 2017 to 2019 baseline wave, the estimated hypertension prevalence among adults ≥ 45 years of age was 45.9% (95% CI, 45.4%–46.5%).¹²⁰ Among those with

hypertension, had been 39.6%) were

- In a 2021 systematic review, prevalence was 7% (95% CI, 4%–10%) among those with obesity and 10% among those with normal weight.¹²¹ The prevalence of hypertension was 7% (95% CI, 4%–10%) among those with obesity and 10% among those with normal weight.
- A systematic review of 31 studies of age-residing examine the six studies years of age countries were of elevated BP individual (95% CI, 7.3%–heterogeneity /
- In an analysis included 721 between 30 hypertension BP monitoring, tern was
- In an analysis of period-cohort SBP–population and from 129.1 Japan, the 63.7 and 24.7 females.
- In a 2022 meta-analysis 1 312 244 from Middle of hypertension 27.9%).¹²⁵ The prevalence was only and the also low at prevalence of was 43.1% high degree of in all the tion and mean were contributed to meta-regression.

Table 8-1. HBP in the United States

Population group	Prevalence, 2017–2020, ≥20 y of	Mortality,* 2022, all ages	Age-adjusted mortality rates per 100 000 (95% CI),* 2022
Both sexes	122 400 000 (46.7%) (95% CI,	131 454	31.5 (31.3–31.7)
Males	62 800 000 (50.4%)	63 901 (48.6%)‡	35.4 (35.2–35.7)
Females	59 600 000 (43.0%)	67 553 (51.4%)‡	27.6 (27.4–27.8)
NH White males	48.9%	44 028	33.3 (33.0–33.6)
NH White females	42.6%	49 115	26.8 (26.5–27.0)
NH Black males	57.5%	11 665	67.3 (66.0–68.6)
NH Black females	58.4%	10 647	44.7 (43.8–45.5)
Hispanic males	50.3%	5132	28.0 (27.2–28.9)
Hispanic females	35.3%	4694	20.4 (19.8–20.9)
NH Asian males	50.2%	1861§	20.7 (19.7–21.6)§
NH Asian females	37.6%	2146§	17.0 (16.3–17.7)§
NH American Indian/Alaska Native	...	861	34.4 (32.0–36.7)
NH Native Hawaiian or Pacific	...	182	31.5 (26.8–36.2)

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹²⁶

Hypertension is defined in terms of NHANES BP measurements and health interviews. A subject was considered to have hypertension if SBP was ≥130 mm Hg or DBP was ≥80 mm Hg, if the subject said “yes” to taking antihypertensive medication, or if the subject was told on 2 occasions that he or she had hypertension. A previous publication that used NHANES 2011 to 2014 data estimated that there were 103.3 million noninstitutionalized US adults with hypertension.¹²⁷ The number of US adults with hypertension in this table includes both noninstitutionalized and institutionalized US individuals. In addition, the previous study did not include individuals who reported having been told on 2 occasions that they had hypertension as having hypertension unless they met another criterion (SBP was ≥130 mm Hg, DBP was ≥80 mm Hg, or the subject said “yes” to taking antihypertensive medication). CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading. In March 2020, the COVID-19 pandemic halted NHANES field operations.

BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; ellipses (...), data not available; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

*Mortality for Hispanic people, American Indian or Alaska Native people, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native decedents, Asian and Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

†Beginning in 2016, a code for hypertensive crisis (*International Classification of Diseases, 10th Revision, Clinical Modification* I16) was added to the Healthcare Cost and Utilization Project inpatient database and is included in the total number of hospital discharges for HBP. The large increase in hospital discharges is attributable to *International Classification of Diseases, 10th Revision* coding changes for heart failure using Agency for Healthcare Research and Quality Prevention Quality Indicator 08, heart failure admission rate.

‡These percentages represent the portion of total HBP mortality that is for males versus females.

§Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.⁵ Percentages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population estimates. Mortality (for underlying cause of HBP): Unpublished NHLBI tabulation using National Vital Statistics System⁷⁹ and CDC WONDER.⁸⁰ These data represent underlying cause of death only.

Table 8-2. Hypertension Awareness, Treatment, and Control: NHANES 1999 to 2002, 2007 to 2010, and 2017 to 2020 Age-Adjusted Percent With Hypertension in US Adults, by Sex and Race and Ethnicity

	Awareness, %	Treatment, %

In March 2020, the COVID-19 pandemic halted NHANES field operations because of the pandemic. Data collected in 1999–2002, 2007–2010, and 2017–2020 are nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹²⁶

Hypertension is defined in terms of NHANES BP measurements and health interviews. A subject was considered to have hypertension if SBP was ≥ 130 mm Hg, DBP was ≥ 80 mm Hg, or the subject said “yes” to taking antihypertensive medication. Controlled hypertension is considered to be SBP < 130 mm Hg or DBP < 80 mm Hg. Total includes race and ethnicity groups not shown (other Hispanic, other race, and multiracial).

BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

*The category of Mexican American people was consistently collected in all NHANES years, but the combined category of Hispanic people was used only starting in 2007. Consequently, for long-term trend data, the category of Mexican American people is used. Total includes race and ethnicity groups not shown (other Hispanic, other race, and multiracial).

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁵

Table 8-3. Deaths Caused by High SBP Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	10.85 (9.22 to 12.54)	5.55 (4.63 to 6.48)	5.30 (4.41 to 6.16)
Percent change (%) in total number,	65.31 (54.16 to 77.29)	77.93 (61.83 to 94.92)	53.89 (41.50 to 66.50)
Percent change (%) in total number,	20.50 (14.29 to 27.17)	22.32 (13.82 to 32.26)	18.65 (11.09 to 26.26)
Rate per 100 000, age	131.10 (111.63 to 151.57)	151.95 (126.65 to 176.70)	113.21 (94.17 to 131.42)
Percent change (%) in rate, age	−32.32 (−36.69 to −27.64)	−27.70 (−33.87 to −21.13)	−36.46 (−41.29 to −31.33)
Percent change (%) in rate, age	−13.63 (−18.07 to −8.97)	−12.26 (−18.35 to −5.49)	−14.94 (−20.29 to −9.49)
PAF (%), all ages, 2021	15.99 (13.52 to 18.19)	14.73 (12.40 to 16.91)	17.56 (14.64 to 20.14)
Percent change (%) in PAF, all	12.28 (6.24 to 18.10)	17.15 (10.45 to 25.31)	8.50 (1.07 to 15.06)
Percent change (%) in PAF, all	−5.79 (−9.17 to −2.55)	−5.75 (−9.79 to −1.31)	−5.57 (−9.86 to −1.83)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; PAF, population attributable fraction; SBP, systolic blood pressure; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹¹⁶

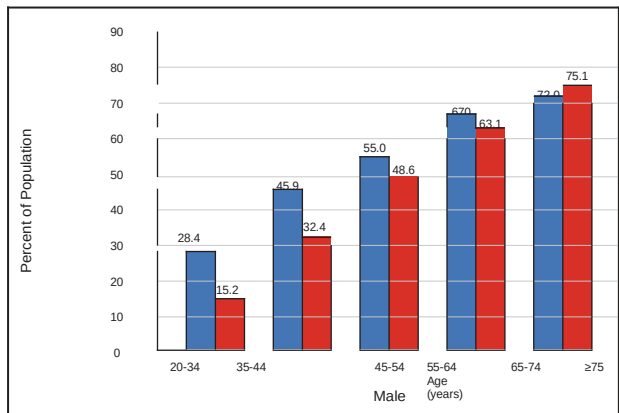
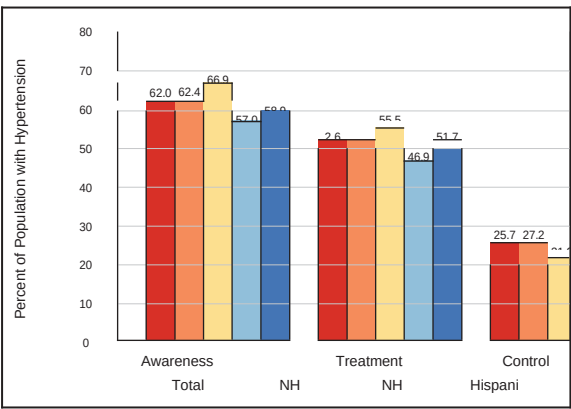


Chart 8-1. Prevalence of hypertension in US adults ≥20 years of age, by sex and age (NHANES 2017–2020).

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020



cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹²⁶ Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥130 mm Hg or DBP ≥80 mm Hg, if he or she said “yes” to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁵

Chart 8-3. Extent of awareness, treatment, and control of HBP, by race and ethnicity, United States (NHANES 2017–2020).

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹²⁶ Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg or if he or she said “yes” to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁵

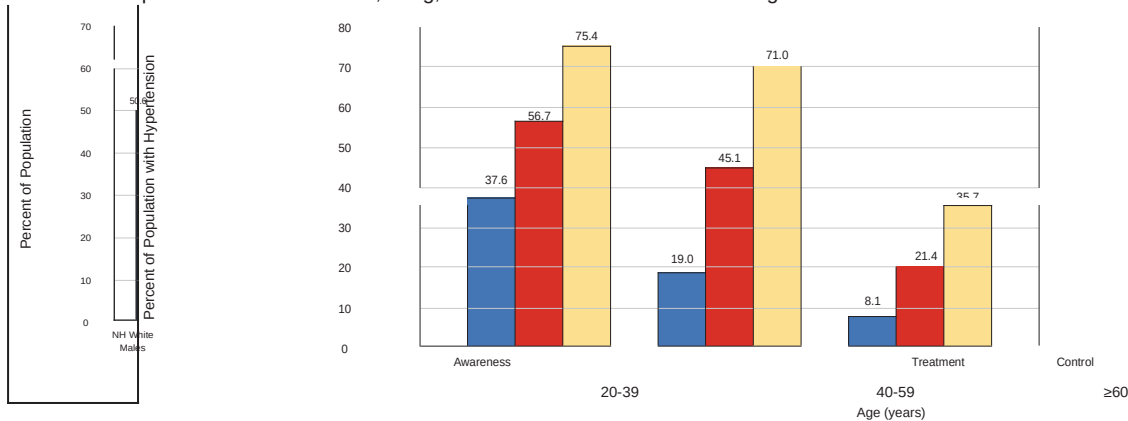


Chart 8-2.

US adults ≥ 20 years of age, by race and ethnicity, sex, and survey year (NHANES 1999–2002, 2007–2010, and 2017–2020).

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally

representative estimates.¹²⁶ Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg or if he or she said “yes” to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure. *The category of Mexican American people was consistently collected in all NHANES years, but the combined category of Hispanic people was used only starting in 2007. Consequently, for long-term trend data, the category of Mexican American people is used.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁵

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹²⁶ Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg or if he or she said “yes” to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁵

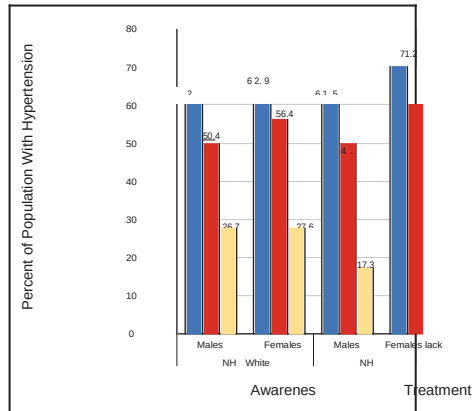


Chart 8-5. Extent of awareness, treatment, and control of HBP, by race and ethnicity and sex, United States (NHANES, 2017–2020).

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹²⁶ Hypertension is defined in terms of NHANES BP measurements and health interviews. A person was considered to have hypertension if he or she had SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg or if he or she said “yes” to taking antihypertensive medication. BP indicates blood pressure; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; HBP, high blood pressure; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁵

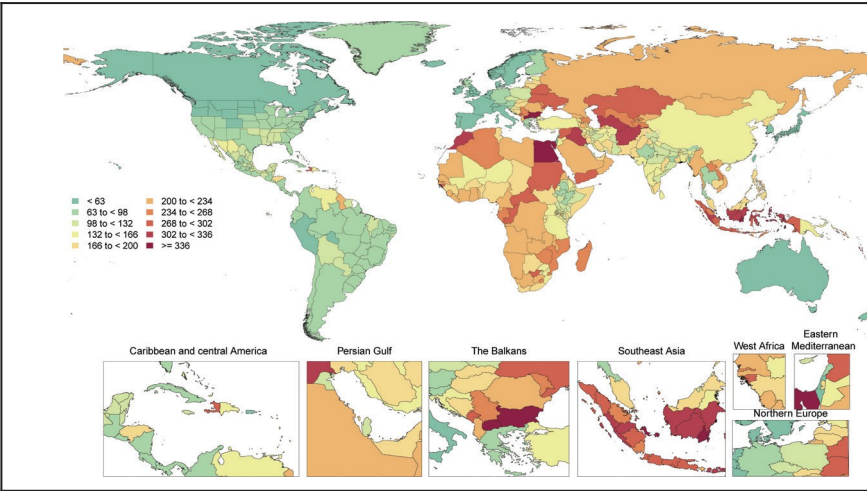


Chart 8-6. Age-standardized global mortality rates attributable to high SBP per 100 000, both sexes, 2021.

During each annual GBD Study cycle, population

1. Clark D 3rd, Colantonio LD, Min YI, Hall ME, Zhao H, Mentz RJ, Shimbo D, Ogedegbe G, Howard G, Levitan EB, et al. Population-attributable risk for cardiovascular disease associated with hypertension in Black adults. <i>JAMA Cardiol.</i> 2019;4:1194–1202. doi: 10.1001/jamacardio.2019.3773	Statistics. Summary health statistics: National Health Interview Survey, 2018: table A-1. Accessed April 1, 2024.
2. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, He J. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. <i>JAMA Cardiol.</i> 2017;2:775–781. doi: 10.1001/jamacardio.2017.1421	17. Abdel Magid HS, Milliren CE, Rice K, Molanphy N, Ruiz K, Gooding HC, Richmond TK, Odden MC, Nagata JM. Adolescent individual, school, and neighborhood influences on young adult hypertension risk. <i>PLoS One.</i> 2022;17:e0266729. doi: 10.1371/journal.pone.0266729
3. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma Lloyd-Jones DM, Wilkins JT. Lifetime risks for hypertension by contemporary guidelines in African American and White men and women. <i>JAMA American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines</i> [published correction appears in <i>Hypertension.</i> 2018;71:e140–e144]. <i>Hypertension.</i> 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065	18. Chen V, Ning H, Allen N, Kershaw K, Khan S, Wilkins JT. Lifetime risks for hypertension by contemporary guidelines in African American and White men and women. <i>JAMA American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines</i> [published correction appears in <i>Hypertension.</i> 2018;71:e140–e144]. <i>Hypertension.</i> 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065
4. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the	5. Centers for Disease Control and Prevention and National Center for

20. Ananth CV, Duzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS. Changes in the prevalence of chronic hypertension in pregnancy, 10.1161/HYPERTENSIONAHA.119.12968
21. Harding CC, Goldstein KM, Goldstein SA, Wheeler SM, Mitchell NS, Serv Res. 2024;59:e14277. doi: 10.1111/1475-6773.14277
22. Joham AE, Kakoly NS, Teede HJ, Earnest A. Incidence and predictors of polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2021;106:1585–1593. doi: 10.1210/clinem/dgab134
6. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 7, 2024.
7. Bourque G, Ilin JV, Ruzicka M, Hundemer GL, Shorr R, Hiremath S. Non-adherence is common in patients with apparent resistant hypertension in a cohort of Australian women with and without polycystic hypertension. 2019;74:1089–1095. doi: 10.1093/ajh/hpad013
23. Chen F, Fu W, Shi O, Li D, Jiang Q, Wang T, Zhou X, Lu Z, Cao S. Impact of exposure to noise on the risk of hypertension: a systematic review and meta-analysis. *Am J Hypertens*. 2023;36:394–403. doi: 10.1093/ajh/hpad013
8. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, et al; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140:e20171904. doi: 10.1210/clinem/dgab134

- meta-analysis of cohort studies. *Environ Res.* 2021;195:110813. doi: 10.1016/j.envres.2021.110813
24. Kourieh A, Giorgis-Allemand L, Bouaoun L, Lefèvre M, Champelovier P, Lambert J, Laumon B, Evrard AS. Incident hypertension in relation to aircraft noise exposure: results of the DEBATS longitudinal study in France. *Occup Environ Med.* 2022;79:268–276. doi: 10.1136/oemed-2021-107921
25. Cheng H, Gu X, He Z, Yang Y. Dose-response relationship between working hours and hypertension: a 22-year follow-up study. *Medicine (Baltimore).* 2021;100:e25629. doi: 10.1097/md.00000000000025629
26. Huang L, Trieu K, Yoshimura S, Neal B, Woodward M, Campbell NRC, Li Q, Lackland DT, Leung AA, Anderson CAM, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: systematic review and meta-analysis of randomised trials. *BMJ.* 2020;368:m315. doi: 10.1136/bmj.m315
9. Overwyk KJ, Zhao L, Zhang Z, Wiltz JL, Dunford EK, Cogswell ME. Trends in blood pressure and usual dietary sodium intake among children and adolescents, National Health and Nutrition Examination

27. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, Zhang J, Tian M, Huang L, Li Z, et al. Effect of salt substitution on cardiovascular events and death.

N Engl J Med. 2021;385:1067–1077. doi: 10.1056/NEJMoa2105675

Survey

2003

to

2016.

Hypertension.

2019;74:260–266. doi:

28. do Rosario

10.1161/HYPERTENSIONAHA.118.12844

10. Cioana M, Deng J, Hou M, Nadarajah A, Qiu Y, Chen SSJ, Rivas A, Banfield L, Chanchlani R, Dart A, et al. Prevalence of hypertension and albuminuria in pediatric type 2 diabetes: a systematic review and meta-

analysis. *JAMA Netw Open*. 2021;4:e216069. doi: 10.1001/jamanetworkopen.2021.6069

11. Hamdani G, Mitsnefes MM, Flynn JT, Becker RC, Daniels S, Falkner BE, Ferguson M, Hooper SR, Hanevold CD, Ingelfinger JR, et al. Pediatric and

29. Sardana M, Lin H, Zhang Y, Liu C, Trinquart L, Benjamin EJ, Manders ES, physical activity with home blood pressure in the Electronic Framingham Heart 2021;23:e25591. adult ambulatory blood pressure thresholds and blood pressure load as predictors of left ventricular hypertrophy in adolescents. *Hypertension*. 2021;78:30–37. doi: 10.1161/HYPERTENSIONAHA.120.16896
12. Crouch SH, Soepnel LM, Kolkenbeck-Ruh A, Maposa I, Naidoo S, Davies J, Norris SA, Ware LJ. Paediatric hypertension in Africa: a systematic review and meta-analysis. *EClinicalMedicine*. 2022;43:101229. doi: 10.1016/j.eclinm.2021.101229
13. Nugent JT, Young C, Funaro MC, Jiang K, Saran I, Ghazi L, Wilson FP, Greenberg JH. Prevalence of secondary hypertension in otherwise healthy youths with a new diagnosis of hypertension: a meta-analysis. *J Pediatr*. 2022;244:30–37.e10. doi: 10.1016/j.jpeds.2022.01.047
14. Chen Y, Ye P, Dong H, Xu X, Shi L, Li B, Dong J, Lv A, Su Z, Zhang Y, et al; Childhood Hypertension Collaboration of Futang Research Center of Pediatric Development (FRCPD). Clinical characteristics of pediatric hypertension: a multicenter study in China. *J Hypertens*. 2023;41:1753–1759. doi: 10.1097/HJH.0000000000003533
15. Chung J, Robinson C, Sheffield L, Paramanathan P, Yu A, Ewusie J, Sanger S, Mitsnefes M, Parekh RS, Sinha MD, et al. Prevalence of pediatric masked hypertension and risk of subclinical cardiovascular outcomes: a systematic review and meta-analysis. *Hypertension*. 2023;80:2280–2292. doi: 10.1161/HYPERTENSIONAHA.123.20967
- Fusco K, Kornej J, Hammond MM, et al. Association of habitual Study (eFHS): cross-sectional study. *J Med Internet Res*. doi: 10.2196/25591

30. Farhangi MA, Fathi Azar E, Manzouri A, Rashnoo F, Shakarami A. Prolonged screen watching behavior is associated with high blood pressure among children and adolescents: a systematic review and dose-response meta-analysis. *J Health Popul Nutr.* 2023;42:89. doi: 10.1186/s41043-023-00437-8
31. Johnson DA, Thomas SJ, Abdalla M, Guo N, Yano Y, Rueschman M, Tanner RM, Mittleman MA, Calhoun DA, Wilson JG, et al. Association between sleep apnea and blood pressure control among Blacks. *Circulation.* 2019;139:1275–1284. doi: 10.1161/CIRCULATIONAHA.118.036675
32. MacIntyre IM, Turtle EJ, Farrah TE, Graham C, Dear JW, Webb DJ; PATH-BP (Paracetamol in Hypertension–Blood Pressure) Investigators. Regular acetaminophen use and blood pressure in people with hypertension: the PATH-BP trial. *Circulation.* 2022;145:416–423. doi: 10.1161/CIRCULATIONAHA.121.056015
33. Li YD, Ren ZJ, Gao L, Ma JH, Gou YQ, Tan W, Liu C. Association between male infertility and the risk of hypertension: a meta-analysis and literature review. *Andrologia.* 2022;54:e14535. doi: 10.1111/and.14535
34. Sheehy S, Palmer JR, Cozier Y, Bertrand KA, Rosenberg L. Vitamin D and risk of hypertension among Black women. *J Clin Hypertens (Greenwich).* 2023;25:168–174. doi: 10.1111/jch.14615

35. Varghese JS, Lu P, Choi D, Kobayashi LC, Ali MK, Patel SA, Li C. Spousal concordance of hypertension among middle-aged and older heterosexual couples around the world: evidence from studies of aging in the United States, England, China, and India. *J Am Heart Assoc.* 2023;12:e030765. doi: 10.1161/JAHA.123.030765
36. Forde AT, Sims M, Muntner P, Lewis T, Onwuka A, Moore K, Diez Roux AV. Discrimination and hypertension risk among African Americans in the Jackson Heart Study. *Hypertension.* 2020;76:715–723. doi: 10.1161/HYPERTENSIONAHA.119.14492
37. Glover LM, Cain-Shields LR, Wvatt SB, Gebreab SY, Diez-Roux AV, Sims M. Life course socioeconomic status and hypertension in African American adults: the Jackson Heart Study. *Am J Hypertens.* 2020;33:84–91. doi: 10.1093/ajh/hnz133
38. Trudel X, Brisson C, Gilbert-Ouimet M, Vezina M, Talbot D, Milot A. Long working hours and the prevalence of masked and sustained hypertension. *Hypertension.* 2020;75:532–538. doi: 10.1161/HYPERTENSIONAHA.119.12926
39. Gamboa Madeira S, Fernandes C, Paiva T, Santos Moreira C, Caldeira D. The impact of different types of shift work on blood pressure and hypertension: a systematic review and meta-analysis. *Int J Environ Res Public Health.* 2021;18:6738. doi: 10.3390/ijerph18136738
40. Liu M, Aggarwal R, Zheng Z, Yeh RW, Kazi DS, Joynt Maddox KE, Evangelou Ntritsos million Nat
50. Giri A. Kovesdy Group. International study of Genet.
51. Surendran L, Mifsud Society pressure Genet.
52. Liang L, Li Wadhera RK. Cardiovascular health of middle-aged U.S. adults by income level, 1999 to March 2020: a serial cross-sectional study. *Ann Intern Med.* 2023;176:1595–1605. doi: 10.7326/M23-2109
41. Liu C, Kraja AT, Smith JA, Brody JA, Franceschini N, Bis JC, Rice K, Morrison AC, Lu Y, Weiss S, et al; CHD Exome+ Consortium; ExomeBP

Y, Jensen RA, Chen G, Yanek LR, et al. Single-trait and multi-trait genome-wide association analyses identify novel loci for blood pressure in African-ancestry populations. *PLoS Genet.* 2017;13:e1006728. doi: 10.1371/journal.pgen.1006728

53. Wan EYF, Fung WT, Schooling CM, Au Yeung SL, Kwok MK, Yu EYT, Wang Y, Chan EWY, Wong ICK, Lam CLK. blood pressure and risk of cardiovascular disease in UK Biobank: a mendelian randomization study. *Hypertension.* 2021;77:367–375. doi: 10.1161/HYPERTENSIONAHA.120.16138

54. Parcha V, Pampana A, Shetty NS, Irvin MR, Natarajan P, Lin HJ, Guo X, Rich SS, Rotter JI, Li P, et al. Association of a multi-ancestry genome-wide blood pressure polygenic risk score with adverse cardiovascular events. Consortium; GoT2DGenes Consortium; T2D-GENES Consortium; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet.* 2016;48:1162–1170. doi: 10.1038/ng.3660

42. Surendran P, Drenos F, Young R, Warren H, Cook JP, Manning AK, Grarup N, Sim X, Barnes DR, Witkowska K, et al; CHARGE-Heart Failure Consortium, EchoGen Consortium, Metastroke Consortium, Giant Consortium, EPIC-InterAct Consortium, Lifelines Cohort Study, Wellcome Trust Case Control Consortium, Understanding Society Scientific Group, Epic-CVD Consortium, Charge Exome Chip Blood Pressure Consortium, T2D-GENES Consortium, GoT2DGenes Consortium, CHD Exome+ Consortium. Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nat Genet.* 2016;48:1151–1161. doi:

- 10.1161/CIRCGEN.122.003946
55. Gouveia MH, Bentley AR, Leonard H, Meeks KAC, Ekoru K, Chen G, Nalls MA, Simonsick EM, Tarazona-Santos E, Lima-Costa MF, et al. Trans-ethnic meta-analysis identifies new loci associated with longitudinal blood pressure traits. *Sci Rep*. 2021;11:4075. doi: 10.1038/s41598-021-83450-3
56. Jia P, Zhan N, Bat BKK, Feng Q, Tsoi KKF. The genetic architecture of blood pressure variability: a genome-wide association study of 9370 participants from UK Biobank. *J Clin Hypertens (Greenwich)*. 2022;24:1370–1380. doi: 10.1111/jch.14552
57. Kauko A, Aittokallio J, Vaura F, Ji H, Ebinger JE, Niiranen T, Cheng S. Sex differences in genetic risk for hypertension. *Hypertension*. 2021;78:1153–1155. doi: 10.1161/HYPERTENSIONAHA.121.17796
58. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, Cheng S. Sex differences in blood pressure trajectories over the life course. *JAMA*. 2016;48:1171–1184. doi: 10.1038/ng.3667
43. Ehret GB, Ferreira T, Chasman DI, Jackson AU, Schmidt EM, Johnson T, Thorleifsson G, Luan J, Donnelly LA, Kanoni S, et al; CHARGE-EchoGen Consortium, CHARGE-HF Consortium, Wellcome Trust Case Control Consortium. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat Genet*. 2016;48:1171–1184. doi: 10.1038/ng.3667
44. Hoffmann TJ, E G, Nandakumar P, Ranatunga D, Schaefer C, Kwok PY, Iribarren C, Chakravarti A, Risch N. Genome-wide association analyses us-

- Cardiol.* 2020;5:19–26. doi: 10.1001/jamacardio.2019.5306
59. Basson J, Sung YJ, de las Fuentes L, Schwander K, Cupple LA, Rao DC. Influence of smoking status and intensity on discovery of blood pressure loci through gene-smoking interactions. *Genet Epidemiol.* 2015;39:480–488. doi: 10.1002/gepi.21904
60. Sung Y, de Las Fuentes L, Schwander K, Simino J, Rao D. Gene-smoking interactions identify several novel blood pressure loci in the Framingham Heart Study. *Am J Hypertens.* 2015;28:343–354. doi: 10.1093/ajh/hpu149
- ing electronic health records identify new loci influencing blood pressure variation. *Nat Genet.* 2017;49:54–64. doi: 10.1038/ng.3715
45. Yu B, Pulit SL, Hwang SJ, Brody JA, Amin N, Auer PL, Bis JC, Boerwinkle E, Burke GL, Chakravarti A, et al; CHARGE Consortium and the National

61. Li C, He J, Chen J, Zhao J, Gu D, Hixson J, Rao D, Jaquish C, Gu C, Chen J, et al. Genome-wide gene-sodium interaction analyses on blood pressure: the Genetic Epidemiology Network of Salt-Sensitivity Study. *Hypertension*. 2016;68:348–355.
- Heart, Lung, and Blood Institute GO ESP. Rare exome sequence variants in *CLCN6* reduce blood pressure levels and hypertension risk. *Circ Cardiovasc Genet*. 2016;9:64–70. doi: 10.1161/CIRCGENETICS.115.001215 46.
- Tragante V, Barnes MR, Ganesh SK, Lanktree MB, Guo W, Franceschini N, Smith EN, Johnson T, Holmes MV, Padmanabhan S, et al. Gene-centric meta-analysis in 87,736 individuals of European ancestry identifies multiple blood-pressure-related loci. *Am J Hum Genet*. 2014;94:349–360. doi: 10.1016/j.ajhg.2013.12.016
47. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, Ntalla I, Surendran P, Liu C, Cook JP, et al; International Consortium of Blood Pressure (ICBP) 1000G Analyses. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat Genet*. 2017;49:403–415. doi: 10.1038/ng.3768 48. He KY, Li X, Kelly TN, Liang J, Cade BE, Assimes TL, Becker LC, Beitelshes AL, Bress AP, Chang YC, et al; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, TOPMed Blood Pressure Working Group. Leveraging linkage evidence to identify low-frequency and rare variants on 16p13 associated with blood pressure using TOPMed whole genome sequencing data. *Hum Genet*. 2019;138:199–210. doi:

62. Sung YJ, de Las Fuentes L, Winkler TW, Chasman DI, Bentley AR, Kraja AT, Ntalla I, Warren HR, Guo X, Schwander K, et al; Lifelines Cohort Study. A multi-ancestry genome-wide study incorporating gene-smoking interactions identifies multiple new loci for pulse pressure and mean arterial pressure. *Hum Mol Genet.* 2019;28:2615–2633. doi: 10.1093/hmg/ddz070

63. Kurniansyah N, Goodman MO, Khan AT, Wang J, Feofanova E, Bis JC, Wiggins KL, Huffman JE, Kelly T, Elfassy T, et al. Evaluating the use of blood pressure polygenic risk scores across race/ethnic background groups. *Nat Commun.* 2023;14:3202. doi: 10.1038/s41467-023-38990-9

64. Honigberg MC, Truong B, Khan RR, Xiao B, Bhatta L, Vy HMT, Guerrero RF, Schuermans A, Selvaraj MS, Patel AP, et al. Polygenic prediction of pre-eclampsia and gestational hypertension. *Nat Med.* 2023;29:1540–1549. doi: 10.1038/s41591-023-02374-9

65. Tyrmi JS, Kaartokallio T, Lokki AI, Jaaskelainen T, Kortelainen E, Ruotsalainen S, Karjalainen J, Ripatti S, Kivioja A, Laisk T, et al; FINNPEC Study Group, FinnGen Project, and the Estonian Biobank Research Team. Genetic risk factors associated with preeclampsia and hypertensive disorders of pregnancy. *JAMA Cardiol.* 2023;8:674–683. doi:

10.1007/s00439-019-01975-0 10.1001/

66. Cooper-DeHoff RM, Johnson JA. Hypertension pharmacogenomics: in search of personalized treatment approaches. *Nat Rev Nephrol.* 2016;12:110–122. doi: 10.1038/nrneph.2015.176
67. Gill D, Georgakis MK, Koskeridis F, Jiang L, Feng Q, Wei WQ, Theodoratou E, Elliott P, Denny JC, Malik R, et al. Use of genetic variants related to antihypertensive drugs to inform on efficacy and side effects. *Circulation.* 2019;140:270–279. doi: 10.1161/CIRCULATIONAHA.118.038814
68. Tapela N, Collister J, Clifton L, Turnbull I, Rahimi K, Hunter DJ. Prevalence and determinants of hypertension control among almost 100 000 treated adults in the UK. *Open Heart.* 2021;8:e001461. doi: 10.1136/openhrt-2020-001461
- Heart Assoc. 2022;11:e025102. doi: 10.1161/jaha.121.025102
70. Di Federico S, Filippini T, Whelton PK, Cecchini M, Iamandii I, Boriani G, Vinceti M. Alcohol intake and blood pressure levels: a dose-response meta-analysis of nonexperimental cohort studies. *Hypertension.* 2023;80:1961–1969. doi: 10.1161/HYPERTENSIONAHA.123.21224
71. Cohen JB, Cohen DL, Herman DS, Leppert JT, Byrd JB, Bhalla V. Testing for primary aldosteronism and mineralocorticoid receptor antagonist use among U.S. veterans: a retrospective cohort study. *Ann Intern Med.* 2021;174:289–297. doi: 10.7326/M20-4873
72. Kassavou A, Wang M, Mirzaei V, Shpendi S, Hasan R. The association between smartphone app-based self-monitoring of hypertension-related behaviors and reductions in high blood pressure: systematic review and meta-analysis. *JMIR Mhealth Uhealth.* 2022;10:e34767.
84. Blood Pressure Lowering Treatment Trialists Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet.* 2021;397:1625–1636. doi: 10.1016/S0140-6736(21)00590-0
85. Kubicki DM, Xu M, Akwo EA, Dixon D, Munoz D, Blot WJ, Wang TJ, Lipworth L, Gupta DK. Race and sex differences in modifiable risk factors and incident heart failure. *JACC Heart Fail.* 2020;8:122–130. doi: 10.2196/34767
73. Feng Y, Zhao Y, Yang X, Li Y, Han M, Qie R, Huang S, Wu X, Zhang Y, Wu Y, et al. Adherence to antihypertensive medication and cardiovascular disease events in hypertensive patients: a dose-response meta-analysis of 2 769 700 participants in cohort study. *QJM.* 2022;115:279–286. doi: 10.1093/qjmed/hcaa349
74. Gnanenthiran SR, Borghi C, Burger D, Caramelli B, Charchar F, Chirinos JA, Cohen JB, Cremer A, Di Tanna GL, Duvignaud A, et al. Renin-angiotensin system inhibitors in patients with COVID-19: a meta-analysis of randomized controlled trials led by the International Society of Hypertension. *J Am Heart Assoc.* 2022;11:e026143. doi: 10.1161/jaha.122.026143
75. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, Ford I, Rorie DA, Guthrie G, Grieve JWK, et al; TIME Study Group. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a pro-

87. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, Ghazi L, Blackshear JL, Chonchol M, Fine LJ, et al. Effect of intensive blood pressure lowering on the risk of atrial fibrillation. *Hypertension*. 2020;75:1491–1496. doi: 10.1161/HYPERTENSIONAHA.120.14766
88. Rouabhi M, Durieux J, Al-Kindi S, Cohen JB, Townsend RR, Rahman M. Orthostatic hypertension and hypotension and outcomes in CKD: the CRIC (Chronic Renal Insufficiency Cohort) study. *Kidney Med*. 2021;3:206–215. doi: 10.1016/j.xkme.2020.10.012
89. Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, Berrut G, Corruble E, Derumeaux G, Falissard B, et al; S.AGES Investigators. Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: the S.AGES cohort. *Hypertension*. 2020;76:1280–1288. doi: 10.1161/HYPERTENSIONAHA.119.14553
90. Mahinrad S, Kurian S, Garner CR, Sedaghat S, Nemeth AJ, Moscufo N, Higgins JP, Jacobs DR Jr, Hausdorff JM, Lloyd-Jones DM, et al. Cumulative blood pressure exposure during young adulthood and mobility and cognitive function in midlife. *Circulation*. 2020;141:712–724. doi: 10.1161/CIRCULATIONAHA.119.042502
91. de Heus RAA, Tzourio C, Lee EJL, Opozda M, Vincent AD, Anstey KJ, Hofman A, Kario K, Lattanzi S, Launer LJ, et al; Variable Brain Consortium. Association between blood pressure variability with dementia and cognitive impairment: a systematic review and meta-analysis. *Hypertension*. 2021;78:1478–1489. doi: 10.1161/HYPERTENSIONAHA.121.17797
92. Peters R, Xu Y, Fitzgerald O, Aung HL, Beckett N, Bulpitt C, Chalmers J, Forette F, Gong J, Harris K, et al; Dementia Risk REDuCTion (DIRECT) Collaboration. Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis. *Eur Heart J*. 2022;43:4980–4990. doi: 10.1093/eurheartj/ehac584
93. spective, randomised, open-label, blinded-endpoint clinical trial. *Lancet*. 2022;400:1417–1425. doi: 10.1016/S0140-6736(22)01786-X
76. Baral N, Volgman AS, Seri A, Chelikani V, Isa S, Javvadi SLP, Paul TK, Mitchell JD. Adding pharmacist-led home blood pressure telemonitoring to usual care for blood pressure control: a systematic review and meta-analysis. *Am J Cardiol*. 2023;203:161–168. doi: 10.1016/j.amjcard.2023.06.109
77. Bryant KB, Rao AS, Cohen LP, Dandan N, Kronish IM, Barai N, Fontil V, Zhang Y, Moran AE, Bellows BK. Effectiveness and cost-effectiveness of team-based care for hypertension: a meta-analysis and simulation study. *Hypertension*. 2023;80:1199–1208. doi: 10.1161/HYPERTENSIONAHA.122.20292
78. O'Hagan ET, McIntyre D, Nguyen T, Chow CK. Hypertension therapy using fixed-dose polypills that contain at least three medications. *Heart*. 2023;109:1273–1280. doi: 10.1136/heartjnl-2022-321496
79. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
80. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.
81. Yano Y, Reis JP, Lewis CE, Sidney S, Pletcher MJ, Bibbins-Domingo K, Navar AM, Peterson ED, Bancks MP, Kanegae H, et al. Association of blood pressure patterns in young adulthood with cardiovascular disease and mortality in middle age. *JAMA Cardiol*. 2020;5:382–389. doi: 10.1001/jamacardio.2019.5682
82. Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR. Cardiovascular events and mortality in white coat hypertension: a systematic review and meta-analysis. *Ann Intern Med*. 2019;170:853–862. doi: 10.1093/eurheartj/ehac584

93. Babroudi S, Tighiouart H, Schrauben SJ, Cohen JB, Fischer MJ, Rahman M, Hsu CY, Sozio SM, Weir M, Sarnak M, et al; CRIC Study Investigators. Blood pressure, incident cognitive impairment, and severity of ckd: findings from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2023;82:443–453.e1. doi: 10.1053/j.ajkd.2023.03.012
94. Schliep KC, McLean H, Yan B, Qeadan F, Theilen LH, de Havenon A, Majersik JJ, Østbye T, Sharma S, Varner MW. Association between hypertensive disorders of pregnancy and dementia: a systematic review and meta-analysis. *Hypertension*. 2023;80:257–267. doi: 10.1161/HYPERTENSIONAHA.122.19399
95. Welters SM, de Boer M, Teunissen PW, Hermes W, Ravelli ACJ, Mol BW, de Groot CJM. Cardiovascular mortality in women in their forties after hypertensive disorders of pregnancy in the Netherlands: a national cohort study. *Lancet Healthy Longev*. 2023;4:e34–e42. doi: 10.1016/S2666-7568(22)00292-6
96. Bohm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Emrich I, Mancía G, Redon J, Schmieder RE, Sliwa K, et al. Renal outcomes and blood pressure patterns in diabetic and nondiabetic individuals at high cardiovascular risk. *J Hypertens*. 2021;39:766–774. doi: 10.1097/HJH.0000000000002697
97. Dionne JM, Jiang S, Ng DK, Flynn JT, Mitsnefes MM, Furth SL, Warady BA, Samuels JA; CKiD Study Group. Mean arterial pressure and chronic kidney disease progression in the CKiD cohort. *Hypertension*. 2021;78:65–73. doi: 10.1161/HYPERTENSIONAHA.120.16692
98. Copland E, Canoy D, Nazarzadeh M, Bidel Z, Ramakrishnan R, Woodward M, Chalmers J, Teo KK, Pepine CJ, Davis BR, et al; Blood Pressure Lowering Treatment Trialists' Collaboration. Antihypertensive treatment and risk of cancer: an individual participant data meta-analysis. *Lancet*. 2021;397:1022–1033. doi: 10.1016/S0140-6736(20)32533-4
83. Yano Y, Tanner RM, Sakhuja S, Jaeger BC, Booth JN 3rd, Abdalla M, Pugliese D, Seals SR, Ogedegbe G, Jones DW, et al. Association of day-time and nighttime blood pressure with cardiovascular disease events among African American individuals. *JAMA Cardiol*. 2019;4:910–917. doi: 10.1001/jamacardio.2019.2845

99. Borrelli S, Garofalo C, Gabbai FB, Chiodini P, Signoriello S, Paoletti E, Ravera M, Bussalino E, Bellizzi V, Liberti ME, et al. Dipping status, ambulatory blood pressure control, cardiovascular disease, and kidney disease progression: a multicenter cohort study of CKD. *Am J Kidney Dis*. 2023;81:15–24.e1. doi: 10.1053/j.ajkd.2022.04.010

100. Bourdillon MT, Song RJ, Musa Yola I, predictors, progression, and prognosis of Framingham Heart Study. *J Am Heart* 10.1161/aha.121.024202
101. Clark CE, Warren FC, Boddv K, McDonagh Alzamora M, Ramos Blanes R, Chuano SY. Higher arm versus lower arm systolic blood pressure outcomes: a meta-analysis of INTERPRESS-IPD collaboration. 10.1161/HYPERTENSIONAHA.121.18921
102. Delker E, Bandoli G, LaCoursiere Y, Ferran Ramos GA, Allison M. Chronic national longitudinal study of adolescents in *Epidemiol*. 2022;36:370–379. doi: 10.1111/ppe.12858
103. Kabia AU, Li P, Jin Z, Tan X, Liu Y, Feng Y, Yu K, Hu M, Jiang D, Cao G. The effects of hypertension on the prognosis of coronavirus disease 2019: a systematic review and meta-analysis on the interactions with age and antihypertensive treatment. *J Hypertens*. 2022;40:2323–2336. doi: 10.1097/HJH.0000000000003266
104. Li M, Fan F, Qiu L, Ma W, Zhang Y. Association of an inter-arm systolic blood pressure difference with all-cause and cardiovascular mortality: a meta-analysis of cohort studies. *J Clin Hypertens (Greenwich)*. 2023;25:1069–1078. doi: 10.1111/jch.14746
105. Pasdar Z, De Paola L, Carter B, Pana TA, Potter JF, Myint PK. Orthostatic hypertension and major adverse events: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2023;30:1028–1038. doi: 10.1093/eurjpc/zwad158
106. Peters CD, Olesen KKW, Laugesen E, Maeng M, Botker HE, Poulsen PL, Buus NH. Invasively measured aortic systolic blood pressure and
114. Gnugesser E, Chwila C, Brenner S, Bärnighausen T, Horstick O, Antia K. den of treating uncomplicated systematic literature review. *BMC* 10.1186/s12889-022-13877-4
115. GBD Risk Factors Collaborators. countries and territories. 1990-2019: a Burden of Disease Study 2019. 10.1016/S0140-6736(20)30752-2
116. Global Burden of Disease Study and Evaluation. University of Washington.
117. Forouzanfar MH, Liu P, Roth GA. Non-office systolic blood pressure in cardiovascular risk assessment in CKD. *Kidney Int Rep*. 2024;9:296–311. doi: 10.1016/j.ekir.2023.11.001
107. Rietz H, Pennlert J, Nordstrom P, Brunstrom M. Blood pressure level in late adolescence and risk for cardiovascular events: a cohort study. *Ann Intern Med*. 2023;176:1289–1298. doi: 10.7326/M23-0112
108. Staplin N, de la Sierra A, Ruilope LM, Emberson JR, Vinyoles E, Gorostidi M, Ruiz-Hurtado G, Segura J, Baigent C, Williams B. Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. *Lancet*. 2023;401:2041–2050. doi: 10.1016/S0140-6736(23)00733-X
109. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024.

L, Estep K, Hassen Abate K, Akinyemiju TF, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA*. 2017;317:165–182. doi: 10.1001/jama.2016.19043

118. Al Kibria GM, Gupta RD, Nayeem J. Prevalence, awareness, and control of hypertension among Bangladeshi adults: an analysis of demographic and health survey 2017-18. *Clin Hypertens*. 2021;27:17. doi: 10.1186/s40885-021-00174-2

119. Bhagavathula AS, Shah SM, Aburawi EH. Prevalence, awareness, treatment, and control of hypertension in the United Arab Emirates: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2021;18:12693. doi: 10.3390/ijerph182312693

120. Lee J, Wilkens J, Meijer E, Sekher TV, Bloom DE, Hu P. Hypertension awareness, treatment, and control and their association with healthcare access in the middle-aged and older Indian population: a nationwide cohort study. *PLoS Med*. 2022;19:e1003855. doi: 10.1371/journal.pmed.1003855

121. Meena J, Singh M, Agarwal A, Chauhan A, Jaiswal N. Prevalence of hypertension among children and adolescents in India: a systematic review and meta-analysis. *Indian J Pediatr*. 2021;88:1107–1114. doi: 10.1007/s12098-021-03686-9

122. Chen A, Waite L, Mocumbi AO, Chan YK, Beilby J, Ojji DB, Stewart S. Elevated blood pressure among adolescents in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health*. 2023;11:e1238–e1248. doi: 10.1016/S2214-109X(23)00218-8

123. Ingabire PM, Ojji DB, Rayner B, Ogola E, Damasceno A, Jones E, Dzudie A, Ogah OS, Poulter N, Sani MU, et al; CREOLE Study Investigators. High prevalence of non-dipping patterns among Black Africans with un-controlled hypertension: a secondary analysis of the CREOLE trial. *BMC Cardiovasc Disord*. 2021;21:254. doi: 10.1186/s12872-021-02074-7

110. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed May 1, 2024.

111. Tang M, Nakamoto CH, Stern AD, Zubizarreta JR, Marcondes FO, Cao J, Eshak ES, Liu K, Arafa A, Sheerah HA, Yu C. Age-period-Uscher-Pines L, Schwamm LH, Mehrotra A. Effects of remote patient monitoring use on care outcomes among Medicare patients with hypertension: an observational study. *Ann Intern Med*. 2023;176:1465–1475. doi:

cohort analysis of stroke mortality attributable to high systolic blood pressure in China and Japan. *Sci Rep.* 2021;11:19083. doi: 10.1038/s41598-021-98072-y

125. Balouchi A, Rafsanjani M, Al-Mutawaa K, Naderifar M, Rafiemanesh H, Ebadi A, Ghezeljeh TN, Shahraki-Mohammadi A, Al-Mawali A. Hypertension and pre-hypertension in Middle East and North Africa (MENA): a meta-analysis of prevalence, awareness, treatment, and control. *Curr Probl Cardiol.* 2022;47:101069. doi: 10.1016/j.cpcardiol.2021.101069

10.7326/M23-1182

126. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, Fryar CD, Gu S,

112. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2024.

Hales CM, Hughes JP, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat*

113. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyas T, Scott KW, et al. US health care spending by payer and

Rep. 2021;158:1–21. doi: 10.15620/cdc:106273
health condition, 1996-2016. *JAMA.* 2020;323:863–
884. doi: 10.1001/jama.2020.0734

127. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Circulation*. 2018;137:109–118. doi: 10.1161/CIRCULATIONAHA.117.032582

9. DIABETES

ICD-9 250; ICD-10 E10 to E11. See Tables 9-1 through 9-3 and Charts 9-1 through 9-9

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Diabetes is a heterogeneous condition glucose dysregulation. In the United States, the most common forms are type 2 diabetes, which affects 90% to 95% of those with diabetes, and type 1 diabetes, which constitutes 5% to 10% of cases of diabetes.¹ For this chapter, diabetes type (ie, type 1 diabetes or type 2 diabetes) is used when reported as such in the original data source; otherwise, the broader term diabetes is used and may include different diabetes types, of which the vast majority will be type 2 diabetes. Diabetes is defined on the basis of FPG ≥126 mg/dL, 2-hour postchallenge glucose ≥200 mg/dL during an oral glucose tolerance test, random glucose ≥200 mg/dL with presentation of hyperglycemia symptoms, or HbA1c ≥6.5%² and may be classified as diagnosed by a health care professional or undiagnosed (ie, meeting glucose or HbA1c criterion but without a clinical diagnosis). Pre-diabetes increases the risk of diabetes and is defined as an FPG of 100 to 125 mg/dL, 2-hour postchallenge glucose of 140 to 199 mg/dL during an oral glucose tolerance test, or HbA1c of 5.7% to 6.4%. Diabetes is a major risk factor for CVD, including CHD, HF, PAD, and stroke.³ The AHA has identified untreated FPG levels of <100 mg/dL for children and adults as 1 of the 8 components of ideal CVH.⁴

Youth

- In 2021, 352 000 children and adolescents <20 years of age, or 35 per 10 000 US youths, had diagnosed diabetes. This includes 304 000 with type 1 diabetes.¹
- Among US adolescents 12 to 18 years of age in 2005 to 2016, the prevalence of prediabetes was

18.0% (95% CI, 16.0%–20.1%). Adolescent males were more likely to have prediabetes than adolescent females (22.5% [95%
• A mathematical prediction model from the SEARCH for Diabetes in Youth study suggests that the number of youths with diabetes will increase from 181 000 in 2017 to 239 000 (type 1 diabetes, 119 000; type 2 diabetes, 120 000) in 2060 if the incidence remains constant as observed in 2017, which corresponds to relative increases of 3% for type 1 diabetes and 69% for type 2 diabetes.⁶ But if one bases this estimate on increasing trends in incidence observed between 2002 and 2017, the projected number of youths with diabetes will be 526 000 (type 1 diabetes, 306 000; type 2 diabetes, 220 000), corresponding to relative increases of 65% for type 1 diabetes and 673% for type 2 diabetes.

Adults

(See Table 9-1 and Charts 9-1 through 9-3)

- On the basis of NHANES 2017 to 2020 data,⁷ 29.3 million adults (10.6%) had diagnosed diabetes, 9.7 million adults (3.5%) had undiagnosed diabetes, and 115.9 million adults (46.4%) had prediabetes. (Table 9-1)

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

2018 to 2019, the age-adjusted prevalence of diagnosed diabetes among American Indian/Alaska Native people was 14.4% for males and 14.7% for females.¹

- On the basis of NHANES 2017 to 2020 data,⁷ the age-adjusted prevalence of diagnosed diabetes in adults ≥20 years of age varied by race and ethnicity and years of education. NH White adults with more than a high school education had the lowest prevalence (7.9%), and Hispanic adults with less than a high school education had the highest prevalence (16.2%; Chart 9-2).
- Geographic variations in diabetes prevalence have been reported in US adults:
 - From state-level data from BRFSS⁸ 2022, Guam (21.3%), Puerto Rico (14.9%), and West Virginia (14.4%) had the highest age-adjusted prevalence of diagnosed diabetes, and Vermont (7.0%) had the lowest prevalence (Chart 9-3).

Incidence

Youth

- During 2017 to 2018, an estimated 1.2 million US youth <20 years of age in the United States were diagnosed with incident type 1 or type 2 diabetes. Youth 10 to 19 years of age with type 2 diabetes increased from 2002 to 2018.⁹
- On the basis of SEARCH 2002 to 2018, the annual incidence of type 2 diabetes in youth was 22.2 per 100 000 and that of type 1 diabetes was 17.9 per 100 000, indicating that type 2 diabetes in youth is becoming more prevalent than type 1 diabetes.
 - For type 1 diabetes, the annual incidence was 7.8 for American Indian or Alaska Native youth, 16.4 for Hispanic youth, and 26.4 for White youth.
 - For type 2 diabetes, the annual incidence (per 100 000) was 46.0 for Hispanic youth, 16.6 for Asian or Pacific Islander youth, 25.8 for Black youth, and 25.8 for White youth.
- In the SEARCH study, the prevalence of type 2 diabetes in youth increased from 2002 to 2018.
 - The annual increase in prevalence varied by age and ethnicity. For type 1 diabetes, the annual increase was 2.9% for Hispanic youth, 4.8% for American Indian or Alaska Native youth, and 0.6% for type 2 diabetes, the annual increase was 6.0% for Black youth, 3.5% for American Indian or Pacific Islander youth, and 0.6% for White youth (Chart 9-4).
- The prevalence of diagnosed type 2 diabetes in youth was higher for both males and females in 2017 to 2020 data than in the 1994 data. Males had a higher prevalence of diagnosed diabetes to 2020 (Chart 9-5).

Adults

(See Table 9-1)

- Approximately 1.2 million US adults ≥18 years of age were diagnosed with incident diabetes in 2021 (Table 9-1). This included ≈620 000 males and 591 000 females, 52 000 NH Asian individuals, 185 000 NH Black individuals, 233 000 Hispanic individuals, and 721 000 NH White individuals.¹
- During 2018 to 2019, adults with less than a high school education had a higher age-adjusted incidence rate for diagnosed diabetes (7.1 per 1000 [95% CI, 5.5–9.1]) than adults with more than a high school education (4.5 per 1000 [95% CI, 3.9–5.1]).

Risk Factors

- In a meta-analysis of 76 513 studies, progression from prediabetes to diabetes was 23.7 per 1000 PY for adults with less than a high school education had a higher age-adjusted incidence rate for diagnosed diabetes (7.1 per 1000 [95% CI, 5.5–9.1]) than adults with more than a high school education (4.5 per 1000 [95% CI, 3.9–5.1]).

dL, 43.8 per 1000 PY for 2-hour postchallenge glucose 140 to 199 mg/dL, and 45.2 per 1000 PY for HbA1c of 5.7% to 6.4%.¹²

- In an analysis of NHANES over the years 2001 through 2018, the top predictors of early-onset type 2 diabetes (age at onset, <50.5 years) in males in multivariable logistic regression were NH Black ethnicity and race (OR, 2.97 [95% CI, 2.24–3.95]), tobacco smoking (OR, 2.79 [95% CI, 2.18–3.58]), and high education level (OR, 1.65 [95% CI, 1.27–2.14]); in females, the top predictors were tobacco smoking (OR, 2.59 [95% CI, 1.90–3.53]), Hispanic ethnicity (OR, 1.49 [95% CI, 1.08–2.05]), and obesity.

- Data from a large UK primary care database of 94 870 South Asian individuals matched with 189 740 White individuals showed that South Asian individuals were at a greater risk of developing type 2 diabetes (aHR, 3.1 [95% CI, 2.97–3.23]), hyper-tension (1.34 [95% CI, 1.29–1.39]), IHD (1.81, [95% CI, 1.68–1.93]), and HF (1.11 [95% CI,

sity (OR, 1.30 [95% CI, 0.91–1.86]).¹³

- In the WHI, the risk of diabetes in females varied by metabolic status. Compared with females who were metabolically healthy and normal weight, the risk of diabetes was increased among those who were metabolically unhealthy and obese (HR, 4.51 [95% CI, 3.82–5.35]), those who were metabolically unhealthy and normal weight (HR, 2.24 [95%

CI, 1.74–2.88]), and those who were metabolically

Secular Trends

(See Charts 9-4 and 9-5)

lar age-adjusted incidence of diagnosed diabetes

- Among adults ≥18 years of age, there was a simi-

healthy and obese (HR, 1.68 [95% CI, 1.40–2.00]).¹⁴ In JHS, the risk of diabetes was increased for adults with obesity who were insulin resistant (IRR, 2.35 [95% CI, 1.53–3.60]), for adults without obesity who were insulin resistant (IRR, 1.59 [95% CI,

1.02–2.46]), and for adults with obesity who were insulin sensitive (IRR, 1.70 [95% CI, 0.97–2.99]) compared with those without obesity who were insulin sensitive.¹⁵

- In a meta-analysis of 42 studies, total dairy and yogurt intake was associated with a dose-dependent 3% and 7% lower risk of developing type 2 diabetes per 200- and 50-g/d intake increase, respectively.¹⁶
- Higher levels of omega-3 polyunsaturated fat markers are associated with lower risk of type 2 diabetes. Among 67 prospective studies comprising 310 955 participants, a significant inverse relation of type 2 diabetes risk was observed across

associated with incident AF both in those with (RR, 1.24 [95% CI, 1.03–1.50]) and in those without (RR, 1.13 [95% CI, 1.00–1.28]) diabetes.²²

- Among 14 randomized controlled trials and 144 334 patients with type 2 diabetes, an intensive glucose-lowering treatment regimen compared with conventional therapy reduced the incidence of MI (OR, categories of α -linolenic acid (RR, 0.89 [95% CI, 0.82–0.96]), EPA (RR, 0.85 [95% CI, 0.72–0.99]), and docosapentaenoic acid (RR, 0.84, [95% CI,

with males with diabetes had an increased risk of all-cause mortality (RR, 1.13 [95% CI, 1.07–1.19]), cardiac mortality (RR, 1.49 [95% CI, 1.11–2.00]), and CHD mortality (RR, 1.44 [95% CI, 1.20–1.73]).¹⁸

- A recent meta-analysis of 8 observational studies showed a 38% higher risk of developing diabetes among individuals in the bottom quintile of highest compared with the lowest serum uric acid quintile had an HR of 1.28 (95% CI, 1.03–1.58) for all-cause mortality and 1.41 (95% CI, 1.03–1.94) for CVD mortality.¹⁹
- In 4468 adults from the Look AHEAD trial, body weight time in target range (per 1 SD) was associated with a decreased risk of adverse cardiovascular outcomes (HR, 0.84 [95% CI, 0.75–0.94]).¹⁸
- Data from mortality follow-up through 2019 from the NHANES surveys 1999 to 2018 showed that among 7101 patients with diabetes, in fully adjusted analyses, those in the

lipoprotein(a) (<3–5 mg/dL) compared with the top quintile of lipoprotein(a) (>27–55 mg/dL).²⁴ In a meta-analysis of 19 clinical trials of statin therapy among 123 940 participants, compared with placebo, low- to moderate-intensity statin allocation was associated with a 10% proportional increase in new-onset diabetes;

for high-intensity statin therapy, this increase was 36%.²⁵ Sixty-two per-cent of the new-onset diabetes cases were among those in the top quartile of the HbA1c distribution (mean HbA1c, 6.14%–6.17%). Among those with prevalent diabetes, the excess risk for worsening glycemia was 10% (95% CI, 6%–14%) for low-intensity or moderate-intensity statin therapy and 24% (95% CI, 6%–44%) for high-intensity statin therapy. In the standard (130–<150 mm Hg) SBP control, after 3.8

versus placebo.

years, those in the intensive group had a lower risk of major cardiovascular events (HR, 0.77 [95% CI,

- Lifestyle factors (higher alcohol consumption, lower PA, higher sedentary time, and unhealthy diet) were independently associated with diabetes risk over a 0.64–0.93]).²⁰
- Among 8 485 539 Korean adults, in adjusted analysis, the upper quartiles of remnant cholesterol were associated with a higher risk of developing type 2 diabetes; multivariable-adjusted HRs were 1.25 (95% CI, 1.24–1.27), 1.51 (95% CI, 1.50–1.53), and 1.95 (95% CI, 1.93–1.97) for those in the second, third, and fourth quartiles compared with the lowest quartile.¹⁹

median 3.8 years of follow-up. Adults with the least favorable lifestyle profile had an increased risk for diabetes compared with those with the most favorable lifestyle profile, with excess alcohol intake (RR, 1.12 [95% CI, 1.03–1.22]), physical inactivity (RR, 1.14 [95% CI, 1.07–1.22]), sedentary behavior (RR, 1.10 [95% CI, 1.04–1.16]), and unhealthy diet (RR, 1.26 [95% CI, 1.18–1.35]) contributing to higher

- In a post hoc analysis of the ACCORD trial, a higher time in target range of 110 to 130 mm Hg for SBP was associated with a reduction in MACEs risks for diabetes.²⁶ (HR, 0.54 [95% CI, 0.43–0.67]), including stroke (HR, 0.19 [95% CI, 0.10–0.36]), MI (HR, 0.67 [95% CI,

- In a meta-analysis of 14 studies, adults with the most favorable combined lifestyle factors had a lower diabetes risk than those with the least favorable combined lifestyle factors (HR, 0.25 [95% CI, 0.51–0.89]), HF (HR, 0.47 [95% CI, 0.33–0.66]), 0.18–0.35]).²⁷ cardiovascular death (HR, 0.63 [95% CI, 0.42–0.93]), and all-cause mortality (HR, 0.70 [95% CI,

- In analyses adjusted for PA, total sedentary behavior view-0.54–0.91]).²¹
- Among 9 cohort studies of 6 877 661 participants, the extent of glycemic variability was significantly

(RR, 1.01 [95% CI, 1.00–1.01]) and television

ing (RR, 1.09 [95% CI, 1.07–1.12]) were associated with diabetes risk in a systematic review and meta-analysis.²⁸

- In a meta-analysis of studies, SSB intake was associated with a lower risk of diabetes (RR per 250 kcal 1.13–1.25). ASB intake was associated with a higher diabetes risk (RR per 250 kcal 1.05–1.26).²⁹
- In NHANES 2007 to 2014, the prevalence of gestational diabetes was highest among Hispanic females (9.3%) and lower among White females (7.0%).
- In adjusted models, a higher SBP was associated with a lower risk of stroke (HR, 0.44–0.71).³⁹
- Among 83 721 patients with a multi-institutional diabetes registry, SBP at levels of 120 to 140 mm Hg increased CVD mortality (HR, 1.45). and in those ≥65 years among NH White females (7.0%) and NH Black females (9.3%)

to 79 mm Hg as the reference, higher CVD mortality risks were seen in those with DBP ≥ 90 mm Hg (HR, 1.55 [95% CI, 1.24–1.95]) and DBP < 70 mm Hg

(6.9%).^{.30}

- In the Nurses' Health Study II, the risk of diabetes was also increased for females with a history of gestational hypertension (HR, 1.65 [95% CI, 1.42–1.91]) or preeclampsia (HR, 1.75 [95% CI,

(HR, 1.19 [95% CI, 1.10–1.29]).^{.40}

1.58–1.93]) during first pregnancy compared with females with normotension.^{.31}

- Among 30 RCTs including 59 934 patients with type 2 diabetes, the lowest risk of major cardiovascular events was found in those patients who achieved SBP levels of 120 to 124 mm Hg (HR, 0.73 [95% CI, 0.52–1.02]) compared with 130 to 134 mm Hg (HR, 0.60 [95% CI, 0.41–0.85]) and 140 to 144 mm Hg.⁴¹
- Among 1 956 452 individuals with type 2 diabetes in the Korean National Health Insurance Service database, those in the highest quartile of remnant cholesterol level had a 28% significantly higher risk of MI and a 22% significantly higher risk of stroke.³²
- An analysis of 11 prospective studies of 355 230 individuals recently showed highest dietary chole-

- In a meta-analysis of 45 cohort studies, an SBP ≥ 140 mm Hg (but not ≥ 130 mm Hg) compared with below these numbers was associated with a greater risk of cardiovascular outcomes (HR, 1.56 [95% CI, 1.04–2.34]).⁴² The risk was greater for each 10-mm Hg increment in SBP (HR, 1.10 [95% CI, 1.04–1.18]).
- Dietary cholesterol intake to be associated with a 15% greater risk of developing type 2 diabetes, with relationships strongest in Western countries (United States, France, and Finland) compared with Eastern countries (China, Japan, and Korea).³³ In a meta-analysis of 9 observational studies, the risk of developing gestational diabetes was 49% greater for the highest compared with lowest categories of dietary cholesterol intake, with a 32% increase per 100-mg/d cholesterol intake.³⁴
- In a systematic review and meta-analysis of 24 prospective cohort studies, olive oil consumption was associated with a 22% lower risk for developing type 2 diabetes.³⁵
- Among 18 908 Japanese participants with prediabetes in an observational cohort study of claims data, nonideal BMI, BP, and TC and the number of nonideal CVH metrics were associated with an increased risk of developing diabetes.³⁶
- Among 1890 studies, the development of type 2 diabetes was associated with unprocessed red meat (HR, 1.27 [95% CI, 1.16–1.39]) and processed red meat (HR, 1.44 [95% CI, 1.27–1.63]).³⁷
- Among participants in the FHS and HCHS/SOL, the risk of incident diabetes increased by $\approx 50\%$ for each 10-year increment in age or 5-unit increment in BMI and was 50% to 70% higher in those with hypertension compared with those without hypertension.³⁸ Among 2829 Black adults in the JHS,

- In an analysis of 9307 participants from the ACCORD trial, cumulative HbA1c exposure measured as the AUC during exposure time was associated with an increased risk of cardiovascular events (HR, 1.32 [95% CI, 1.22–1.43]), all-cause mortality (HR, 1.33 [95% CI, 1.21–1.46]), and cardiovascular death (HR, 1.45 [95% CI, 1.27–1.67]).⁴³

Social Determinants of Health/Health Equity

- In NHIS 2013 to 2017, adults with diabetes who were <65 years of age were more likely to report overall financial hardship from medical bills (41.1%) than adults with diabetes ≥65 years of age (20.7%).
Among adults with diabetes <65 years of age, the prevalence of cost-related medication nonadherence was 34.7%, and the prevalence of delayed medical care was 55.5%.⁴⁴
- In NHANES 2011 to 2016, 83.4% of adults with diabetes had an HbA1c test in the past year. Testing rates were higher for individuals with health insurance (86.6%) than for those without health insurance (55.9%).⁴⁵
- According to BRFSS 2013, individuals with private health insurance were more likely than those without health insurance to have had HbA1c testing (OR, 2.60 [95% CI, 2.02–3.35]), a foot examination (OR, 1.72 [95% CI, 1.32–2.25]), or an eye

examination (OR, 2.01 [95% CI, 1.56–2.58]) in the past year.⁴⁶

- In the SEARCH study (Washington and South Carolina sites), the prevalence of food insecurity among individuals with type 1 diabetes was 19.5%.

Youths and young adults from food-insecure households were more likely to have an HbA1c >9.0% (OR, 2.37 [95% CI, 1.10–5.09]).⁴⁷

to be associated with a higher adjusted prevalence of type 2 diabetes (PR, 1.17 [95% CI, 1.11–1.22]) after adjustment, with even stronger associations in those 31 to 49 years of age (PR, 1.36 [95% CI, 1.20–1.54]) and in Hispanic/Latino women 18 to 30 years (PR, 3.70 [95% CI, 1.40–9.80]).⁴⁸

- In a case-control study using Geisinger electronic health records (2008–2016), compared with people living in rural affordable residence tracts, higher odds of new-onset type 2 diabetes were found in those categorized as living in extreme poverty (OR, 1.11 [95% CI, 1.02–1.21]) or those categorized as multilingual working (OR, 1.07 [95% CI, 1.03–1.23]).⁴⁸

Risk Prediction: Risk Scores, Risk-Enhancing Factors, and Coronary Calcium

- Diabetes is associated with great heterogeneity in risk of CVD, and in many individuals with

introduced the PREVENT risk score, which predicts the 10-year risk of total CVD and the components of ASCVD separately.⁵³ It requires input of eGFR and allows input of HbA1c, urine ACR, and zip code for further refinement of risk estimation, including among individuals with diabetes.

- In a recent analysis of 27 730 subjects with diabetes, their risk is not equivalent to the risk in those with preexisting CVD, with only 19% of those with diabetes without CVD recently estimated to be a CVD risk equivalent.⁴⁹
 - Individuals with type 2 diabetes have a wide spectrum of risks that warrant comprehensive CVD risk assessment, including global risk scoring, consideration of risk-enhancing factors, and, in subgroups, evaluation of subclinical atherosclerosis to inform treatment.⁵⁰
 - Currently, the US PCE includes a diabetes factor and can be used in individuals with diabetes to predict the 10-year risk of ASCVD (for those 40–79 years of age) and lifetime risk of ASCVD (for those 20–59 years of age).⁵¹ However, this equation does not include diabetes-specific risk enhancers that can be used to inform the treatment decision, including (1) long duration (≥10 years for type 2 diabetes or ≥20 years for type 1 diabetes), (2) albuminuria (≥30 µg albumin/mg creatinine), and (3) eGFR (<60 mL·min⁻¹·1.73 m⁻², retinopathy, neuropathy, and an ABI <0.9 if uncertain).⁵² There is currently no available US-based pooled cohort risk

with diabetes. A high HbA1c, long diabetes duration, and diabetes medication use were predictors of being a CVD risk equivalent. Moreover, diabetes was a CVD risk equivalent for women, White people, those of younger age, people with higher triglycerides or CRP, or people with reduced kidney function.⁴⁹

- CAC is also an effective risk stratifier for individuals with diabetes. In MESA, annual CHD event rates ranged from 0.4%/y in those with CAC scores of 0 to 4%/y for CAC scores of ≥ 400 , and CAC provided significant improvements in the C statistic beyond duration of diabetes of at least 10 years further risk factors.⁵⁴ A subsequent report noted that a stratified risk, especially at higher CAC scores.⁵⁵ Moreover, the incidence and progression of CAC and the relation of progression of CAC with subse-quent CHD events also are greater for those with MetS or diabetes compared with individuals without these conditions.⁵⁶ More recently, in the Coronary Calcium Consortium, among 4503 adults with dia-betes (32.5% women) 21 to 93 years of age, higher levels of CAC were more strongly related to CVD and total mortality in women compared with men.⁵⁷ For CVD mortality, HRs for CAC scores of 101 to 400 and >400 were 3.67 and 6.27, respectively, for women and 1.63 and 3.48, respectively, for men ($P_{\text{interaction}}=0.04$). For total mortality, HRs were 2.56 (CAC scores 101–400) and 4.05 (CAC scores >400) for women and 1.88 (CAC scores 101–400) and 2.66 (CAC scores >400 ; $P_{\text{interaction}}=0.01$) for men.

- CONFIRM recently showed baseline statin therapy to be associated with a reduction in MACEs in those with CAC scores ≥ 100 who also had a segment involvement score of ≥ 3 (HR, 0.24 [95% CI, 0.07–0.87]).⁵⁸
- A recent report from the CLARIFY registry of 6462 patients with diabetes showed higher levels of CAC (>400 versus 0) to be associated with greater statin and high-intensity statin initiation and CAC scores of >400 compared with lower levels to be associated with reductions in SBP, TC, LDL-C, and triglycerides.⁵⁹ score developed specifically in individuals with diabetes. However, the new AHA scientific statement on cardiovascular-kidney-metabolic health has

tion, and diabetes medication use were predictors of being a CVD risk equivalent for women, White people, those of younger age, people with higher triglycerides or CRP, or people with reduced kidney function.⁴⁹

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patients with diabetes showed higher levels of CAC statin and high-intensity statin initiation and CAC associated with reductions in SBP, TC, LDL-C, and triglycerides.⁵⁹

- An analysis from MESA and MASALA studies among 7562 participants showed that CAC >0 and

CAC ≥ 100 in those with NH White adults (80% and adults (72% and 41%).⁶⁰

Chinese adults had the (2.28 and 2.27, respectively; cose and glycated associated with CAC among

- In an analysis from the CAC 2246 individuals with a CAC betes (HR, 2.04 [95% CI, left main CAC (HR, 2.32 [95% associated with a similar risk

ity.⁶¹ In a follow-up of the DPP Outcomes Study, in analyses adjusted for demographic, genetic, meta-bolic, vascular, and behavioral covariates, a CAC score >300 compared with 0 remained associated with greater decline in only Spanish English Verbal Learning Test Delayed Recall in women ($\beta = -1.09$ [95% CI, -1.87 to -0.31]) but not men with prediabetes or diabetes.⁶²

- From a recent systematic review of 15 observational studies reporting 7 risk models with >1 validation cohort, the Risk Equations for Complications of Type 2 Diabetes had the best calibration in primary studies with the greatest

sexes. Of note, 68% of males of females before 55 years of CVD risk ($P < 0.001$ comparing between sexes).⁷⁰

- A machine learning model for HF in individuals with from NHANES 2007 to 2018 showed that age, poverty-to-chest pain, and glucose-dom forest model showing the (AUC, 0.978).⁷¹

discrimination measures for all-cause mortality (C statistic, 0.75 [95% CI, 0.70–0.80]; high certainty), cardiovascular mortality (0.79 [95% CI, 0.75–0.84]; low certainty), ESKD (0.73 [95% CI, 0.52–0.94]; low certainty), MI (0.72 [95% CI, 0.69–0.74]; moderate certainty), and stroke (0.71 [95% CI, 0.68–0.74]; moderate certainty).⁶³ • The updated version of the QDiabetes risk prediction algorithm had C statistics between 0.81 and

- The European SCORE2 diabetes risk score for prediction of cardiovascular events in individuals with diabetes was recently developed and incorporates conventional risk factors (ie, age, smoking, SBP, total, and HDL-C), as well as diabetes-related variables (ie, age at diabetes diagnosis, HbA1c, and creatinine-based eGFR).⁷² External validation showed good discrimination and improvement over SCORE2 (C index change from 0.009 to 0.031).

Family History and Genetics

- Diabetes is heritable. Twin and family studies have demonstrated a range of heritability estimates from 30% to 70%, depending on age at onset.^{73,74} In the FHS, having a parent or sibling with diabetes conferred a 3.4-fold increased risk of diabetes, which increased to 6.1 if both parents were affected.⁷⁵ On the basis of data from NHANES 2009 to 2014, individuals with diabetes had an adjusted PR for family history of diabetes of 4.27 (95% CI, 3.57–0.89).⁶⁴ or 5.12) compared with individuals without diabetes or prediabetes.⁷⁶
- Risk prediction algorithms for CVD among individuals with diabetes have also been developed.^{65–67} A meta-analysis found an overall pooled C statistic of 0.67 for 15 algorithms developed in populations with diabetes and 0.64 for 11 algorithms originally developed in a general population.⁶⁶
- The TIMI risk score for CVD events performed moderately well among adults with type 2 diabetes and high CVD risk. The C statistic was 0.71 (95% CI, 0.69–0.73) for CVD death and 0.66 (95% CI, 0.64–0.67) for a composite end point of CVD death, MI, or

- There are monogenic forms of diabetes such as maturity-onset diabetes of the young (caused by variants in *GCK* [glucokinase] and other genes) and latent autoimmune diabetes in adults. In the TODAY study of children and adolescents with overweight and obesity with type 2 diabetes, 4.5% of individuals were found to have monogenic diabetes.⁷⁷ Genetic testing can be considered if maturity-onset diabetes is suspected and can guide the management and screening of family members.

stroke.⁶⁸

character-

- A diabetic kidney disease risk prediction model including age, BMI, smoking, diabetic retinopathy, HbA1c, SBP, HDL-C, triglycerides, and ACR performed well in a validation cohort (C statistic, 0.77 [95% CI, 0.71–0.82]).⁶⁹ Using the Steno Type 1 risk engine, a cross-sectional multicenter study of 2041 patients with type 1 diabetes estimated the

- Diabetes is most often a complex disease

10-year CVD risk to be 15.4% overall, but it was significantly higher ($P<0.001$) in males than females before 55 years of age, after which the risk equalized between

ized by a polygenic architecture and gene-gene and gene-environment interactions. Diabetes GWASs have identified >500 genetic variants associated with diabetes,⁷⁸ with ORs in a GWAS of 74 124 cases with type 2 diabetes and 824 006 controls ranging from 1.04 to 8.05 per coded allele.⁷⁹

- A common intronic variant in the *TCF7L2* (transcription factor 7 like 2) gene is the most consistently identified diabetes variant.^{80–83} Together, common variants account for 18% of type 2 diabetes risk.⁷⁹

Several of these variants have also been associated with gestational diabetes (see Chapter 11 [Adverse Pregnancy Outcomes]).⁸⁴

- Few GWASs have examined type 2 diabetes in youths. Using data from n=3006 youth type 2 diabetes cases and n=6061 controls, the multiethnic ProDiGY Consortium identified 7 genome-wide significant loci, including a novel locus in *PHF2*.⁸⁵ *PHF2* may influence adipogenesis and fat storage through CCAAT-enhancer binding protein transcriptional regulation in adipose tissue.⁸⁶ The 6 known loci previously identified in adult populations that generalized to youths at genome-wide significant levels were *TCF7L2*, *MC4R*, *CDC123*, *KCNQ1*, *IGF2BP2*, and *SLC16A11*.
- Genetic studies in non-European ancestral populations have also identified significant risk loci for diabetes. For example, the DIAMANTE

European populations, African populations, and Hispanic populations.⁹³ However, prediction accuracy remained highest for European populations (AUC, 0.66) and lowest for African populations (AUC, 0.58).

- Several studies have examined whether genetic risk modifies the effect of a poor lifestyle on diabetes incidence. In a study of the UK Consortium of n=180 834 cases and n=1 159 055 controls (48.9% European ancestry) identified 338 independent variants at 237 loci.⁸⁷ Population diversity was particularly valuable for fine mapping, in which 54.4% of associations were localized to a single variant with high posterior probability. Such efforts enable assessment of causal genes and molecular

and in the group at low genetic risk.⁹⁴ However, lifestyle factors was detected ($P>0.3$). A second study in the UK Biobank assessed the interaction between diet quality and a type 2 diabetes GRS with $n=5663$ incident type 2 diabetes cases (N=357 419 participants of European ancestry at study baseline). The authors reported an antagonistic interaction in which a simultaneous 1-SD was associated with a 3% lower type 2 diabetes risk associated with a reduced type 2 diabetes risk

- Genetic variants associated with traits that are risk mechanisms.
- GWASs of quantitative glycemic traits (eg, fasting glucose, fasting insulin, and HbA1c) also have been published. These GWASs have identified >600 loci in genes and pathways related to

no evidence of interaction between genetic risk and lifestyle factors was detected ($P>0.3$). A second study in the UK Biobank assessed the interaction between diet quality and a type 2 diabetes GRS with $n=5663$ incident type 2 diabetes cases (N=357 419 participants of European ancestry at study baseline). The authors reported an antagonistic interaction in which a simultaneous 1-SD was associated with a 3% lower type 2 diabetes risk associated with a reduced type 2 diabetes risk among individuals with higher genetic risk.⁹⁵

factors for diabetes have been shown to be associated with glucose metabolism, regulation of circadian rhythms, and cell proliferation.⁸⁸ These loci include common and low-frequency variants, some of which may be popula-

ated with diabetes. For example, in a genome-wide study in the UK Biobank, a waist-specific GRS was associated with a higher risk of diabetes (OR, 1.57 [95% CI, 1.34–1.83]; absolute risk increase per 1000 participant-years, 4.4 [95% CI, 2.7–6.5]; $P < 0.001$).⁹⁶ Providing additional evidence are studies examining coheritability or evidence of a shared

tion specific.⁸⁹

- Postprandial or random glucose GWASs also have been published.⁹⁰ A multiancestry GWAS of 476 326 participants identified 120 loci. Of these loci, 13 demonstrated sex-dimorphic effects, and 44 were novel. Functional

genetic architecture between type 2 diabetes and annotation supported a role of the intestine in glycemic regulation, which is consistent with diabetes resolution after gastric bypass surgery.

- A diabetes GRS composed of >6 million diabetes-

cardiometabolic diseases. For example, a prior study reported significant positive genetic correlation between type 2 diabetes and BMI ($rg=0.36$), extreme BMI ($rg=0.34$), overweight ($rg=0.38$), obesity ($rg=0.34$), hip circumference ($rg=0.27$), WC ($rg=0.40$), glycemic traits ($rg=0.58$), triglycerides ($rg=0.31$), and CAD ($rg=0.38$).⁹⁷ Conversely, inverse genetic correlations for type 2 diabetes were observed with HDL-C ($rg=-0.45$) and birth

associated variants was associated with incident diabetes in >130 000 individuals in the FINRISK study (HR, 1.74 [95% CI, 1.72–1.77]; $P<1\times10^{-300}$), with the GRS showing improved reclassification over a clinical model (net reclassification index, 4.5% [95% CI, 3.0%–6.1%]).⁹¹ However, a GRS composed in European ancestral populations may

weight (-0.37).

not transfer to other ancestral populations, potentially requiring population-specific optimization.⁹²• A transancestry diabetes GRS developed in populations of European, African, and East Asian ancestry significantly predicted type 2 diabetes in external

- In the ACCORD trial, 2 genetic markers were identified with excess CVD mortality in the intensive treatment arm. A GRS including these genetic markers was associated with the effect of intensive glycemic treatment of cardiovascular outcomes: Those with a GRS of 0 had a substantial reduction in risk in response to intensive treatment (HR, 0.24 [95% CI, 0.07–0.86]); those with a GRS of 1 experienced no difference (HR, 0.92 [95% CI, 0.54–1.56]); and those with a GRS ≥ 2 experienced a 3-fold increase in risk (HR, 3.08 [95% CI, 1.82–5.21]).⁹⁸

Type 1 Diabetes

- Type 1 diabetes is also heritable. studies identified the role of (human leukocyte antigen) gene the greatest contributor being an antigen region. estimated to be of the genetic risk.⁹⁹ Other additional loci, including rare *LRP1B*.¹⁰⁰
- A GRS composed of 9 type 1 risk variants has been shown to predict type 1 diabetes from birth (OR 0.87).¹⁰¹ In a study of 7798 individuals, a score combining type 1 autoantibodies, and clinical prediction of incident type 1

Genetic Factors and Diabetes Complications

- The risk of complications from diabetes is also heritable:
 - Diabetic kidney disease shows familial clustering, with diabetic siblings of patients with diabetic kidney disease having a 2-fold increased risk of also developing diabetic kidney disease.¹⁰³
 - Genetic variants have also been identified that increase the risk of CAD or dyslipidemia in patients with diabetes^{104,105} and that are associated with end-organ complications in diabetes (retinopathy,¹⁰⁶ nephropathy,¹⁰⁷ and neuropathy¹⁰⁸).
 - A GRS of type 2 diabetes variants was associated with diabetes-related retinopathy (OR of the highest GRS decile compared with the low-est GRS decile, 1.59 [95% CI, 1.44–1.77]), CKD (OR, 1.16 [95% CI, 1.07–1.26]), PAD (OR, 1.20 [95% CI, 1.11–1.29]), and neuropathy (OR, 1.21 [95% CI, 1.12–1.30]).⁷⁸

Role of Nongenetic Factors

- Metabolomic profiling has identified several strong type 2 diabetes markers that

Prevention

- Among adults without diabetes to 2012, 37.8% met the goal of ≥ 150 min/wk. and 58.6% maintenance goal for diabetes with prediabetes were less weight goals than adults with
- In NHANES 2011 to 2014 prediabetes, 36.6% had dyslipidemia, 24.3% smoked, and 4.6% had reduced
- In the DPP of adults with 2-hour postchallenge glucose the absolute risk reduction for those adherent to the intervention and 9% for those appear to have causal effects on diabetes:
 - Branched-chain amino acids are associated with insulin resistance¹⁰⁹ and incident type 2 diabetes risk. For example, a meta-analysis reported that every 1-SD increase in isoleucine, leucine, and valine was associated with type 2 diabetes ORs of 1.54 (95% CI, 1.36–1.74), 1.40 (95% CI, 1.29–1.52), and 1.40 (95% CI, 1.25–1.57), respectively.¹¹⁰ Branched-chain amino acids also respond to weight loss interventions.¹¹¹
 - Circulating glycine levels are associated with lower diabetes risk (meta-analysis RR, 0.89 [95% CI, 0.81–0.96]).¹¹² Other metabolites associated with type 2 diabetes include complex lipid species such as triacylglycerols¹¹³ and α amino-

intervention compared with those receiving placebo effective among those with higher predicted risk at baseline, whereas lifestyle intervention was effective regardless of baseline predicted risk.¹¹⁷

over a median 3-year follow-up. Metformin was baseline, whereas lifestyle intervention was effective

• Among 599 participants with prediabetes, a 12-month digital diabetes prevention program was shown to result in greater reductions (relative to education comparison control groups) in 10-year ASCVD risk, which were significant only at 4 months (−0.96% [95% CI, −1.58% to −0.34%]) but not at 12 months, indicating the need for additional interventions for a sustained effect.¹¹⁸

• Among older adults with diabetes, a meta-analysis of 16 RCTs showed mobile health interventions (including telemonitoring, telecommunication, online education programs, and wearable devices) to have significant benefits on reducing HbA1c (−0.24% [95% CI, −0.44% to −0.05%]) and postprandial blood glucose (−2.91 mmol/L [95% CI, −4.78 to −1.03]) but not total cholesterol, LDL-C, or BP.¹¹⁹ In a study of high-risk patients with prediabetes or diabetes assigned to a 15-week lifestyle intervention or usual care, there were improvements in BMI, HbA1c, total cholesterol, LDL-C, triglycerides, and BP, with significant reductions in the European Society of Cardiology–SCORE pre-post intervention from 8.07% to 6.33% ($P<0.001$) in the intent-to-treat group and 8.52% to 5.85% ($P<0.001$) in the per-protocol analysis group.¹²⁰

• Acarbose was associated with a lower diabetes risk (RR, 0.82 [95% CI, 0.71–0.94]) compared with placebo among adults with impaired glucose tolerance and CHD over a median 5 years of follow-up.¹²¹

Awareness, Treatment, and Control

Although lifestyle management through diet and exercise is the foundation for treatment of diabetes, metformin

is the foundation for treatment of diabetes, metformin

has for many years been recommended as first-line pharmacological treatment. However, more recently, SGLT-2 inhibitors and GLP-1RAs have been shown to reduce cardiovascular outcomes¹²² and are now currently recommended as first-line therapy in higher-risk individuals with diabetes with preexisting CVD or multiple risk factors. In particular, SGLT-2 inhibitors have a dramatic benefit on reducing the risk of subsequent HF hospitalizations both in those with diabetes and in

Furthermore, aspirin therapy is recommended for those with both diabetes and ASCVD to reduce future ASCVD risk. Control of diabetes in most individuals includes a reduction of HbA1c to <7% (<8% may be appropriate for those with limited life expectancy or when harms outweigh benefits), BP reduction to

likely and those with private insurance or with coronary disease more likely to be on optimal medical therapy.

- Among 1 001 542 outpatients from 391 US sites within the Diabetes Collaborative Registry, the percentage of patients prescribed an SGLT-2 inhibitor or GLP-1RA increased over time (7.3% in 2013 to <130/80 mm Hg, and control of LDL-C with statin therapy. For those at highest risk, high-intensity statin is recommended with additional nonstatin therapy if LDL-C remains ≥ 55 mg/dL in those with ASCVD or LDL-C ≥ 70 mg/dL among those with additional risk factors after maximally tolerated statin therapy.

of patients without any of these comorbidities.¹²⁸ Among data from 324 706 patients with diabetes and established ASCVD in the National Patient-Centered Research Network studied during 2018, 58.6% were prescribed a statin, but only 26.8% were prescribed a GLP-1RA and 2.8% were prescribed all 3 classes of therapies, and 42.6% were high-intensity statin were more likely to be male or apy.¹²³ It has been estimated that aggressive control of lipids, BP, and glucose in individuals with diabetes could prevent up to 51% of CHD events in males and 61% of CHD events in females.¹²⁴

Awareness

- Of 38.1 million adults ≥ 18 years of age with diabetes in 2021, 8.7 million were not aware of or did not report having diabetes (undiagnosed diabetes), representing 22.8% of all US adults with diabetes.¹²⁵
- A recent NHANES study of trends in awareness of prediabetes shows that the age-adjusted prevalence of prediabetes based on FPG/HbA1c definition increased from 32.1% in 2005 to 2006 to 39.6% in 2007 to 2008 and then plateaued to 38.6% in 2017 to March 2020 without a significant trend for improvement.¹²⁶

to have ASCVD.

Treatment

(See Chart 9-6)

- Among 1590 patients with ASCVD and diabetes from 107 sites/physicians in the United States followed up prospectively from December 2016 to July 2018, by the end of follow-up, 58% were on high-intensity statin, 87% were on antithrombotic therapy, 71% were on ACE inhibitor/ARB/angiotensin receptor/neprilysin inhibitor, and 17% were on SGLT-2 inhibitor or GLP-1RA, with 11% overall on comprehensive optimal medical therapy, which was a modest improvement from 8% at baseline ($P=0.002$).¹²⁷ Patients treated by cardiologists were more likely to be on high-intensity lipid lowering but less likely to be on an SGLT-2 inhibitor/GLP1-RA and had lower rates of being on comprehensive optimal medical therapy. Older individuals were less

- Among 321 304 patients with type 2 diabetes and ASCVD in 88 US health care systems, from January 2018 to March 2021, the use of SGLT-2 inhibitors increased from 5.8% to 12.9%, and the use of GLP1-RAs increased from 6.9% to 13.8% (and either agent from 11.4% to 23.2%).¹³⁰ Those taking either of these agents were younger, less likely to have been hospitalized in the past year, and more likely to be taking other secondary prevention medications.
- In the US Precision Medicine Initiative All of Us Research Program including >80 000 patients with diabetes studied during 2018 to 2022, among those with both diabetes and ASCVD, only 8.6% were on an SGLT-2 inhibitor and 11.9% were on a GLP1-RA, with <10% of those with HF or CKD on an SGLT-2 inhibitor. ¹³¹ Moreover, only 18.2% were on high-intensity statins, and use of ezetimibe and PCSK9 inhibitors was also low (5.1% and 0.6%, respectively). Among those with triglycerides >150 mg/dL, only 1.9% were taking icosapent ethyl.¹³² • A large meta-analysis of glucose-lowering agents showed GLP1-RAs and SGLT-2 inhibitors to be associated with significant reductions in all-cause mortality (OR, 0.88 [95% CI, 0.83–0.95] and 0.85 [95% CI, 0.79–0.91], respectively) and MACEs (OR, 0.89 [95% CI, 0.84–0.94] and 0.90 [95% CI, 0.84–0.96], respectively), with SGLT-2 inhibitors additionally associated with a reduced risk of HF hospitalizations (OR, 0.68 [95% CI, 0.62–0.85]).¹³³ Metformin and pioglitazone were also associated with a lower risk of MACEs (OR, 0.60 [95% CI, 0.47–0.80] and 0.85 [95% CI, 0.74–0.97], respectively), but pioglitazone was associated with a higher

- risk of HF hospitalizations (OR, 1.04–1.62]), and insulin initiated with higher risks of (OR, 1.12 [95% CI, 1.01–1.19 [95% CI, 1.02–1.39]).
 - In the long-term 21-year follow-up among 3234 participants with tolerance, neither lifestyle min (compared with placebo) a reduction in the incidence of cular events, despite the long-diabetes.¹³⁴
- In a recent analysis of 2 large US health insurance databases (Clinformatics and Medicare) examining adult patients with type 2 diabetes who initiated diabetes treatment from 2013 through 2019, met-formin was the most frequently initiated medication, used by 80.6% of Medicare beneficiaries and 83.1% of commercially insured patients, followed by sulfo-nylureas at 8.7% and
- According to NHANES 2017 to adults with diabetes, 20.7% treated and controlled with a mg/dL; however, 48% still had tes despite being treated, and and not diagnosed (Chart 9-6).
- In NHANES, the percentage of years of age with diabetes was 48.5% in 2011 through 2015 through 2018
- In NHANES 2011 to 2016, 4.7%, respectively.¹³⁵ However, use of newer cardioprotective diabetes agents was low: SGLT-2 inhibitor in 0.8% (Medicare) and 1.7% (commercial) and GLP-1RA in 1.0% (Medicare) and 3.5% (commercial), although with trends of greater

diabetes who were taking antihypertensive medications did not meet BP treatment goals according to both the 2017 Hypertension Clinical Practice Guidelines and the American Diabetes Association Standards of Medical Care.¹⁴⁰

- Continuous glucose monitoring allows more granular monitoring of glucose levels compared with a single glucose measurement.¹⁴¹ In a meta-analysis of 22 studies of 2188 people with type 1 diabetes, continuous glucose monitoring was associated with a 2.46–mmol/mol mean decrease in HbA1c levels compared with single glucose monitoring

use over time ($P<0.01$). Those using an SGLT-2 inhibitor and GLP-1RA were more likely to be younger or to have prevalent CVD and higher SES *Control* compared with those initiating metformin.

- From an analysis of NHANES 2017 to 2018 data, among individuals with type 2 diabetes representing 33.2 million adults nationally, 52.6% had an indication for SGLT-2 inhibitors, 32.8% for GLP-1RAs, and 26.6% for both medications.¹³⁶

However, only 4.5% were treated with SGLT-2 inhibitors and 1.5% with GLP-1RAs. ASCVD, HF, or CKD was associated with their use.

- Among 1 202 596 adults with type 2 diabetes in a

- In a pooled analysis of ARIC, MESA, and JHS, 41.8%, 32.1%, and 41.9% of participants were at target levels for BP, LDL-C, and HbA1c, respectively; 41.1%, 26.5%, and 7.2% were at target levels for any 1, 2, or all 3 factors, respectively. Having 1, 2, and 3 factors at goal was associated with 36%, 52%, and 62% lower risk of CVD events, respectively, compared with having no risk factors at goal.¹⁴² This study showed multivariable-adjusted risk reductions of 62% for CVD events and 60% for

large US administrative claims database, of whom 45.2% had established ASCVD, the use of GLP-1RAs and SGLT-2 inhibitors was low overall (<12%) and even lower in the ASCVD group (<9%), and use of either was ≤5% in the subgroup ≥65 years of age, regardless of ASCVD status.¹³⁷

- In a secondary analysis examining the association of race and ethnicity with the initiation of newer diabetes medications (GLP-1RAs, dipeptidyl peptidase-4 inhibitors, SGLT-2 inhibitors) in the Look AHEAD trial, initiation was lower among

CHD events.

Black participants (HR, 0.81 [95% CI, 0.70–0.94]) and American

Indian/Alaska Native participants (HR, 0.51 [95% CI, 0.26–0.99]), and yearly family income was inversely associated with initiation of newer diabetes medications (HR, 0.78 [95% CI, 0.62–0.98]) when the lowest and highest income groups were compared, findings that were influenced mostly by

- Recent data from the All of Us Research Program (2018–2022) show that 73% of US adults with diabetes have an HbA1c <7%, with control slightly better in women (73.6%) than in men (69.8%) and in NH White individuals (78.3) and Asian individuals (76.3%) compared with NH Black individuals (65.1%) or Hispanic/Latino individuals (60.8%).¹³¹ Overall, 50.6% of the participants had LDL-C levels <100 mg/dL, although only 16.0% had levels <70 mg/dL, and among those with diabetes and ASCVD, only 21.1% had LDL-C <70 mg/dL. Overall, 64.4% had triglyceride levels <150 mg/dL, and 31.6% had levels <100 mg/dL.¹³²
- Data from the US Diabetes Collaborative Registry of 74 393 adults with diabetes show 74% at HbA1c <7%, 40% at BP <130/80 mm Hg, and 49% at LDL-C <100 mg/dL (<70 mg/dL if with ASCVD) but only 15% at target GLP-1RAS.¹³⁸

- In a study of 1179 adults with type 2 diabetes (representing 19.7 million in the US population in 2013–2016), 56% of adults were at target control of HbA1c (<7% or <8% if with CVD), 51% for BP (<130/80 mm Hg), and 49% for LDL-C (<100 mg/dL or <70 mg/dL if with CVD); 84% were non-smokers.¹⁴⁴ Only 9% had BMI <25 kg/m². Only 17% were at all targets for HbA1c, BP, and LDL-C. • According to data from NHANES diabetes, there were a significant increase in the proportion of individuals with HbA1c <7% (59.8% for 1998–1994 versus 73.7% for 2009–2018) and decreases in mean HbA1c (7.0% versus 6.7%), mean BP (130.1/77.5 mm Hg versus

Death rates by sex, race, and ethnicity are located in Table 9-1. In 2022, diabetes was the eighth leading cause of death in the United States.¹⁵²

- In NIS 2017, the mortality rate for diabetic ketoacidosis was higher among males (40.5 per 10 000 admissions) compared with females (35.3 per 10 000 admissions) and 126.0/72.1 mm Hg), and mean TC (219.4 mg/dL versus 182.4 mg/dL). The proportion with HbA1c <7.0%, BP <140/90 mm Hg, and TC <240 mg/dL improved from 31.6% to 56.2%.¹⁴⁵
- Among HCHS/SOL study participants with diabe-

- From a systematic review and meta-analysis including 20 studies among individuals after MI, in adjusted analyses, diabetes was associated with increased short-term (males: RR, 1.16 [95% CI, 1.12–1.20]; females: RR, 1.29 [95% CI, 1.15–1.46]), midterm (males: RR, 1.39 [95% CI, 1.31–1.46]; females: RR, 1.38 [95% CI, 1.20–1.58]), and long-term (males: RR, 1.58 [95% CI, 1.22–2.05]; females: RR, 1.76 [95% CI, 1.25–2.47]) mortality.¹⁵⁴

tes in 2008 to 2011, 43.0% had HbA1c <7.0%, 48.7% had BP <130/80 mm Hg, and 36.6% had LDL-C <100 mg/dL; 8.4% had reached all 3 treatment targets.¹⁴⁶

Complications

Peripheral Artery Disease

- In a cohort study of patients in Denmark

- In a national cohort of 1 140 634 veterans with diabetes, in adjusted models, higher levels of HbA1c (≥8% versus <7%) were more likely in NH

Black people and Hispanic people than in White people (OR, 1.11 [95% CI, 1.09–1.14] for NH Black people and 1.36 [95% CI, 1.32–1.41] for Hispanic

ing coronary angiography, those with diabetes but not CAD had an increased risk of PAD (HR, 1.73 [95% CI, 1.51–1.97]) and lower-limb revascularization (HR, 1.73 [95% CI, 1.51–1.97]) compared with those with neither diabetes nor CAD.¹⁵⁵ Patients with both diabetes and CAD also had an increased risk of PAD (HR, 3.90 [95% CI, 3.55–4.28]) and

- Among those with type 1 diabetes in the SEARCH study, 60% reported having ≥ 3 HbA1c measurements in the past year. Other screening tests reported were as follows: 93% for BP assessment, 81% for eye examination, 71% for lipid level assessment, 64% for foot examination, and 63% for albuminuria screening.¹⁴⁸
- In a decision analytical model, the BRAVO diabetes microsimulation model applied to adults with type 2 diabetes from NHANES (2015–2016) with linked short-term mortality data showed that improvements in BMI, SBP, LDL-C, and HbA1c were estimated to be associated with up to 3.9, 1.9, 0.9, and 3.8 years of gain in life expectancy, respectively.¹⁴⁹

- lower-limb revascularization (HR, 4.61 [95% CI, 3.85–5.52]).¹⁵⁵
- In the Freemantle Diabetes Study of adults with type 2 diabetes, the rate of incident hospitalization for diabetic foot ulcers increased between the 2 study phases (1993–1996 and 2008–2011) from 1.9 (95% CI, 0.9–3.3) per 1000 PY to 4.5 (95% CI, 3.0–6.4) per 1000 PY.¹⁵⁶
- In the Swedish National Diabetes Register using data from 1998 to 2013, type 1 diabetes was associated with an HR for amputation of 40.1 (95% CI, 32.8–49.1) compared with no diabetes. The incidence has been decreasing and was 3.09 per 1000 PY in 1998 to 2001 compared with 2.64 per 1000 PY in 2011 to 2013.¹⁵⁷

Mortality

(See Table 9-1)

- According to data from Medicare fee-for-service claims from 2000 to 2017, among

- Diabetes was listed as the underlying cause of mortality for 101 209 people (57 557 males and 43 652 females) in the United States in 2022 (Table 9-1).¹⁵⁰
- The 2022 overall age-adjusted death rate attributable to diabetes was 24.1 per 100 000 (unpublished NHLBI tabulation using CDC WONDER¹⁵¹).

2009 but then increased to 4.8 in 2017.¹⁵⁸

- From data from NIS and NHIS 2000 through 2015, the age-adjusted rate of nontraumatic lower-extremity amputation among individuals with diabetes decreased from 5.38 (95% CI, 4.93–5.84) per 1000 adults with diabetes in 2000 to 3.07 (95%

CI, 2.79–3.34) per 1000 increased to 4.62 (95% CI, adults in 2015. The increase individuals 18 to 44 and 45 to 64

- Reasons for stagnation or even in recent years in lower-rates could be explained by patients with diabetes in in prevention practices: in longer duration of diabetes, complications; and increasing other therapies, which may back on some therapies, risks of complications.¹⁶⁰

Retinopathy

- In the multicenter, population-based SEARCH study of youths and young adults <20 years of age with youth-onset type 1 diabetes (n=2519) and type 2 diabetes (n=447), diabetic retinopathy was found in 52% of those with type 1 diabetes and 56% of those with type 2 diabetes.¹⁶¹ Higher baseline HbA1c (per 0.1 unit) was associated with retinopathy (aRR, 1.10 [95% CI, 1.05–1.15]), and increases in DBP and SBP were associated with the observation of diabetic retinopathy at follow-up for both diabetes types (among those with type 1 diabetes, change in SBP z score: aRR, 1.05 [95% CI, 1.01–1.09]; change in DBP z score: aRR, 1.08 [95% CI, 1.02–1.15]).
- In DCCT/EDIC, over >30 years of follow-up, the rates of ocular events per 1000 PY were 12 for proliferative diabetic retinopathy, 14.5 for clinically significant macular edema, and 7.6 for ocular surgeries.¹⁶²
- Among US adults ≥18 years of age with diagnosed diabetes in 2021, 10.1% (95% CI, 9.6%–11.3%) reported severe vision difficulty or blindness.¹

HbA1c levels, being highest tively) in those who had

Chronic Kidney Disease

- Among adults ≥18 years of years of age) with type 2 2007 to 2014, the prevalence (mildly to moderately was 10.4% (95% CI, 9.1%–(moderately to severely was 5.4% (95% CI, 4.5%–(severely decreased kidney (95% CI, 1.3%–2.4%), and failure) was 0.4% (95% CI, 0.0%–0.8%).
- According to data from
 - Among American Indian and Alaska Native individuals with diabetes using primary care clinics of the US Indian Health Service, tribal, and urban Indian health care facilities, 17.7% had nonproliferative diabetic retinopathy, 2.3% had proliferative diabetic retinopathy, and 2.3% had diabetic macular edema.¹⁶³
 - According to NHIS 2016 and 2017, among individuals with young-onset diabetes (diagnosed <40 years of age), individuals with type 1 diabetes had a higher prevalence of retinopathy (24.7% [95% CI, 17.1%–32.2%]) compared with those with type 2 diabetes (11.4% [95% CI, 8.9%–13.9%]) but similar rates of kidney disease, CHD, MI, and stroke.¹⁶⁴
 - Among patients with type 1 diabetes diagnosed before 35 years of age, after 32 years since diagnosis, the prevalence of proliferative diabetic retinopathy and macroalbuminuria increased with increasing

2018, among adults with newly diagnosed diabetes, there was a significant decrease in the prevalence of any CKD (40.4% for 1988–1994 and 25.5% for 2009–2018). This was driven by a decrease in albuminuria (38.9% to 18.7%). There was no significant change in the prevalence of reduced eGFR (7.5%–9.9%).¹⁴⁵

- According to data from 142 countries representing 97.3% of the world population, the global annual incidence of ESKD increased from 375.8 to 1016.0 per million with diabetes from 2000 to 2015. The percentage of individuals with ESKD with diabetes increased from 19.0% to 29.7% over this same period.¹⁶⁷

- Among 4217 patients with type 1 diabetes from the FinnDiane Study, reduced eGFR was associated with increased risks for cardiovascular and diabetes-related mortality (HRs of 3.27 [95% CI, 1.76–6.08], 3.62 [95% CI, 1.69–7.73], and 4.03 [95% CI, 2.24–7.26], for eGFR categories grades 3, 4, and 5, respectively).¹⁶⁸• In a systematic review of 15 studies globally (most in North America and Europe) examining CKD outcomes in individuals diagnosed with type 2 diabetes before 20 years of age, incidence rates per 1000 PY varied from 12.4 to 114.8 for albuminuria, 10 to 35.0 for macroalbuminuria, 0.4 to 25.0 for end-stage kidney disease, and 1.0 to 18.6 for total mortality, being greatest in Australian Aboriginal populations and Pima Indian populations.¹⁶⁹

Neuropathy

- In the T1D Exchange Clinic Registry, from 2016 to 2018, the prevalence of self-reported diabetic peripheral neuropathy was 11%.¹⁷⁰

CVD Complications

- From the UK Clinical Practice Research Datalink for 734 543 adults with and without type 2 diabetes diagnosed in 2000 to 2006 with follow-up for first CVD events over 11 years, type 2 diabetes was associated with a small increase in CVD events (aHR, 1.06 [95% CI, 1.02–1.09]) in White individuals, but a greater increase was seen in individuals of

South Asian ethnicity (1.28 [95% CI, 1.09–1.51]), attributable primarily to an increased risk of MI (1.53 [95% CI, 1.08–2.18]).¹⁷¹

- Data from a large clinical trial of youths with early-onset type 2 diabetes followed up for >13 years since diagnosis of diabetes showed a cumulative incidence of 67.5% for hypertension, 51.6% for dyslipidemia, 54.8% for diabetic kidney disease, and 28.4% for 2 complications occurred in 28.4%. Risk factors for the development of complications included under-represented racial or ethnic group, hyperglycemia, hypertension, and dyslipidemia.
- In the Look AHEAD study of 4095 participants with type 2 diabetes, microvascular disease in adults free of HF was associated with a 2.5-fold higher risk of incident HF than no microvascular

• In data from the Cardiovascular Disease Lifetime Risk Pooling Project, the 30-year risk of CVD was positively associated with fasting glucose at midlife, even within the range of nondiabetic values.¹⁷⁸

- Among females, the absolute risk of CVD was 15.3% (95% CI, 12.3%–18.3%) for fasting glucose <5.0 mmol/L and 18.6% (95% CI, 15.3%–21.9%) for fasting glucose ≥5.0 mmol/L.¹⁷⁸ The HRs for HF by type of microvascular disease were 2.22 (95% CI, 1.51–3.27), 1.30 (95% CI, 0.72–2.36), and 1.33 (95% CI, 0.86–2.07) for nephropathy, retinopathy, and neuropathy, respectively.
- A systematic review and meta-analysis of 26 observational studies among 1 325 493 individuals

cose <5.0 mmol/L and 31.0% (95% CI, 25.6%–36.3%) for fasting glucose 6.3 to 6.9 mmol/L.

- In the Freemantle Diabetes Study of adults with MI, stroke, and HF improved between the 2 study phases (1993–1996 and 2008–2011), with IRRs of 0.61 (95% CI, 0.47–0.78), 0.55 (95% CI, 0.35–0.85), and 0.62 (95% CI, 0.50–0.77), respectively.¹⁷⁹
- In MESA, 63% of participants with diabetes had a CAC score >0 compared with 48% of those without diabetes.¹⁸⁰ A longer duration of diabetes was associated with CAC presence (per 5-year-longer duration: HR, 1.15 [95% CI, 1.06–1.25]) and worse cardiac function, including early diastolic relaxation and higher diastolic filling pressure, in the CARDIA study.¹⁸¹
- Across 30 countries showed age at diabetes diagnosis to be inversely associated with all-cause mortality and macrovascular and microvascular disease risk (all $P < 0.001$).¹⁷⁴ Each 1-year increase in age at diabetes diagnosis was associated with a 4%, 3%, and 5% decreased risk of all-cause mortality, macrovascular disease, and microvascular disease, respectively, adjusted for average follow-up of 9.8 years showed reduced cardiovascular outcomes from replacement analyses of saturated fat with polyunsaturated fat (RR for 2% energy replacement, 0.87 [95% CI, 0.77–0.99]) or carbohydrate (RR for 5% energy replacement, 0.82 [95% CI, 0.67–1.00]).¹⁷⁵
- In the UK Biobank, the association between previously diagnosed diabetes and MI was stronger in females (HR, 2.33 [95% CI, 1.96–2.78]) than in males (HR, 1.96 [95% CI, 1.68–2.28]).¹⁸²
- A systematic review and meta-analysis of 5 eligible prospective studies of 22 591 participants with an

- In the Swedish National Diabetes Register from 2001 to 2013, the IRR for AF compared with diabetes and matched control subjects was 1.35 (95% CI, 1.33–1.36).¹⁸² In another meta-analysis of 4 cohort studies, type 1 diabetes was shown to be associated with a higher risk of AF compared with controls (HR, 1.30 [95% CI, 1.15–1.47]).²²
- From a 29-year follow-up of patients with type 1 diabetes among the combined DCCT and EDIC studies at 27 clinical centers in the United States and Canada, although females achieved BP <130/80 mm Hg (90% versus 77%; $P<0.001$) and triglycerides <150 mg/dL (97% versus 91%; $P<0.001$) protective medications (ACE inhibitors/ARBs [30% versus 40%; $P=0.001$] and lipid-lowering medication [25% versus 40%; $P<0.001$]) was less, and they did not have a lower burden of cardiovascular events.¹⁸³•

In the REGARDS study, the HRs of CHD events comparing participants with diabetes only, diabetes and prevalent CHD, and neither diabetes nor prevalent CHD with individuals with prevalent CHD were 0.65 (95% CI, 0.54–0.77), 1.54 (95% CI, 1.30–1.83), and 0.41 (95% CI, 0.35–0.47), respectively, after adjustment for demographics

Hypoglycemia

and risk factors.¹⁷⁷ Compared with participants who had prevalent CHD, the HR of CHD events for participants with severe diabetes (defined as insulin use or presence of albuminuria) was 0.88 (95% CI, 0.72–1.09).

- In the Veterans Affairs Diabetes Trial, severe hypoglycemia within the prior 3 months was associated with an increased risk of a CVD event (HR, 1.9 [95% CI, 1.06–3.52]), CVD mortality (HR, 3.7 [95% CI, 1.3–10.4]), and all-cause mortality (HR, 2.4 [95% CI, 1.1–5.1]).¹⁸⁴
- In the LEADER trial, patients with type 2 diabetes who experienced a severe hypoglycemic event had an increased risk of MACEs, defined as

cardiovascular (HR, 3.7 trial, an 1.27–

- In an analysis of patients who followed up with
- Among 450 patients with COVID-19 at Massachusetts General Hospital, 178 (39.6%) had diabetes. In adjusted models, diabetes was associated with a 2.19 [95% CI, 1.24–3.88] increase in the risk of severe hypoglycemia was associated with ASCVD events, with
- In a cohort of adults with diabetes receiving care at a large integrated health care system, severe

with COVID-19, compared with individuals without diabetes. Individuals with diabetes had a higher rate of hospitalization (OR, 3.90 [95% CI, 1.75–8.69] for type 1 diabetes and 3.36 [95% CI, 2.49–4.55] for type 2 diabetes) and greater illness severity (OR, 3.35 [95% CI, 1.53–7.33] for type 1 diabetes and 3.42 [95% CI, 2.55–4.58] for type 2 diabetes).¹⁹⁷

ated with greater odds of ICU admission (OR, 1.59 [95% CI, 1.01–2.52]), mechanical ventilation (OR, 1.97 [95% CI, 1.21–3.20]), and death (OR, 2.02 [95% CI, 1.01–4.03]) within 14 days of presenta-

an unadjusted HR of 3.2 (95% CI, 2.9–3.6) and an tion to care.¹⁹⁸

aHR of 1.3 (95% CI, 1.2–1.5).¹⁸⁸

requiring medical assistance was associated with a 38% higher risk

- Among patients in the ACCORD study, severe hypo- glycemia was noted in 4% (n=365) of the 9208 participants; severe hypoglycemia

- In a nationwide retrospective study in England, the adjusted ORs for in-hospital COVID-19–related death were 2.86 (95% CI, 2.58–3.18) for individuals with type 1 diabetes and 1.80 (95% CI, 1.76–1.86) for individuals with type 2 diabetes.¹⁹⁹ Among

of incident HF.¹⁸⁹

individuals hospitalized with COVID-19, patients with type 2 diabetes were at increased risk of death

Coronavirus Disease 2019

(HR, 1.23 [95% CI, 1.14–1.32]).²⁰⁰

Individuals with diabetes are at increased risk of severe disease, hospitalization, and death resulting from COVID-19.

Health Care Use

- Studies from Northern California and New York reported a prevalence of diabetes among individuals hospitalized with COVID-19 of 31% to 36%.^{190–193} • From an internet survey that included 760 adults with diabetes during February to March 2021, younger adults (18–29 years of age) with diabetes were more likely

- According to the 2020 US Nationwide

to report having missed medical care during the past 3 months (87%) than those 30 to 59 years of age (63%) or ≥60 years of age (26%), with 44% of younger adults reporting difficulty accessing diabetes medications and a lower

Department Sample, the rate of ED visits was 716 per 1000 people with diabetes for diabetes as any listed diagnosis (16.8 million visits), 8.6 per 1000 people with diabetes for hypoglycemia (202 000 visits), and 11.4 per 1000 people with diabetes for hyperglycemia (267 000 visits).¹

- In 2021, there were 682 279 principal diagnosis discharges for diabetes and 12 426 181 all-listed diagnosis discharges for diabetes (HCUP,²⁰¹ unpublished NHLBI tabulation).²⁰²

intention to receive COVID-19 vaccination (66%) compared with adults ≥60 years of age (85%; $P<0.001$).¹⁹⁴

Cost

- According to data from MEPS, spending in the

- In a meta-analysis of 158 observational studies of 270 212 of participants, patients with diabetes had a higher risk of COVID-19–related mortality (OR, 1.87 [95% CI, 1.61–2.17]), ventilator use (OR, 1.44 [95% CI, 1.20–1.73]), and severe or critical presentation (OR, 2.88 [95% CI, 2.29–3.63]).¹⁹⁵ Patients with diabetes had increased odds of ICU admissions (OR, 1.59 [95% CI, 1.15–2.18]); however, this was driven by studies from East Asia (OR, 1.94 [95% CI,

1.51–2.49]). In another meta-analysis of 145 original studies, the presence of diabetes was also associated with an increased risk of COVID-19 mortality (aRR, 1.43 [95% CI, 1.32–1.54]).¹⁹⁶

- According to data from the Vanderbilt University Medical Center data warehouse of 6451 individuals

United States on glucose-lowering medications increased by \$40.6 billion between 2005 through 2007 and 2015 through 2017, an increase of 240%.²⁰³ From 2007 to 2018, list prices of branded insulins increased by 262% and of branded noninsulin antidiabetic agents by 165%.²⁰⁴ In the Optum Labs Data Warehouse data from 2016 to 2019, there were higher rates of initiation of newer diabetes agents among individuals with commercial health plans compared with Medicare Advantage plans.²⁰⁵ In 2022 in the United States, the cost of diabetes was \$412.9 billion. Of this cost, \$306.6 billion was direct medical costs; medications and supplies accounted for 17% of these costs.²⁰⁶ Indirect costs were \$106.3 billion, including reduced employment

due to disability (\$28.3 billion), presenteeism (\$35.8 billion), and lost productivity due to 338 526 premature deaths	4.49–6.11) million total deaths in 2021, an increase of 144.69% (95% UI, 130.26%–158.94%) since 1990 (Table 9-2). ²¹⁰ The number of prevalent cases of diabetes increased by 285.80% (95% UI, 276.65%–295.92%) for males and 269.80% (95% UI, 262.61%–276.99%) for females between 1990 and 2021. Overall, 270.84 (95% UI, 252.69–291.09) million males and 254.81 (95% UI, 237.40–273.99) million females worldwide had diabetes. In 2021, 1.66 (95% UI, 1.54–1.76) million total deaths were attributable to diabetes (Table 9-3).
tion, US health care costs attributable to diabetes have increased by \$80 billion in the past 10 years, from \$227 billion in 2012 to \$307 billion in 2022. After adjustment for inflation, the total cost of insulin and other medications to manage blood glucose increased by 26% from 2017 to 2022.	• In an economic evaluation of manufacturing costs, estimated annual cost-based prices for treatment with insulin in a reusable pen device were as low as \$96 (human insulin) or \$111 (insulin analogs) for a basal-bolus regimen, \$61 using twice-daily injections of mixed human insulin, and \$50 (human insulin) or \$72 (insulin analogs) for a once-daily basal insulin injection (for type 2 diabetes), which

- In 2021, the age-standardized prevalence of diabetes among regions was estimated to be highest for Oceania, followed by North Africa and the Middle East, the Caribbean, and high-income North America (Chart 9-7).
 - In 2021, age-standardized mortality rates attributable to high FPG among regions were highest for Oceania followed by southern and central sub-Saharan Africa and North Africa and the Middle East (Chart 9-8).
 - In 2021, among regions, age-standardized mortality estimated for diabetes was highest for Oceania, followed by southern sub-Saharan Africa. Rates were lowest for high-income Asia Pacific (Chart 9-9).
- According to 2001 to 2013 MarketScan data, the per capita total excess medical expenditure for individuals with diabetes in the first 10 years after diagnosis is \$50 445.²⁰⁹
 - In the United States, nearly one-third of the expenditures for people with CVD are attributable to
- included the cost of injection devices and needles.²⁰⁷ Cost-based prices ranged from \$1.30 to \$3.45 per month for SGLT-2 inhibitors (except canagliflozin: \$25.00–\$46.79) and from \$0.75 to \$72.49 per month for GLP1-RAs. Current prices in the 13 countries surveyed were substantially higher than these cost-based prices.
 - Informal care is estimated to cost \$1192 to \$1321 annually per person with diabetes.²⁰⁸

- The global diabetes prevalence in those 20 to 79 years of age was estimated to be 10.5% (536.6 million people) in 2021 and expected to increase to 12.2% (783.2 million) by 2045 with a similar prevalence in males and females.²¹¹ A higher prevalence in 2021 was seen in urban (12.1%) compared with rural (8.3%) areas and among higher-income (11.1%) compared with lower-income (5.5%) countries. Through 2045, a greater relative increase in the prevalence of diabetes is projected to be seen in middle-income countries (21.1%) than in high- (12.2%) and low- (11.9%) income countries. Global health care costs attributable to diabetes were estimated at US \$966 billion in 2021, projected to reach US \$1054 billion

Global Burden of Diabetes

(See Tables 9-2 and 9-3 and Charts 9-7 through 9-9)

- Based on 204 countries and territories in 2021, high FPG caused an estimated 5.29 (95% UI,

by 2045. Approximately 4.2 million deaths (11.1% of deaths) worldwide among individuals 20 to 79 years of age are attributable to diabetes according to 2019 estimates.²¹² The IDF atlas global prevalence estimate did not include all ages and used a different methodology from the GBD prevalence estimate reported here.

Table 9-1. Diabetes in the United States

Population group	Prevalence of diagnosed diabetes, 2017–2020: ≥20 y of age	Prevalence of undiagnosed diabetes, 2017–2020: ≥20 y of age	Prevalence of prediabetes, 2017–2020: ≥20 y of age	Incidence of diagnosed diabetes, 2021: y of age
Both sexes	29 300 000 (10.6%)	9 700 000 (3.5%)	115 900 000 (46.4%)	1 211 000
Males	16 400 000 (12.2%)	4 600 000 (3.5%)	63 500 000 (52.9%)	620 000
Females	12 900 000 (9.1%)	5 100 000 (3.5%)	52 400 000 (40.0%)	591 000
NH White males	11.5%	2.6%	57.2%	...
NH White females	7.7%	2.8%	38.8%	...
NH Black males	11.8%	5.6%	35.3%	...
NH Black females	13.3%	3.2%	35.7%	...
Hispanic males	14.5%	5.3%	50.7%	...

Undiagnosed diabetes is defined as those whose fasting glucose is ≥126 mg/dL but who did not report being told by a health care professional that they had diabetes. Prediabetes is a fasting blood glucose of 100 to <126 mg/dL (impaired fasting glucose); prediabetes includes impaired glucose tolerance. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.²¹³

COVID-19 indicates coronavirus disease 2019; ellipses (...), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Mortality for Hispanic people, American Indian or Alaska Native people, Asian people, and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native decedents, Asian and Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total diabetes mortality that is for males versus females.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Prevalence of diagnosed and undiagnosed diabetes: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.⁷ Percentages for sex and racial and ethnic groups are age adjusted for Americans ≥20 years of age. Incidence: Centers for Disease Control and Prevention, National Diabetes Statistics Report.¹ Mortality (for underlying cause of diabetes): Unpublished NHLBI tabulation using National Vital Statistics System¹⁵⁰ and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.¹⁵¹ These data represent diabetes as the underlying cause of death only.

Table 9-2. Deaths Caused by High FPG Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total number (millions), 2021	5.29 (4.49 to 6.11)	2.69 (2.32 to 3.10)	2.60 (2.17 to 3.03)
Percent change (%) in total number,	144.69 (130.26 to 158.94)	152.74 (134.77 to 171.76)	136.87 (118.56 to 153.65)
Percent change (%) in total number,	37.09 (31.14 to 43.54)	37.34 (29.10 to 46.25)	36.83 (29.98 to 43.81)
Rate per 100 000, age	63.73 (54.02 to 73.84)	73.86 (63.32 to 85.23)	55.63 (46.48 to 64.83)
Percent change (%) in rate, age	1.63 (−4.19 to 7.29)	2.62 (−4.21 to 9.60)	−0.31 (−7.74 to 6.73)
Percent change (%) in rate, age	−1.92 (−6.03 to 2.46)	−2.47 (−7.97 to 3.51)	−1.64 (−6.47 to 3.43)
PAF (%), all ages, 2021	7.80 (6.69 to 8.90)	7.15 (6.20 to 8.08)	8.61 (7.31 to 10.03)
Percent change (%) in PAF, all	66.18 (57.43 to 73.73)	66.41 (58.33 to 74.52)	67.00 (55.43 to 76.63)
Percent change (%) in PAF, all	7.19 (4.34 to 9.63)	5.85 (2.77 to 8.97)	8.89 (5.44 to 11.77)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

FPG indicates fasting plasma glucose; GBD, Global Burden of Diseases, Injuries, and Risk Factors; PAF, population attributable fraction; and UI, uncertainty interval.

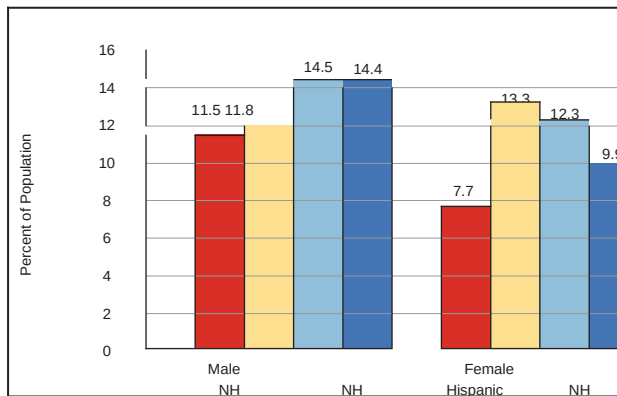
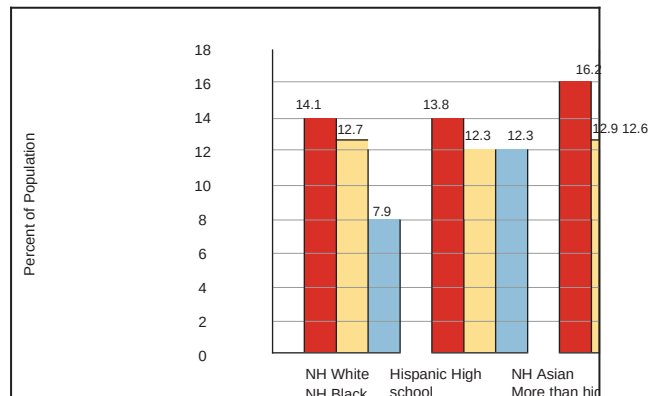
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²¹⁰

Table 9-3. Global Prevalence and Mortality of Diabetes, 2021

	Both sexes		Males		Females	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number	1.66 (1.54 to 1.76)	525.65 (490.92 to 560.38)	0.80 (0.74 to 0.86)	270.84 (252.69 to 288.99)	0.86 (0.79 to 0.92)	254.81 (237.40 to 272.22)
Percent change (%) in total number, 1990–2021	146.52 (128.75 to 162.26)	277.88 (269.98 to 286.40)	160.14 (130.39 to 186.96)	285.80 (276.65 to 295.92)	135.12 (115.76 to 150.89)	269.80 (262.61 to 278.61)
Percent change (%) in total number, 2010–2021	41.13 (33.05 to 47.60)	61.17 (59.54 to 63.12)	41.17 (29.81 to 50.51)	61.35 (59.69 to 63.31)	41.10 (33.65 to 48.50)	60.99 (59.17 to 63.15)
Rate per 100 000, age standardized, 2021	19.61 (18.12 to 20.83)	6123.59 (5723.41 to 6523.77)	20.91 (19.33 to 22.54)	6530.75 (6101.93 to 6959.57)	18.57 (17.06 to 19.86)	5742.93 (5351.76 to 6134.10)
Percent change (%) in rate, age standardized, 1990–2021	7.95 (0.42 to 14.63)	90.43 (85.98 to 95.31)	11.66 (−0.53 to 22.99)	93.17 (88.64 to 98.20)	4.49 (−3.85 to 11.49)	87.13 (82.74 to 91.82)
Percent change (%) in rate, age standardized, 2010–2021	2.58 (−3.15 to 7.18)	26.44 (25.14 to 27.89)	1.72 (−6.30 to 8.40)	26.60 (25.27 to 28.06)	3.04 (−2.44 to 8.35)	26.13 (24.62 to 27.87)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²¹⁰

**Chart 9-1. Age-adjusted prevalence of diagnosed diabetes in US adults ≥20 years of age, by race and ethnicity and sex (NHANES 2017–2020).**

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.²¹³

COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁷

Chart 9-2. Age-adjusted prevalence of diagnosed diabetes in US adults ≥ 20 years of age, by race and ethnicity and years of education (NHANES 2017–2020).

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.²¹³

COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁷

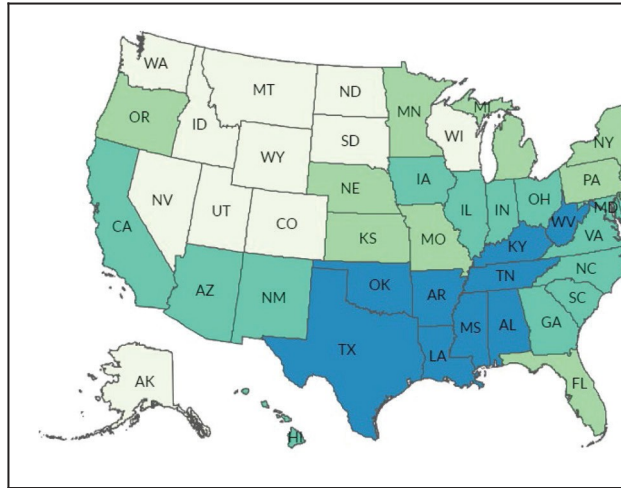


Chart 9-3. Age-adjusted percentage of adults with diagnosed diabetes, US states and territories, 2022.

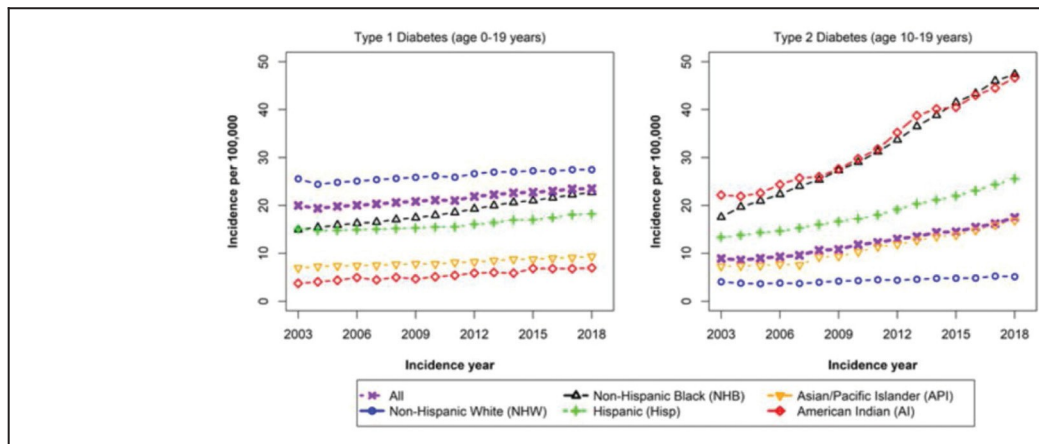


Chart 9-4. Incidence of type 1 and type 2 diabetes, overall and by race and ethnicity, among US youths ≤19 years of age (SEARCH study, 2002–2015).

Models included a change point at the year 2011 to compare trends in incidence rates between 2002 to 2010 and 2011 to 2015. People who were AI were primarily from 1 southwestern tribe. SEARCH includes data on youths (<20 years of age) in Colorado (all 64 counties plus selected Indian reservations in Arizona and New Mexico under the direction of Colorado), Ohio (8 counties), South Carolina (all 46 counties), and Washington (5 counties) and in California for Kaiser Permanente Southern California health plan enrollees in 7 counties. AI indicates American Indian; and SEARCH, Search for Diabetes in Youth.

Source: Reprinted from Wagenknecht et al,⁹*The Lancet*, Copyright © 2023, with permission from Elsevier.

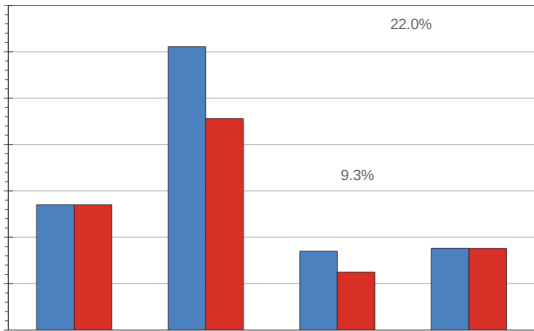


Chart 9-6. Awareness, treatment, and control of diabetes in US adults ≥20 years of age (NHANES 2017–2020).

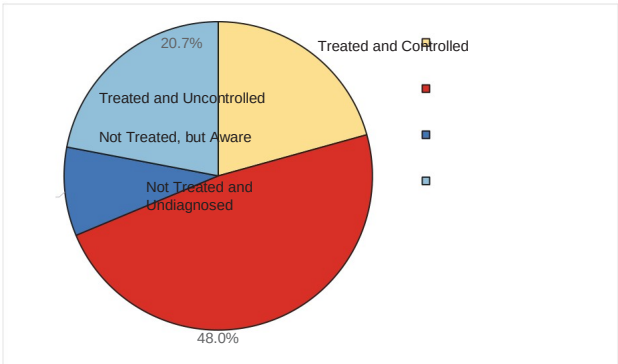


Chart 9-5. Prevalence of diagnosed and undiagnosed diabetes in

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020

cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative

estimates.²¹³ Controlled is defined as currently treated (taking insulin or diabetic pills to lower blood sugar) and fasting glucose <126 mg/ dL. Uncontrolled is defined as currently treated (taking insulin or diabetic pills to lower blood sugar) and fasting glucose $\geq$ 126 mg/dL.

estimates.²¹³

COVID-19 indicates coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

COVID-19 indicates coronavirus disease 2019; and NHANES, *The definition of diabetes changed in 1997 (from glucose $\geq$ 140 to $\geq$ 126 mg/dL). Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.⁷

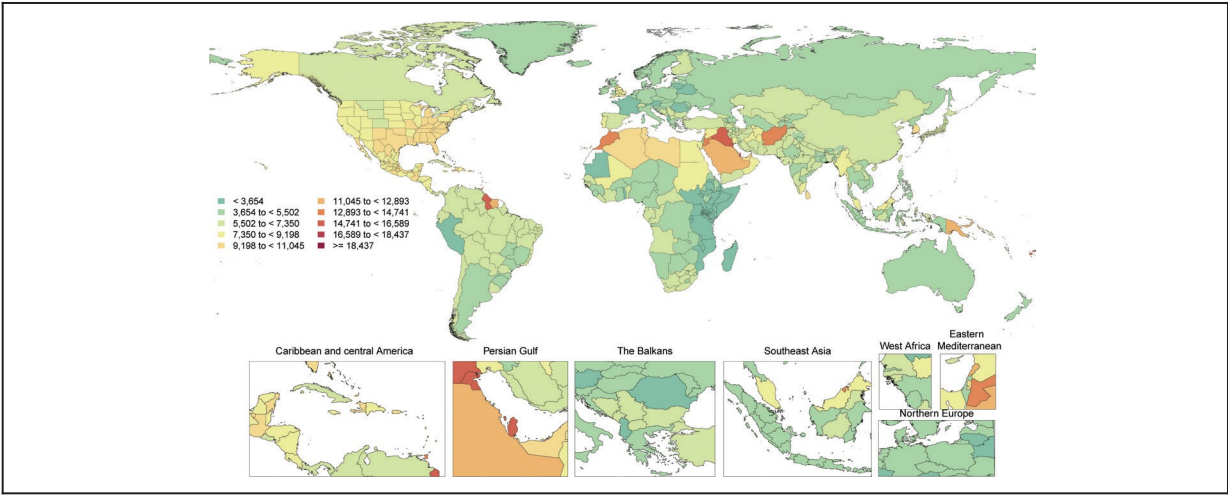


Chart 9-7. Age-standardized global prevalence rates of diabetes per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²¹⁰

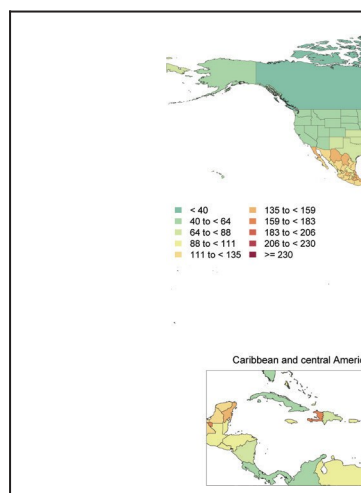


Chart 9-8. Age-standardized global mortality rates attributable to high FPG per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

FPG indicates fasting plasma glucose; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²¹⁰

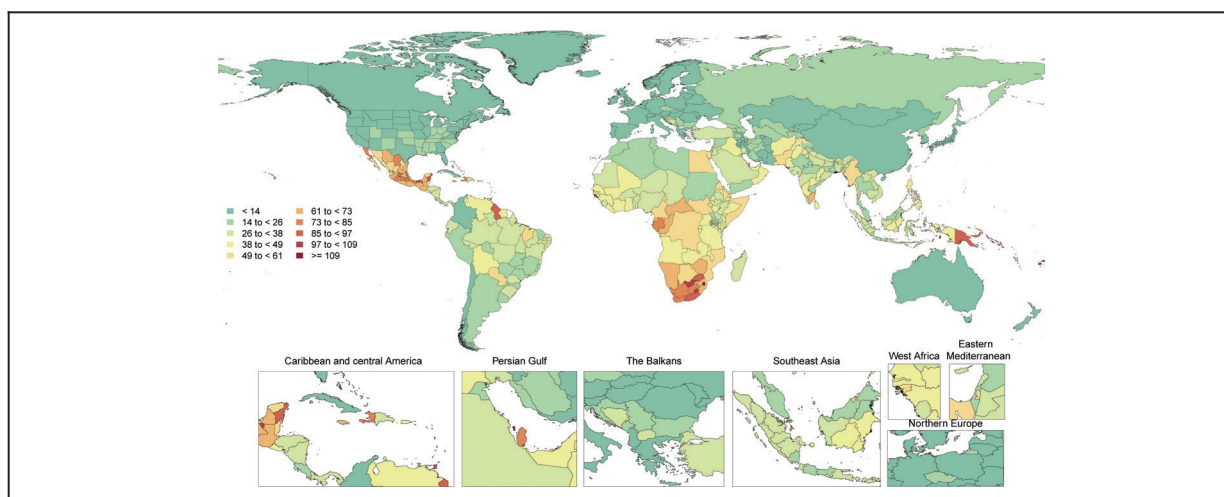


Chart 9-9. Age-standardized global mortality rates of diabetes per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²¹⁰

REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report website. Accessed May 4, 2024.

2. American Diabetes Association. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2020. *Diabetes Care*. 2020;43:S14–S31. doi: 10.2337/dc20-S002

3. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215–2222. doi: 10.1016/S0140-6736(10)60484-9

4. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al; on behalf of the American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078

5. Andes LJ, Cheng YJ, Rolka DB, Gregg EW, Imperatore G. Prevalence of prediabetes among adolescents and young adults in the United States, 2005-2016. *JAMA Pediatr*. 2019;174:e19449. doi: 10.1001/jamapediatrics.2019.4498

6. Tonnie T, Brinks R, Isom S, Dabelea D, Divers J, Mayer-Davis EJ, Lawrence JM, Pihoker C, Dolan L, Liese AD, et al. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2060: the SEARCH for Diabetes in Youth Study. *Diabetes Care*. 2023;46:313–320. doi: 10.2337/dc22-0945

7. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2024.

8. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 7, 2024.

9. Wagenknecht LE, Lawrence JM, Isom S, Jensen ET, Dabelea D, Liese AD, Dolan LM, Shah AS, Bellatorre A, Sauder K, et al; SEARCH for Diabetes in Youth Study. Trends in incidence of youth-onset type 1 and type 2 diabetes in the USA, 2002-18: results from the population-based SEARCH for Diabetes in Youth Study. *Lancet Diabetes Endocrinol*. 2023;11:242–250. doi: 10.1016/S2213-8587(23)00025-6

10. Divers J, Mayer-Davis EJ, Lawrence JM, Isom S, Dabelea D, Dolan L, Imperatore G, Marcovina S, Pettitt DJ, Pihoker C, et al. Trends in incidence of type 1 and type 2 diabetes among youths—selected counties and Indian reservations, United States, 2002-2015. *MMWR Morb Mortal Wkly Rep*. 2020;69:161–165. doi: 10.15585/mmwr.mm6906a3

11. Almulhem M, Chandan JS, Gokhale K, Adderley NJ, Thayakaran R, Khunti K, Tahrani AA, Hanif W, Nirantharakumar K. Cardio-metabolic outcomes in South Asians compared to White Europeans in the United Kingdom: a matched controlled population-based cohort study. *BMC Cardiovasc Disord*. 2021;21:320. doi: 10.1186/s12872-021-02133-z

12. Lee CMY, Colagiuri S, Woodward M, Gregg EW, Adams R, Azizi F, Gabriel R, Gill TK, Gonzalez C, Hodge A, et al. Comparing different definitions of prediabetes with subsequent risk of diabetes: an individual participant data meta-analysis involving 76 513 individuals and 8208 cases of incident diabetes. *BMJ Open Diabetes Res Care*. 2019;7:e000794. doi: 10.1136/bmjdr-2019-000794

13. Fouotsa NCM, Ndjabou R, Ngueta G. Race/ethnicity and other predictors of early-onset type 2 diabetes mellitus in the US population [published online March 21, 2024]. *J Racial Ethn Health Disparities*.

doi: 10.1007/s40615-024-01980-8.

14. Cordola Hsu AR, Ames SL, Xie B, Peterson DV, Garcia L, Going SB, Phillips LS, Manson JE, Anton-Culver H, Wong ND. Incidence of diabetes according to metabolically healthy or unhealthy normal weight or overweight/obesity in postmenopausal women: the Women's Health Initiative. *Menopause*. 2020;27:640–647. doi: 10.1097/GME.0000000000001512

15. Lee S, Lacy ME, Jankowich M, Correa A, Wu WC. Association between obesity phenotypes of insulin resistance and risk of type 2 diabetes in African Americans: the Jackson Heart Study. *J Clin Transl Endocrinol*.

32. Huh JH, Han KD, Cho YK, Roh E, Kang JG, Lee SJ, Ihm SH. Remnant cholesterol and the risk of cardiovascular disease in type 2 diabetes: a nationwide longitudinal cohort study. *Cardiovasc Diabetol*. 2022;21:228. doi: 10.1186/s12933-022-01667-6
16. Feng Y, Zhao Y, Liu J, Huang Z, Yang X, Qin P, Chen C, Luo X, Li Y, Wu Y, et al. Consumption of dairy products and the risk of overweight or obesity, 33. Li Y, Pei H, Zhou C, Lou Y. Dietary cholesterol consumption and incidence of type 2 diabetes mellitus: a dose-response meta-analysis of

- prospective cohort studies. *Nutr Metab*. 2022;10:1016/i.nu.2022.07.016. doi: 10.1016/i.nu.2022.07.016
34. Gao F, Cui CY. Dietary cholesterol intake and type 2 diabetes mellitus: a meta-analysis of 2022;41:107–115. doi: 10.1016/j.atherosclerosis.2022.04.015
 35. Martínez-González MA, Savón-Orea C, Rodríguez-Artalejo F, Yusta-Bovo MJ. Oil consumption on cardiovascular disease, all-cause mortality: a systematic review and 2022;41:2659–2682. doi: 10.1016/j.atherosclerosis.2022.04.015
 36. Suzuki Y, Kaneko H, Okada A, Matsuoka S, Takeda N, Morita H, et al. Prediabetes in relation to cardiovascular health metrics in the 2022;107:1843–1853. doi: 10.1210/clinem/dgac247
 37. Shi W, Huang X, Schooling CM, Zhao JV. Red meat consumption, cardiovascular diseases, and diabetes: a systematic review and meta-analysis. *Eur Heart J*. 2023;44:2626–2635. doi: 10.1093/eurheartj/ehad336
 38. Kaplan RC, Song RJ, Lin J, Xanthakis V, Hua S, Chernofsky A, Evenson KR, Walker ME, Cuthbertson C, Murabito JM, et al. Predictors of incident diabetes in two populations: Framingham Heart Study and Hispanic Community Health Study/Study of Latinos. *BMC Public Health*. 2022;22:1053. doi: 10.1186/s12889-022-13463-8
 39. Agoons DD, Musani SK, Correa A, Golden SH, Bertoni AG, Echouffo-Tcheugui JB. High-density lipoprotein-cholesterol and incident type 2 diabetes mellitus among African Americans: the Jackson Heart Study. *Diabet Med*. 2022;39:e14895. doi: 10.1111/dme.14895
 40. Seng LL, Hai Kiat TP, Bee YM, Jafar TH. Real-world systolic and diastolic blood pressure levels and cardiovascular mortality in patients with type 2 diabetes: results from a large registry cohort in Asia. *J Am Heart Assoc*. 2023;12:e028888. doi: 10.1177/2047903123118888
 41. Goff DC Jr, Lloyd-Jones DM, Bennett G, R. Greenland P, Lackland DT, Levv D. the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 assessment of cardiovascular risk: a guideline of the American Heart Association/American College of Cardiology. *Circulation*. 2013;127:S433–S503. doi: 10.1161/01.cir.0000437741.48606.98
 42. Grundy SM, Stone NJ, Bailey AL, Beam AL, Birtcher KK, Borra R, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACCP/ASNC/AATS/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2019;140:e596–e646. doi: 10.1161/JAHA.118.033912
 43. Yang Q, Zheng R, Wang S, Zhu J, Li M, Wang T, Zhao Z, Xu M, Lu J, Chen Y, et al. Systolic blood pressure control targets to prevent major cardiovascular events and death in patients with type 2 diabetes: a systematic review and network meta-analysis. *Hypertension*. 2023;80:1640–1653. doi: 10.1161/HYPERTENSIONAHA.123.20954
 44. Seidu S, Hambling CE, Kunutsor SK, Topsever P. Associations of blood pressure with cardiovascular and mortality outcomes in over 2 million older persons with or without diabetes mellitus: a systematic review and meta-analysis of 45 cohort studies. *Prim Care Diabetes*. 2023;17:554–567. doi: 10.1016/j.pcd.2023.09.007
 45. Cheng Y, Zou J, Chu R, Wang D, Tian J, Sheng CS. Cumulative HbA1c exposure as a CVD risk in patients with type 2 diabetes: a post hoc analysis of ACCORD trial. *Diabetes Res Clin Pract*. 2023;206:111009. doi: 10.1016/j.diabres.2023.111009

- lished corrections appear in *Circulation*. 2019;139:e1182–e1186 and 10.1161/CIR.0000000000000625
53. Khan SS, Coresh J, Pencina MJ, Ndumele CE, Rangaswami J, Chow the American Heart Association. Novel prediction equations for ab- cardiovascular-kidney-metabolic health: a scientific statement from the 10.1161/CIR.0000000000001191
54. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, Szklo M, cardiovascular- lar disease events in individuals with metabolic syndrome and diabetes: 2290. doi: 10.2337/dc11-0816
55. Malik S, Zhao Y, Budoff M, Nasir K, Blumenthal RS, Bertoni AG, Wong individuals with type 2 diabetes and metabolic syndrome from the Multi- 10.1001/jamacardio.2017.4191
56. Wong ND, Nelson JC, Granston T, Bertoni AG, Blumenthal RS, Carr JJ, betes, and incidence and progression of coronary calcium: the Multiethnic 2012;5:358– 366. doi: 10.1016/j.jcmg.2011.12.015
57. Wong ND, Cordola Hsu AR, Rozanski A, Shaw LJ, Whelton SP, Budoff ences in coronary artery calcium and mortality from coronary heart dis- Coronary Calcium Consortium. *Diabetes Care*. 2020;43:2597–2606. doi: 10.1016/j.diabres.2023.111009
44. Caraballo C, Valero-Elizondo J, Khera R, Mahajan S, Grandhi GR, Virani SS, Mszar R, Krumholz HM, Nasir K. Burden and consequences of financial hardship from medical bills among nonelderly adults with diabetes mellitus in the United States. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006139. doi: 10.1161/CIRCOUTCOMES.119.006139
45. Twarog JP, Charyalu AM, Subhani MR, Shrestha P, Peraj E. Differences in HbA1C% screening among U.S. adults diagnosed with diabe- tes: findings from the National Health and Nutrition Examination Survey (NHANES). *Prim Care Diabetes*. 2018;12:533–536. doi: 10.1016/j.pcd.2018.07.006
46. Doucette ED, Salas J, Wang J, Scherrer JF. Insurance coverage and diabetes quality indicators among patients with diabetes in the US general population. *Prim Care Diabetes*. 2017;11:515–521. doi: 10.1016/j.pcd.2017.05.007
47. Mendoza JA, Haaland W, D'Agostino RB, Martini L, Pihoker C, Frongillo EA, Mayer-Davis EJ, Liu LL, Dabelea D, Lawrence JM, et al. Food insecurity is associated with high risk glycemic control and higher health care utilization among youth and young adults with type 1 diabetes. *Diabetes Res Clin Pract*. 2018;138:128–137. doi: 10.1016/j.diabres.2018.01.035
48. Williams PC, Alhasan DM, Gaston SA, Henderson KL, Braxton Jackson W 2nd, Jackson CL. Neighborhood social cohesion and type 2 diabetes mellitus by age, gender, and race/ethnicity in the United States. *Prev Med*. 2023;170:107477. doi: 10.1016/j.ypmed.2023.107477
49. Zhao Y, Malik S, Budoff MJ, Correa A, Ashley KE, Selvin E, Watson KE, Wong ND. Identification and predictors for cardiovascular disease risk equivalents among adults with diabetes mellitus. *Diabetes Care*. 2021;44:2411–2418. doi: 10.2337/dc21-0431
50. Wong ND, Sattar N. Cardiovascular risk in diabetes mellitus: epidemiol-ogy, assessment and prevention. *Nat Rev Cardiol*. 2023;20:685–695. doi: 10.1038/s41569-023-00877-z
- SL, Palaniappan LP, Sperling LS, Virani SS, Ho JE, et al; on behalf of solute risk assessment of total cardiovascular disease incorporating American Heart Association. *Circulation*. 2023;148:1982–2004. doi: 10.2337/dc20-0166
- Barr RG, Wong ND. Impact of subclinical atherosclerosis on the Multi-Ethnic Study of Atherosclerosis.
- ND. Coronary artery calcium score for long-term risk classification in in- Ethnic Study of Atherosclerosis. *JAMA Cardiol*. 2017;2:1332–1340. doi: 10.2337/dc20-0166
- Guerci A, Jacobs DR Jr, Kronmal R, Liu K, et al. Metabolic syndrome, dia- Study of Atherosclerosis study. *JACC Cardiovasc Imaging*.
- MJ, Nasir K, Miedema MD, Rumberger J, Blaha MJ, et al. Sex differ- ease, cardiovascular disease, and all causes in adults with diabetes: the 10.2337/dc20-0166

58. Shaikh K, Ahmed A, Gransar H, Lee J, Leipsic J, Nakanishi R, Alla V, Bax JJ, Chow BJW, Berman DS, et al. Extent of subclinical atherosclerosis on coronary computed tomography and impact of statins in patients with diabetes without known coronary artery disease: results from CONFIRM registry. *J Diabetes Complications*. 2022;36:108309. doi: 10.1016/j.jdiacomp.2022.108309

59. Al-Kindi S, Dong T, Chen W, Tashtish N, Neeland IJ, Nasir K, Rajagopalan S. Relation of coronary calcium scoring with cardiovascular events in patients with diabetes: the CLARIFY Registry. *J Diabetes Complications*. 2022;36:108269. doi: 10.1016/j.jdiacomp.2022.108269

60. Premyodhin N, Fan W, Arora M, Budoff MJ, Kanaya AM, Kandula N, Palaniappan L, Rana JS, Younus M, Wong ND. Association of diabetes with coronary artery calcium in South Asian adults and other race/ethnic groups: the Multi-Ethnic Study of Atherosclerosis and the Mediators of Atherosclerosis in South Asians Living in America study. *Diab Vasc Dis Res*. 2023;20:14791641231204368. doi: 10.1177/14791641231204368

61. Razavi AC, Shaw LJ, Berman DS, Budoff MJ, Wong ND, Vaccarino V, van Assen M, De Cecco CN, Quyyumi AA, Mehta A, et al. Left main coronary artery calcium and diabetes confer very-high-risk equivalence in coronary artery calcium >1,000. *JACC Cardiovasc Imaging*. 2024;17:766–776. doi: 10.1016/j.jcmg.2023.12.006

62. Gadde KM, Yin X, Goldberg RB, Orchard TJ, Schlogl M, Dabelea D, Ibebuogu UN, Watson KE, Pi-Sunyer FX, Crandall JP, et al; Diabetes Prevention Program Research Group. Coronary artery calcium and cognitive decline in the Diabetes Prevention Program Outcomes Study. *J Am Heart Assoc*. 2023;12:e029671. doi: 10.1161/JAHA.123.029671

63. Buchan TA, Malik A, Chan C, Chambers J, Suk Y, Zhu JW, Ge FZ, Huang LM, Vargas LA, Hao Q, et al. Predictive models for cardiovascular and kidney outcomes in patients with type 2 diabetes: systematic review and meta-analyses. *Heart*. 2021;107:1962–1973. doi: 10.1136/heartjnl-2021-319243

64. Hippisley-J, Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. *BMJ*. 2017;359:j5019. doi: 10.1136/bmj.j5019
65. Read SH, van Diepen M, Colhoun HM, Halbesma N, Lindsay RS, McKnight JA, McAllister DA, Pearson ER, Petrie JR, Philip S, et al; Scottish Diabetes Research Network Epidemiology Group. Performance of cardiovascular disease risk scores in people diagnosed with type 2 diabetes: external validation using data from the National Scottish Diabetes Register. *Diabetes Care*. 2018;41:2010–2018. doi: 10.2337/dc18-0578
66. Chowdhury MZI, Yeasmin F, Rabi DM, Ronksley PE, Turin TC. Prognostic tools for cardiovascular disease in patients with type 2 diabetes: a systematic review and meta-analysis of C-statistics. *J Diabetes Complications*. 2019;33:98–111. doi: 10.1016/j.jdiacomp.2018.10.010
67. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:j2099. doi: 10.1136/bmj.j2099
68. Bergmark BA, Bhatt DL, Braunwald E, Morrow DA, Steg PG, Gurmu Y, Cahn A, Mosenzon O, Raz I, Bohula E, et al. Risk assessment in patients with diabetes with the TIMI risk score for atherothrombotic disease. *Diabetes Care*. 2018;41:577–585. doi: 10.2337/dc17-1736
69. Jiang W, Wang J, Shen X, Lu W, Wang Y, Li W, Gao Z, Xu J, Li X, Liu R, et al. Establishment and validation of a risk prediction model for early diabetic kidney disease based on a systematic review and meta-analysis of 20 cohorts. *Diabetes Care*. 2020;43:925–933. doi: 10.2337/dc19-1897
70. Dei Cas A, Aldigeri R, Mantovani A, Masulli M, Palmisano L, Cavalot F, Bonomo K, Baroni MG, Cossu E, Cavallo G, et al. Sex differences in car-

84. Rosta K, Al-Aissa Z, Hadarits O, Harreiter J, Nadasdi A, Kelemen F, study with 77 SNPs confirms the robust role for the rs10830963/G diabetes mellitus development. <i>PLoS One</i> . 2017;12:e0169781. doi: 10.1371/journal.pone.0169781	Bancher-Todesca D, Komlosi Z, Nemeth L, Rigo J Jr, et al. Association of <i>MTNR1B</i> variant and identifies two novel associations in gestational
85. Srinivasan S, Chen L, Todd J, Divers J, Gidding S, Chernausek S, wide association study for type 2 diabetes in youth: the Progress in Diabetes	Gubitosi-Klug RA, Kelsey MM, Shah R, Black MH, et al. the first genome-
2021;70:996–1005.	Genetics in Youth (ProDiGY) Consortium. <i>Diabetes</i> .
diovascular disease and cardiovascular risk estimation in patients with type 1 diabetes. <i>J Clin Endocrinol Metab</i> . 2023;108:e789–e798. doi: 10.1210/clinem/dgad127	doi: 10.2337/db20-0443
71. Wang Y, Hou R, Ni B, Jiang Y, Zhang Y. Development and validation of	

86. Lee KH, Ju UI, Song JY, Chun YS. The histone demethylase PHF2 promotes fat cell differentiation as an epigenetic activator of both C/EBPalpha and C/EBPdelta. *Mol Cells*. 2014;37:734–741. doi: 10.14348/molcells.2014.0180
- prediction model based on machine learning algorithms for predicting the risk of heart failure in middle-aged and older US people with prediabetes or diabetes. *Clin Cardiol*. 2023;46:1234–1243. doi: 10.1002/clc.24104
- SCORE2-Diabetes Working Group and ESC Cardiovascular Risk Collaboration. SCORE2-Diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe. *Eur Heart J*. 2023;44:2544–2556. doi: 10.1093/eurheartj/ehad260
73. Almgren P, Lehtovirta M, Isomaa B, Sarelin L, Taskinen MR, Lyssenko V, Tuomi T, Groop L; Botnia Study Group. Heritability and familiarity of type 2 diabetes and related quantitative traits in the Botnia Study. *Diabetologia*. 2011;54:2811–2819. doi: 10.1007/s00125-011-2267-5
74. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance: a population-based twin study. *Diabetologia*. 1999;42:139–145. doi: 10.1007/s00125-011-2267-5

87. Mahajan A, Spracklen CN, Zhang W, Ng MCY, Petty LE, Kitajima H, Yu GZ, Rueger S, Speidel L, Kim YJ, et al. Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation. *Nat Genet.* 2022;54:560–572. doi: 10.1038/s41588-022-01058-3
88. Chen J, Spracklen CN, Marenne G, Varshney A, Corbin LJ, Luan J, Willems SM, Wu Y, Zhang X, Horikoshi M, et al; Meta-Analysis of Glucose and Insulin-Related Traits Consortium (MAGIC). The trans-ancestral genomic architecture of glycemic traits. *Nat Genet.* 2021;53:840–860. doi: 10.1038/s41588-021-00852-9
89. Downie CG, Dimos SF, Bien SA, Hu Y, Darst BF, Polfus LM, Wang Y, Wojcik GL, Tao R, Raffield LM, et al. Multi-ethnic GWAS and fine-mapping of glycaemic traits identify novel loci in the PAGE study. *Diabetologia.* 2022;65:477–489. doi: 10.1007/s00125-021-05635-9
90. Lagou V, Jiang L, Ulrich A, Zudina L, Gonzalez KSG, Balkhiyarova Z, Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes.* 2000;49:2201–2207. doi: 10.2337/diabetes.49.12.2201
75. Moonesinghe R, Beckles GLA, Liu T, Khoury MJ. The contribution of family history to the burden of diagnosed diabetes, undiagnosed diabetes, and prediabetes in the United States: analysis of the National Health and Nutrition Examination Survey, 2009–2014. *Genet Med.* 2018;20:1159–1166. doi: 10.1038/gim.2017.238
76. Kleinberger JW, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, Linder B, Shuldiner AR, Tollefsen S, White NH, Pollin TI. Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. *Genet Med.* 2018;20:583–590. doi: 10.1038/gim.2017.150
78. Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, Huffman JE, Assimes TL, Lorenz K, Zhu X, et al; HPAP Consortium. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat Genet.* 2020;52:680–691. doi: 10.1038/s41588-020-0637-y
79. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, Payne AJ, Steinthorsdottir V, Scott RA, Grarup N, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet.* 2018;50:1505–1513. doi: 10.1038/s41588-018-0241-6
80. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, Strawbridge RJ, Khan H, Grallert H, Mahajan A, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet.* 2012;44:981–990. doi:

- Faggian A, Maina JG, Chen S, Todorov PV, et al; Meta-Analysis of Glucose in 476,326 individuals provide insights into diabetes pathophysiology, complications and treatment stratification. *Nat Genet.* 2023;55:1448–1461. doi: 10.1038/s41588-023-01462-3
91. Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiovascular and metabolic diseases and common cancers. *Nat Med.* 2020;26:549–557. doi: 10.1038/s41591-020-0800-0
92. Hodgson S, Huang QQ, Sallah N, Griffiths CJ, Newman WG, Trembath RC, Wright J, Lumbers RT, Kuchenbaecker K, van Heel DA, et al; Genes and Health Research Team. Integrating polygenic risk scores in the prediction of type 2 diabetes risk and subtypes in British Pakistanis and Bangladeshis: a population-based cohort study. *PLoS Med.* 2022;19:e1003981. doi: 10.1371/journal.pmed.1003981
93. Ge T, Irvin MR, Patki A, Srinivasasainagendra V, Lin YF, Tiwari HK, Armstrong ND, Benoit B, Chen CY, Choi KW, et al. Development and validation of a trans-ancestry polygenic risk score for type 2 diabetes in diverse populations. *Genome Med.* 2022;14:70. doi: 10.1186/s13073-022-01074-2
94. Said MA, Verweij N, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK Biobank study. *JAMA Cardiol.* 2018;3:693–702. doi: 10.1001/jamacardio.2018.1717
95. Zhuang P, Liu X, Li Y, Wan X, Wu Y, Wu F, Zhang Y, Jiao J. Effect of diet quality and genetic predisposition on hemoglobin A1c and type 2 diabetes risk: gene-diet interaction analysis of 357,419 individuals. *Diabetes Care.* 2021;44:2470–2479. doi: 10.2337/dc21-1051
- 10.1038/ng.2383

96. Lotta LA, Wittemans LBL, Zuber V, Stewart Li C, Bowker N, Cai L, et al. Association of gluteofemoral vs abdominal fat distribution disease, and cardiovascular risk factors. doi: 10.1001/jama.2018.19329
97. Bulik-Sullivan B, Finucane HK, Anttila V, Duncan L, Perry JR, Patterson N, Robinson Consortium. Psychiatric Genomics Anorexia Nervosa of the Wellcome Trust las of genetic correlations across human 2015;47:1236–1241. doi: 10.1038/ng.3406
98. Shah HS, Gao H, Morieri ML, Skunien J, GC, Buranasunkaorn P, Mendonca C. tors of cardiovascular mortality during intensive glycemic control in type 2 diabetes: findings from the ACCORD clinical trial. *Diabetes Care*. 2016;39:1915–1924. doi: 10.2337/dc16-0285
99. Pociot F, Lernmark A. Genetic risk factors for type 1 diabetes. *Lancet*. 2016;387:2331–2339. doi: 10.1016/S0140-6736(16)30582-7
100. Forgetta V, Manousaki D, Istomine R, Ross S, Tessier MC, Marchand L, Li M, Qu HQ, Bradfield JP, Grant SFA, et al; DCCT/EDIC 101. Oram RA, Patel K, Hill A, Shields B, McDonald TJ, Jones A, Hattersley AT, Weedon MN. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. *Diabetes Care*. 2020;69:784–795. doi: 10.2337/db19-0831
101. Rhee EP, Cheng S, Larson MG, E. Farrell L, Fox CS, O'Donnell CJ, et al. lcerol signature of insulin resistance humans. *J Clin Invest*. 2010;1172/JCI64801
113. Wann TJ, Nao D, Psychodios N, Ghorbani A, O'Sullivan J, Chen S. a biomarker for diabetes risk. *J Clin* 10.1172/JCI64801
114. Siegel KR, Bullard KM, Imperatore G, Green EW. Prevalence of maior *Diabetes Care*. 2018;41:1032–1039.
115. Ali MK, Bullard KM, Savdah S, and renal burdens of prediabetes in Research Group. Rare genetic variants of large effect influence risk of type 1 diabetes. *Diabetes*. 2020;69:784–795. doi: 10.2337/db19-0831
116. Ali MK, Bullard KM, Savdah S, and renal burdens of prediabetes in Research Group. Rare genetic variants of large effect influence risk of type 1 diabetes. *Diabetes*. 2020;69:784–795. doi: 10.2337/db19-0831

- rial cross-sectional surveys, 1988-2014. *Lancet Diabetes Endocrinol.* 2018;6:392–403. doi: 10.1016/S2213-8587(18)30027-5
117. Herman WH, Pan Q, Edelstein SL, Mather KJ, Perreault L, Barrett-Connor Program Research Group. Impact of lifestyle and metformin interventions regulation in overweight or obese people with impaired glucose regulation. *Diabetes Care.* 2017;40:1668–1677. doi: 10.2337/dc17-1116
 118. Michaud TL, Almeida FA, Porter GC, Kittel CA, Schwab RJ, Brito FA, Wilson KE, Katula JA, Castro Sweet C, Estabrooks PA, et al. Effects of a digital diabetes prevention program on cardiovascular risk among individuals with prediabetes. *Prim Care Diabetes.* 2023;17:148–154. doi: 10.1016/j.pcd.2023.01.007
 102. Ferrat LA, Vehik K, Sharp SA, Lernmark A, Rewers MJ, She JX, Ziegler AG, Toppari J, Akolkar B, Krischer JP, et al; TEDDY Study Group. A combined risk score enhances prediction of type 1 diabetes among susceptible children. *Nat Med.* 2020;26:1247–1255. doi: 10.1038/s41591-020-0930-4
 103. Langefeld CD, Beck SR, Bowden DW, Rich SS, Wagenknecht LE, Freedman BI. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. *Am J Kidney Dis.* 2004;43:796–800. doi: 10.1053/j.ajkd.2003.12.043
 104. Qi L, Qi Q, Prudente S, Mendonca C, Andreozzi F, di Pietro N, Sturma M, Novelli V, Mannino GC, Formoso G, et al. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. *JAMA.* 2013;310:821–828. doi: 10.1001/jama.2013.276305
 105. Słomiński B, Ławrynówicz U, Ryba-Stanisławowska M, Skrzypkowska M, Myśliwska J, Myśliwiec M. CCR5-Δ32 polymorphism is a genetic risk factor associated with dyslipidemia in patients with type 1 diabetes. *Cytokine.* 2018;114:81–85. doi: 10.1016/j.cyto.2018.11.005
 106. Cao M, Tian Z, Zhang L, Liu R, Guan Q, Jiang J. Genetic association of *AKR1B1* gene polymorphism rs759853 with diabetic retinopathy risk: a meta-analysis. *Gene.* 2018;676:73–78. doi: 10.1016/j.gene.2018.07.014
 107. Guan M, Keaton JM, Dimitrov L, Hicks PJ, Xu J, Palmer ND, Ma L, Das SK, Chen YI, Coresh J, et al; FIND Consortium. Genome-wide association study identifies novel loci for type 2 diabetes-attributed end-stage kidney disease in African Americans. *Hum Genomics.* 2019;13:21. doi: 10.1186/s40246-019-0205-7
 108. Tang Y, Lenzini PA, Pop-Busui R, Ray PR, Campbell H, Perkins BA, E, Dabelea DM, Horton E, Kahn SE, Knowler WC, et al; Diabetes Prevention on the risk of progression to diabetes and regression to normal glucose

119. Lee JJN, Abdul Aziz A, Chan ST, Raja Abdul Sahrizan R, Ooi AYY, Teh YT, Iqbal U, Ismail NA, Yang A, Yang J, et al. Effects of mobile health inter-ventions on health-related outcomes in older adults with type 2 diabetes: a systematic review and meta-analysis. *J Diabetes*. 2023;15:47–57. doi: 10.1111/1753-0407.13346
120. Brinkmann C, Hof H, Gysan DB, Albus C, Millentrup S, Bjarnason-Wehrens B, Latsch J, Herold G, Wegscheider K, Heming C, et al. Lifestyle intervention reduces risk score for cardiovascular mortality in company employees with pre-diabetes or diabetes mellitus: a secondary analysis of the PreFord randomized controlled trial with 3 years of follow-up. *Front Endocrinol (Lausanne)*. 2023;14:1106334. doi: 10.3389/fendo.2023.1106334
121. Gerstein HC, Coleman RL, Scott CAB, Xu S, Tuomilehto J, Ryden L, Holman RR; ACE Study Group. Impact of acarbose on incident diabetes and regression to normoglycemia in people with coronary heart disease and impaired glucose tolerance: insights from the ACE trial. *Diabetes Care*. 2020;43:2242–2247. doi: 10.2337/dc19-2046
122. Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL Jr, Kalyani RR, Kosiborod M, Magwire M, Morris PB, Neumiller JJ, et al. 2020 Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76:1117–1145. doi: 10.1016/j.jacc.2020.05.037
123. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Das SR, Hilliard ME, Isaacs D, et al; American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Care in Diabetes–2023. *Diabetes Care*. 2023;46:S158–S190. doi: 10.2337/dc23-S010
- Callaghan B, Wagner MJ, Motsinger-Reif AA, Buse JB, et al. A genetic locus on chromosome 2q24 predicting peripheral neuropathy risk in type 2 diabetes: results from the ACCORD and BARI 2D studies. *Diabetes*. 2019;68:1649–1662. doi: 10.2337/db19-0109
109. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab*. 2009;9:311–326. doi:

124. Wong ND, Patao C, Malik S, Iloeje U. Preventable coronary heart dis-ease events from control of cardiovascular risk factors in US adults with diabetes (projections from utilizing the UKPDS risk engine). *Am J Cardiol.* 2014;113:1356–1361. doi: 10.1016/j.amjcard.2013.12.042

125. Centers for Disease Control and Prevention. Prevalence of both diagnosed and undiagnosed diabetes from the National Diabetes Statistics Report. Accessed November 6, 2024. <https://www.cdc.gov/diabetes/php/data-research/index.html>

110. Morze J, Wittenbecher C, Schwingshackl L, Danielewicz A, Rynkiewicz A, Hu FB, Guasch-Ferre M. Metabolomics and type 2 diabetes risk: an up-dated systematic review and meta-analysis of prospective cohort studies.

126. Xia PF, Tian YX, Geng TT, Li Y, Tu ZZ, Zhang YB, Guo K, Yang K, Liu G, Pan A. Trends in prevalence and awareness of prediabetes among adults in the U.S., 2005-2020. *Diabetes Care*. 2022;45:e21–e23. doi: 10.2337/dc21-1705
111. Yu D, Richardson NE, Green CL, Spicer AB, Murphy ME, Flores V, Jang C, Kasza I, Nikodemova M, Wakai MH, et al. The adverse metabolic effects of branched-chain amino acids are mediated by isoleucine and valine. *Cell Metab*. 2021;33:905–922.e6. doi: 10.1016/j.cmet.2021.03.025
112. Guasch-Ferre M, Hruby A, Toledo E, Clish CB, Martinez-Gonzalez MA, Salas-Salvado J, Hu FB. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2016;39:833–846. doi: 10.2337/dc21-2100

127. Arnold SV, de Lemos JA, Zheng L, Rosenson RS, Ballantyne CM, Alam S, Bhatt DL, Cannon CP, Kosiborod M; Gould Investigators. Use of optimal medical therapy in patients with diabetes and atherosclerotic cardiovascular disease: insights from a prospective longitudinal cohort study. *Diabetes Obes Metab*. 2023;25:1750–1757. doi: 10.1111/dom.15032
128. Arnold SV, Gosch K, Kosiborod M, Wong ND, Sperling LS, Newman JD, Gamble CL, Hamersky C, Rajpura J, Vaduganathan M. Contemporary use of cardiovascular risk reduction strategies in type

- the Diabetes Collaborative Registry. *Am Heart J*. 2023;263:104–111. doi: 10.1016/j.ahj.2023.05.002
129. Nelson AJ, O'Brien EC, Kaltenbach LA, Green JB, Lopes RD, Morse CG, Al-Khalidi HR, Aroda VR, Cavender MA, Gaynor T, et al. Use of lipid-, blood pressure-, and glucose-lowering pharmacotherapy in patients with type 2 diabetes and atherosclerotic cardiovascular disease. *JAMA Netw Open*. 2022;5:e2148030. doi: 10.1001/jamanetworkopen.2021.48030
130. Nanna MG, Kolkailah AA, Page C, Peterson ED, Navar AM. Use of sodium-glucose cotransporter 2 inhibitors and glucagonlike peptide-1 receptor agonists in patients with diabetes and cardiovascular disease in community practice. *JAMA Cardiol*. 2023;8:89–95. doi: 10.1001/jamacardio.2022.3839
131. Devineni D, Akbarpour M, Gong Y. Groups in US adults with diabetes in the NIH Precision Medicine Initiative All of Us Research Program. *Cardiovasc Drugs Ther*. 2022;38:347–357. doi: 10.1007/s10557-022-07403-2
132. Akbarpour M, Devineni D, Gong Y, Wong ND. Dyslipidemia treatment and lipid control in US adults with diabetes by sociodemographic and cardiovascular risk groups in the NIH Precision Medicine Initiative All of Us Research Program. *J Clin Med*. 2023;12:1668. doi: 10.3390/jcm12041668
133. Mannucci E, Gallo M, Giaccari A, Candido R, Pintaudi B, Targher G, Monami M; SID-AMD Joint Panel for Italian Guidelines on Treatment of Type 2 Diabetes. Effects of glucose-lowering agents on cardiovascular
144. Andary R, Fan W, Wong ND. Control of cardiovascular risk factors among US adults with type 2 diabetes with and without cardiovascular disease. *Am J Cardiol*. 2019;124:522–527. doi: 10.1016/j.amjcard.2019.05.035
145. Fang M, Selvin E. Thirty-year trends in complications in U.S. adults with newly diagnosed type 2 diabetes. *Diabetes Care*. 2021;44:699–706. doi: 10.2337/dc20-2304
146. Casagrande SS, Aviles-Santa L, Corsino L, Daviglus ML, Gallo LC, Espinoza Giacinto RA, Llabre MM, Reina SA, Savage PJ, Schneiderman N, et al. Hemoglobin A1C, blood pressure, and LDL- and renal outcomes in subjects with type 2 diabetes: an updated meta-analysis of randomized controlled trials with external adjudication of events. *Diabetes Obes Metab*. 2023;25:444–453. doi: 10.1111/dom.14888
134. Goldberg RB, Orchard TJ, Crandall JP, Boyko EJ, Budoff M, Dabelea D, Gadde KM, Knowler WC, Lee CG, Nathan DM, et al; Diabetes Prevention Program Research Group. Effects of long-term metformin and lifestyle interventions on cardiovascular events in the Diabetes Prevention Program and its outcome study. *Circulation*. 2022;145:1632–1641. doi: 10.1161/CIRCULATIONAHA.121.056756
135. Shin H, Schneeweiss S, Glynn RJ, Paterno E. Trends in first-line glucose-lowering drug use in adults with type 2 diabetes in light of emerging evidence for SGLT-2i and GLP-1RA. *Diabetes Care*. 2021;44:1774–1782. doi: 10.2337/dc20-2926

Neelon B. Geographic and racial/ethnic variation in glycemic control and treatment in a national sample of veterans with diabetes. *Diabetes Care*. 2020;43:2460–2468. doi: 10.2337/dc20-0514

148. Malik FS, Stafford JM, Reboussin BA, Klingensmith GJ, Dabelea D, Lawrence JM, Mayer-Davis E, Saydah S, Corathers S, Pihoker C; SEARCH for Diabetes in Youth Study. Receipt of recommended complications and comorbidities screening in youth and young adults with type 1 diabetes: associations with metabolic status and satisfaction with care. *Pediatr Diabetes*. 2020;21:349–357. doi: 10.1111/pedi.12948
149. Kianmehr H, Zhang P, Luo J, Guo J, Pavkov ME, Bullard KM, Gregg EW, Ospina NS, Fonseca V, Shi L, et al. Potential gains in life expectancy associated with achieving treatment goals in US adults with type 2 diabetes. *JAMA Netw Open*. 2022;5:e227705. doi: 10.1001/jamanetworkopen.2022.7705
150. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
151. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.
152. Kochanek KD, Murphy SL, Xu J, Arias E. Mortality in the United States, 2022. *NCHS Data Brief*. 2022;1:8.
153. Ramphul K, Joynauth J. An update on the incidence and burden of diabetic ketoacidosis in the U.S. *Diabetes Care*. 2020;43:e196–e197. doi: 10.2337/dc20-1258
136. Nargesi AA, Jeyashanmugaraja GP, Desai N, Lipska K, Krumholz H, Khera R. Contemporary national patterns of eligibility and use of novel cardioprotective antihyperglycemic agents in type 2 diabetes mellitus. *J Am Heart Assoc*. 2021;10:e021084. doi: 10.1161/JAHA.121.021084
137. Weng W, Tian Y, Kong SX, Ganguly R, Hersloev M, Brett J, Hobbs T.

154. Ding Q, Funk M, Spatz ES, Lin H, Batten J, Wu E, Whittemore R. Sex-specific impact of diabetes on all-cause mortality among adults with acute myocardial infarction: an updated systematic review and meta-analysis, 1988-2021. *Front Endocrinol (Lausanne)*. 2022;13:918095. doi: 10.3389/fendo.2022.918095
- The prevalence of cardiovascular disease and antidiabetes treatment characteristics among a large type 2 diabetes population in the United States. *Endocrinol Diabetes Metab*. 2019;2:e00076. doi: 10.1002/edm2.76
138. Elhussein A, Anderson A, Bancks MP, Coday M, Knowler WC, Peters A, Vaughan EM, Maruthur NM, Clark JM, Pilla S, Look ARG. Racial/ethnic and socioeconomic disparities in the use of newer
155. Olesen KKW, Gyldenkerne C, Thim T, Thomsen RW, Maeng M. Peripheral artery disease, lower limb revascularization, and amputation in diabetes patients with and without coronary artery disease: a cohort study from diabetes medications in the Look AHEAD study. *Lancet Reg Health Am*. 2022;6:100111. doi: 10.1016/j.lana.2021.100111

the Western Denmark Heart Registry. *BMJ Open Diabetes Res Care*.

2021;9:e001803. doi: 10.1136/bmjdr-2020-001803

156. Hamilton EJ, Davis WA, Siru R, Baba M, Norman PE, Davis TME. Temporal trends in incident hospitalization for diabetes-related foot ulcer in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*. 2021;44:722–730.
139. Leino AD, Dorsch MP, Lester CA. Changes in statin use among U.S. adults with diabetes: a population-based analysis of NHANES 2011–2018. *Diabetes Care*. 2020;43:3110–3112. doi: 10.2337/dc20-1481
140. Muntner P, Whelton PK, Woodward M, Carey RM. A Comparison of the 2017 American College of Cardiology/American Heart Association blood pressure guideline and the 2017 American Diabetes Association diabetes and hypertension position statement for U.S. adults with diabetes. *Diabetes Care*. 2018;41:2322–2329. doi: 10.2337/dc18-1307
141. Teo E, Hassan N, Tam W, Koh S. Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis. *Diabetologia*. 2022;65:604–619. doi: 10.1007/s00125-021-05648-4

157. Olafsdottir AF, Svensson AM, Pivodic A, Gudbjornsdottir S, Nystrom T, Wedel H, Rosengren A, Lind M. Excess risk of lower extremity amputations in people with type 1 diabetes compared with the general population: amputations and type 1 diabetes. *BMJ Open Diabetes Res Care*. 2019;7:e000602. doi: 10.1136/bmjdr-2018-000602
158. Harding JL, Andes LJ, Rolka DB, Imperatore G, Gregg EW, Li Y, Albright A. National and state-level trends in nontraumatic lower-extremity amputation among U.S. Medicare beneficiaries with diabetes, 2000-2017. *Diabetes Care*. 2020;43:2453–2459. doi: 10.2337/dc20-0586
159. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult U.S. Population. *Diabetes Care*. 2019;42:50–54.
142. Wong ND, Zhao Y, Patel R, Patao C, Malik S, Bertoni AG, Correa A, doi: 10.2337/dc18-1380
- Folsom AR, Kachroo S, Mukherjee J, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care*. 2016;39:668–676. doi: 10.2337/dc15-2439
143. Fan W, Song Y, Inzucchi SE, Sperling L, Cannon CP, Arnold SV, Kosiborod M, Wong ND. Composite cardiovascular risk factor target achievement and its predictors in US adults with diabetes: the Diabetes Collaborative Registry.

160. Centers for Disease Control and Prevention. US Diabetes Surveillance System Diabetes Atlas. Accessed April 4, 2024.
161. Jensen ET, Rigdon J, Rezaei KA, Saaddine J, Lundeen EA, Dabelea D, Dolan LM, D'Agostino R, Klein B, Meuer S, et al. Prevalence, progression, and modifiable risk factors for diabetic retinopathy in youth and young adults with youth-onset type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. *Diabetes Care*. 2023;46:1252–1260. doi: 10.2337/dc22-2503
- Diabetes Obes Metab*. 2019;21:1121–1127. doi: 10.1111/dom.13625

162. Diabetes Study. *J Clin Endocrinol Metab.* 2020;105:dqaa215. doi: 10.1093/clinem/dqaa215
- J. White
- Complic 180. Bertoni AG, Kramer H, Watson K, Post WS. Diabetes and clinical and subclinical CVD. *Glob Heart.* 2016;11:337– doi: 10.1016/j.ogheart.2016.07.005
- Complic 1
- 10.2337 181. Reis JP, Allen NB, Bancks MP, Carr JJ, Lewis CE, Lima JA, Rana JS, Giddins SS, Schreiner PJ. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age: the CARDIA study. *Diabetes Care.* 2018;41:731–738. doi: 10.2337/dc17-2233
163. Bursell nonathv mologv 2018:13
164. Fano M. 182. Seved Ahmadi S, Svensson AM, Pivodic A, Rosenaren A, Lind M. Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *U.S.* 2020;43
165. Arnqvist HJ, Westerlund MC, Fredrikson M, Ludvigsson J, Nordwall M. Impact of HbA1c followed 32 years from diagnosis of type 1 diabetes on development of severe retinopathy and nephropathy: the VISS Study. *Diabetes Care.* 2022;45:2675–2682. doi: 10.2337/dc22-0239
166. Wang T, Xi Y, Lubwama R, Hannanachi H, Iglay K, Koro C. Chronic kidney disease among US adults with type 2 diabetes and cardiovascular diseases: a national estimate of prevalence by KDIGO 2012 classification. *Diabetes Metab Syndr.* 2019;13:612–615. doi: 10.1016/j.dsx.2018.11.026
167. Cheng HT, Xu X, Lim PS, Hung KY. Worldwide epidemiology of diabetes-related end-stage renal disease, 2000–2015. *Diabetes Care.* 2021;44:89– 97. doi: 10.2337/dc20-1913
168. Smidtslund P, Jansson Sigfrids F, Ylinen A, Elonen N, Harjutsalo V, Groop PH, Thorn LM. Prognosis after first-ever myocardial infarction in type 1 diabetes is strongly affected by chronic kidney disease. *Diabetes Care.*

- Cardiovasc Diabetol.* 2020;19:9. doi: 10.1186/s12933-019-0983-1 183. Braffett BH, Bebu I, El Ghormli L, Cowie CC, Sivitz WI, Pop-Busui R, Larkin ME, Gubitosi-Klug RA, Nathan DM, Lachin JM, et al. Cardiometabolic risk factors and incident cardiovascular disease events in women vs men with type 1 diabetes. *JAMA Netw Open.* 2022;5:e2230710. doi: 10.1001/jamanetworkopen.2022.30710
184. Davis SN, Duckworth W, Emanuele N, Hayward RA, Wiitala WL, Thottapurathu L, Reda DJ, Reaven PD; Investigators of the Veterans Affairs Diabetes Trial. Effects of severe hypoglycemia on cardiovascular outcomes and death in the Veterans Affairs Diabetes Trial. *Diabetes Care.* 2019;42:157–163. doi: 10.2337/dc18-1144
185. Zinman B, Marso SP, Christiansen E, Calanna S, Rasmussen S, Buse JB; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Hypoglycemia, cardiovascular outcomes, and death: the LEADER experience. *Diabetes Care.* 2018;41:1783–1791. doi: 10.2337/dc17-2677
169. Fan Y, Lau ESH, Wu H, Yang A, Chow E, So WY, Kong APS, Ma RCW, Chan JCN, Luk AOY. Incidence of long-term diabetes complications and mortality in youth-onset type 2 diabetes: a systematic review. *Diabetes Res Clin Pract.* 2022;191:110030. doi: 10.1016/j.diabres.2022.110030
170. Mizokami-Stout KR, Li Z, Foster NC, Shah V, Aleppo G, McGill JB, Pratley R, Toschi E, Ang L, Pop-Busui R; T1D Exchange Clinic Network. The contemporary prevalence of diabetic neuropathy in type 1 diabetes: findings from the T1D Exchange. *Diabetes Care.* 2020;43:806–812. doi:

186. Heller SR, Bergenstal RM, White WB, Kupfer S, Bakris GL, Cushman WC, Mehta CR, Nissen SE, Wilson CA, Zannad F, et al; EXAMINE Investigators. Relationship of glycated haemoglobin and reported hypoglycaemia to cardiovascular outcomes in patients with type 2 diabetes and recent acute coronary syndrome events: the EXAMINE trial. *Diabetes Obes Metab*. 2017;19:664–671. doi: 10.1111/dom.12871
187. Echouffo-Tcheugui JB, Daya N, Lee AK, Tang O, Ndumele CE, Windham BG, Shah AM, Selvin E. Severe hypoglycemia, cardiac structure and function, and risk of cardiovascular events among older adults with diabetes. 10.2337/dc19-1583
171. Coles B, Zaccardi F, Ling S, Davies MJ, Samani NJ, Khunti K. Cardiovascular events and mortality in people with and without type 2 diabetes: an observational study in a contemporary multi-ethnic population. *J Diabetes Investig*. 2021;12:1175–1182. doi: 10.1111/jdi.13464
172. Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, Tryggestad J, White NH, Zeitler P; TODAY Study Group. Long-term complications in youth-onset type 2 diabetes. *N Engl J Med*. 2021;385:416–426.

- Diabetes Care*. 2021;44:248–254. doi: 10.2337/dc20-0552
188. Rana JS, Moffet HH, Liu JY, Karter AJ. Severe hypoglycemia and risk of atherosclerotic cardiovascular disease in patients with diabetes. *Diabetes Care*. 2021;44:e40–e41. doi: 10.2337/dc20-2798
 189. Echouffo-Tcheugui JB, Kaze AD, Fonarow GC, Dagogo-Jack S. Severe hypoglycemia and incident heart failure among adults with type 2 diabetes. *J Clin Endocrinol Metab*. 2022;107:e955–e962. doi: 10.1056/NEJMoa2100165
 173. Kaze AD, Santhanam P, Erqou S, Ahima RS, Bertoni A, Echouffo-Tcheugui JB. Microvascular disease and incident heart failure among individuals with type 2 diabetes mellitus. *J Am Heart Assoc*. 2021;10:e018998. doi: 10.1161/JAHA.120.018998
 174. Nanayakkara N, Curtis AJ, Heritier S, Gadowski AM, Pavkov ME, Kenealy

190. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, et al; Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052–2059. doi: 10.1001/jama.2020.6775
- T, Owens DR, Thomas RL, Song S, Wong J, et al. Impact of age at type 2 diabetes mellitus diagnosis on mortality and vascular complications: systematic review and meta-analyses. *Diabetologia*. 2021;64:275–287. doi: 10.1007/s00125-020-05319-w
175. Schwab U, Reynolds AN, Sallinen T, Rivellese AA, Riserus U. Dietary fat intakes and cardiovascular disease risk in adults with type 2 diabetes: a systematic review and meta-analysis. *Eur J Nutr*. 2021;60:3355–3363. doi: 10.1007/s00394-021-02507-1
176. de Jong M, Woodward M, Peters SAE. Diabetes, glycosylated hemoglobin, and the risk of myocardial infarction in women and men: a prospective cohort study of the UK Biobank. *Diabetes Care*. 2020;43:2050–2059. doi: 10.2337/dc200111

191. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395:1763–1770. doi: 10.1016/S0140-6736(20)31189-2
192. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020;369:m1966. doi: 10.1136/bmj.m1966
193. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized absolute risk for cardiovascular disease stratified by fasting glucose level. *Diabetes Care*. 2019;42:457–465. doi: 10.2337/dc18-1773
177. Mondesir FL, Brown TM, Muntner P, Durant RW, Carson AP, Safford MM, Levitan EB. Diabetes, diabetes severity, and coronary heart disease risk equivalence: REasons for Geographic and Racial Differences in Stroke (REGARDS). *Am Heart J*. 2016;181:43–51. doi: 10.1016/j.ahj.2016.08.002
178. Bancks MP, Ning H, Allen NB, Bertoni AG, Carnethon MR, Correa A, Echouffo-Tcheugui JB, Lange LA, Lloyd-Jones DM, Wilkins JT. Long-term
179. Davis WA, Gregg EW, Davis TME. Temporal trends in cardiovascular complications in people with or without type 2 diabetes: the Fremantle

- adults with COVID-19 in an integrated health care system in California.
JAMA. 2020;323:2195–2198. doi: 10.1001/jama.2020.7202
194. Czeisler ME, Barrett CE, Siegel KR, Weaver MD, Czeisler CA, Rajaratnam SMW, Howard ME, Bullard KM. Health care access and use among adults with diabetes during the COVID-19 pandemic—United States, February- March 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1597–1602. doi: 10.15585/mmwr.mm7046a2
195. Kastora S, Patel M, Carter B, Delibegovic M, Myint PK. Impact of diabetes on COVID-19 mortality and hospital outcomes from a global perspective: an umbrella systematic review and meta-analysis. *Endocrinol Diabetes Metab*. 2022;5:e00338. doi: 10.1002/edm2.338

196. Li C, Islam N, Gutierrez JP, Gutierrez-Barreto SE, Castaneda Prado A, Moolenaar RL, Lacey B, Richter P. Association of s of

199. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N, et al. Associations of type 1 and type

205. McCoy RG, Van Houten HK, Deng Y, Mandic PK, Ross JS, Montori VM, Shah ND. Comparison of diabetes medications used by adults with commercial insurance vs Medicare Advantage. 2016 to 2019. *JAMA Netw Open*. 2021;4:e2035792. doi: 10.1001/jamanetworkopen.2020.35792

206. Parker ED, Lin J, Mahoney T, Ume N, Yang G, Gabbay RA, ElSayed NA, Bannuru RR. Economic costs of diabetes in the U.S. in 2022. *Diabetes Care*. 2024;47:26–43. doi: 10.2337/dci23-0085

207. Barber MJ, Gotham D, Bygrave H, Cepuch C. Estimated sustainable cost-based prices for diabetes medicines. *JAMA Netw Open*. 2024;7:e243474. doi: 10.1001/jamanetworkopen.2024.3474

208. Joo H, Zhang P, Wang G. Cost of informal care for patients with cardiovascular disease or diabetes: current evidence and research challenges. *Qual*

2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol*. 2020;8:813–822. doi:

- Life Res.* 2017;26:1379–1386. doi: 10.1007/s11136-016-1478-0
209. Shrestha SS, Zhang P, Hora IA, Gregg EW. Trajectory of excess medical expenditures 10 years before and after diabetes diagnosis among U.S. adults aged 25-64 years, 2001-2013. *Diabetes Care.* 2019;42:62–68. doi: 10.1016/S2213-8587(20)30272-2
200. Dennis JM, Mateen BA, Sonabend R, Thomas NJ, Patel KA, Hattersley AT, Denaxas S, McGovern AP, Vollmer SJ. Type 2 diabetes and COVID-19-related mortality in the critical care setting: a national cohort study in England, March-July 2020. *Diabetes Care.* 2021;44:50–57. doi: 10.2337/dc20-1444
201. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024.
202. Collins J, Abbass IM, Harvey R, Suehs B, Uribe C, Bouchard J, Prewitt T, DeLuzio T, Allen E. Predictors of all-cause-30-day-readmission among Medicare patients with type 2 diabetes. *Curr Med Res Opin.* 2017;33:1517–1523. doi: 10.1080/03007995.2017.1330258
- doi: 10.2337/dc17-2683
210. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed July 1, 2024.
211. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2022;183:109119. doi: 10.1016/j.diabres.2021.109119
203. Zhou X, Shrestha SS, Shao H, Zhang P. Factors contributing to the rising national cost of glucose-lowering medicines for diabetes during 2005-2007 and 2015-2017. *Diabetes Care.* 2020;43:2396–2402. doi:

212. Saeedi P, Salpea P, Karuranga S, Petersohn I, Malanda B, Gregg EW, Unwin N, Wild SH, Williams R. Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract.* 2020;162:108086. doi: 10.1016/j.diabres.2020.108086
213. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, Fryar CD, Gu S, Hales CM, Hughes JP, Ostchega Y, Storandt RJ, Akinbami LJ. National Health and Nutrition Examination Survey 2017–March 2020 prepanemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Rep.* 2021;158. doi: 10.15620/cdc:106273
204. Hernandez I, San-Juan-Rodriguez A, Good CB, Gellad WF. Changes in list prices, net prices, and discounts for branded drugs in the US, 2007-2018. *JAMA.* 2020;323:854–862. doi: 10.1001/jama.2020.1012

10. METABOLIC

See Charts 10-1 through 10-4

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Definition

- MetS is a multicomponent risk and type 2 diabetes that of individual cardiometabolic to abdominal obesity and is a useful entity for lifestyle-related and clinicians. Although MetS have been proposed, and others recommended a for MetS based on the following 5 risk factors¹:
 - FPG ≥ 100 mg/dL or for elevated glucose
 - HDL-C < 40 mg/dL in males in females or undergoing reduced HDL-C
 - Triglycerides ≥ 150 mg/dL or treatment for elevated
 - WC > 102 cm in males or people of most ancestries States. Ethnicity- and olds can be used for particularly Asian non-European ancestry dominantly outside the recommendations for WC overestimate MetS in US females.²
 - SBP ≥ 130 mm Hg, DBP ≥ 85 going drug treatment for hypertensive drug history of hypertension
- Several adverse health MetS but are not part of its include MASLD, (erectile dysfunction in males syndrome in females), OSA,

and possibly osteoarthritis, as inflammatory and

- Type 2 diabetes, defined as ~~dem or 2-hour postchallenge~~ HbA1c $\geq 6.5\%$, or taking is a separate clinical however, many individuals have MetS.

Prevalence

Youths

(See Chart 10-1)

- According to NHANES 1999 to prevalence of MetS in of age in the United States region and was higher in females across all regions NHANES 2011 to 2016, the according to the IDF definition 19 years of age was CI, 2.49%–5.99%) overall, 9.16%) in adolescent males, 2.08%–3.48%) in adolescent
- According to data from the prevalence of MetS years of age was 3.73% (95% for Hispanic youths, 1.58% 2.10%) for NH Black youths, 2.25%–3.43%) for NH White
- Uncertainty remains the abdominal obesity and nent of MetS in the pediatric it is age dependent. BP percentiles⁶ has been nition⁷ generally provided the 0.3% to 9.5% globally, of de Ferranti et al⁸ yields the 26.4%.⁹
- The prevalence of MetS varied cational attainment, level of household food security prevalence of MetS among of age was 6.53% (95% CI, parental education of less 2.51% (95% CI, 1.39%–

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published

data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

cation of college degree or above according to data from NHANES 1999 to 2018.¹⁰

- The prevalence of MetS significantly differed by BMI category according to data from NHANES 1999 to 2018. The prevalence of MetS was 0.18% (95% CI, 0.05%–0.62%) for children with underweight and normal weight, 2.56% (95% CI, 1.65%–3.96%) for children with overweight, and 20.1% (95% CI, 17.0%–23.6%) for children with obesity.¹⁰

Adults

The following estimates include many who also have diabetes, in addition to those with MetS without diabetes:

- On the basis of prevalence of MetS was 34.7% (95% CI, 33.1%–36.3%) and was similar for males (35.1%, [95% CI, 32.9%–37.3%]) and females (34.3%, [95% CI, 32.7%–36.0%]).¹¹ The prevalence of MetS was higher with older age group, from 19.5% (95% CI, 17.8%–21.4%) among people 20 to 39 years of age to 39.4% (95% CI, 37.2%–41.7%) for people 40 to 59 years of age and 48.6% (95% CI, 46.0%–51.2%) among people ≥60 years of age.
- In 2017 to 2018, Mexican American adults generally had the highest prevalence of MetS at 52.2% (95% CI, 47.0%–54.2%), whereas NH White adults had 46.6% (95% CI, 42.9%–50.2%), NH Black adults had 47.6% (95% CI, 44.7%–50.5%), other Hispanic adults had 45.9% (95% CI, 41.9%–50.0%), and Asian/other including multiracial adults had 46.7% (95% CI, 41.9%–51.4%).¹²
- In 2017 to 2018, the prevalence of MetS was the lowest among adults who were college graduates or above at 39.3% (95% CI, 34.9%–43.6%).¹² In contrast, adults with lower educational attainment had a higher prevalence of MetS at 49.1% (95% CI, 44.7%–53.6%) for those less than high school graduates, 51.9% (95% CI, 47.5%–56.2%) for those who were high school graduates, and 50.2% (95% CI, 46.9%–53.4%) for those with some college.
- In 2017 to 2018, adults with a higher family income (ratio of family income to the FPL ≥3.0) had a lower prevalence of MetS at 44.2%

palsy³²; spinal cord injury³³ in veterans; and chronic opiate dependence,³⁴ as well as in individuals in select professions,

Secular Trends

Youths

- A recent NHANES analysis from 1999 to 2018 among youths 12 to 19 years of age reported that the prevalence of MetS remained stable at 4.36% (95% CI, 3.65%–5.20%) over the study (95% CI, 40.9%–47.6%) compared with those with lower family income (ratio <1.30) with a prevalence of MetS at 50.6% (95% CI, 47.0%–54.2%).¹²
- A meta-analysis including 28 193 768 participants showed that the global MetS prevalence varied from 12.5% (95% CI, 10.2%–15.0%) to 31.4% (95% CI, 29.8%–33.0%) according to the definition used.¹³ The prevalence was significantly higher in the Eastern Mediterranean region and Americas and was directly related to the country's level of income. • The prevalence of MetS has been noted to be higher in individuals with certain conditions, including schizophrenia spectrum disorders¹⁴ and bipolar disorder¹⁵; prior solid-organ transplantations¹⁶; prior hematopoietic cell transplantation¹⁷; HIV infection¹⁸; chronic obstructive pulmonary disease¹⁹; prior treatment for blood cancers^{17,20}; systemic inflammatory disorders such as psoriasis,²¹ ankylosing spondylitis,²² and rheumatoid arthritis²³; type 1 diabetes^{24,25}; latent autoimmune diabetes in adults²⁵; prior gestational diabetes²⁶; prior HDP²⁷; acne keloidalis nuchae²⁸; periodontitis^{29,30}; gallstones³¹; cerebral

Adults

(See Chart 10-2)

- Secular trends in MetS differed according to the definition used.^{38,39} Chart 10-2 demonstrates trends using the harmonized MetS criteria in NHANES 2009 to 2010 until 2017 to 2018.
- Data from NHANES 2011 to 2016 showed that the prevalence of MetS increased significantly among those between 20 to 39 years of age (16.2% to 21.3%; $P_{\text{trend}}=0.02$), women (31.7% to 36.6%; $P_{\text{trend}}=0.008$), and Hispanic participants (32.9% to 40.4%; $P_{\text{trend}}=0.01$).¹¹
- According to data from NHANES 1999 to 2018, the overall MetS prevalence (according to the AHA/NHLBI definition) increased from 36.2% (95% CI, 33.2%–39.1%) to 47.3% (95% CI, 45.3%–49.3%; $P_{\text{trend}}<0.001$).¹²

Risk Factors

Youths

- Early-life famine exposure and adulthood obesity aggravated the risk of MetS (OR, 17.52 [95% CI, 10.07–30.48]) compared with individuals without either condition.⁴⁰
- A meta-analysis including 13 305 adolescents and children suggested that short sleep duration was not associated with MetS (OR, 0.92 [95% CI, 0.48–1.37]); however, long sleep duration was associated with lower risk of MetS (OR, 0.57 [95% CI, 0.38–0.76]).⁴¹
- In a single-center retrospective case-control study among children and adolescents <18 years of age, bipolar disorder was associated with prevalent MetS compared with healthy controls (OR, 2.33 [95% CI, 1.37–4.0]).⁴²
- A recent review summarized the evidence identifying obesity and weight gain among obese children as important risk factors for MetS among youths.⁴³

Respiratory Exposures

- Exposure to parental smoking after birth was associated with increased risk of MetS among school

children 6 to 18 years of age 1.11–1.85]) after adjustment stages. lifestyle factors. and

- Among 9897 children and years of age in China. long-term air pollution (eq. PM_{2.5}. <10- μ m diameter, and NO₂) was positively m₃ increase in PM_{2.5}. fine μ m diameter, and NO₂, the odds of MetS increased by 1.32 [95% CI. 1.08–1.62]).

[95% CI, 1.03–1.72]), respectively.⁴⁵

Diet and PA

- Daily intake of added and free sugar (incremented by quintiles) was associated with higher MetS score (defined⁴⁶ on the basis of BMI, HDL-C, triglycerides, glucose, SBP, and DBP) among adolescents ($P_{\text{trend}} < 0.01$).⁴⁷ Higher consumption of ultraprocessed foods was associated with greater prevalence of MetS. A study using data from NHANES 2009 to 2014 reported that a 10% increase in dietary contribution of ultraprocessed foods was associated with a 4% greater prevalence of MetS (PR, 1.04 [95% CI, 1.02–1.07]).⁴⁸ Furthermore, compared with ultraprocessed food contribution <40% (first population quintile), the dietary contribution of ultraprocessed foods >71% (fifth population quintile) was associated with a 28% higher prevalence of MetS (40.4 versus 37.5; PR, 1.28 [95% CI, 1.09–1.50]).
- Among 6009 children and adolescents 9 to 18 years of age with device-based accelerometer data from the International Children's Accelerometry Database, total PA and moderate- to vigorous-intensity PA were directly associated with prevalent MetS according to the IDF definition.⁴⁹ The odds of MetS decreased by

like growth factor binding was an independent risk hood (OR, 10.72 [95% CI,

- In ERICA, a cross-sectional Brazilian adolescents 12 to 17 adiponectin levels were MetS z score ($\beta = -0.40$ [95% $P = 0.005$].⁵² Total serum molecular-weight adiponectin. ated with MetS according to in Mexican children 8 to 11 years of age.⁵³ 17% (OR, 0.83 [95% CI, 0.76–0.91]) for every 100-count/min (total PA) increase in average total PA and by 9% (OR, 0.91 [95% CI, 0.84–0.99]) for every 10-min increase in moderate- to vigorous-intensity PA after adjustment for sedentary time.

Serum Biomarkers

- Among Chinese adolescents 12 to 16 years of age, aspartate aminotransferase/alanine aminotransferase ratio was inversely associated with prevalent MetS. Students in the lowest tertile of aspartate aminotransferase/alanine aminotransferase ratio had 6-fold higher odds of MetS compared with those in the highest tertile (OR, 6.02 [95% CI, 1.93–18.76]).⁵⁰ In addition, a lower ratio of insulin-like growth factor 1 to insulin-like growth factor binding protein 3 was an independent risk factor for prevalent MetS (OR, 2.35 [95% CI, 1.04–5.30]) in Chinese adolescents 12 to 16 years of age. Lower baseline ratio of insulin-like growth factor 1 to insulin-

Adults

Incident MetS

Diet

• Dietary habits have been directly associated with incident MetS, including a Western dietary pattern,^{54,55} high inflammatory diet pattern,^{56–58} and higher intake of SSBs or AABs,⁵⁹ carbohydrates, ⁶⁰ total fat,⁶¹ and meats (total, red, and processed but not white meat).^{62,63}

• Subjects in the highest versus lowest quintile of an unhealthful plant-based diet index, a composite measure of a diet with a higher intake of refined grains, potatoes, SSBs, sweets, and salty food and lower intake of whole grains, fruits, vegetables, nuts, legumes, tea, and coffee, had a 50% higher risk of developing incident MetS.⁶⁴

• Restrained and emotional eating behaviors⁶⁵ and a problematic relationship with eating and food⁶⁶ were risk factors for incident MetS. In women, emotional eating behavior had 2.14 increased risk of incident MetS (95% CI, 1.50–3.06). In the CARDIA study, the risk of MetS was 25% higher per 1 problem-atic relationship to eating and food score increase through 5 years of follow-up (95% CI, 1.17–1.34).

• Dietary habits were also inversely associated with incident MetS, including fiber intake,⁶⁷ Mediterranean diet,⁶⁸ fruit consumption (≥4 servings/d versus <1 serving/d),⁶⁹ dairy consumption,⁷⁰ coffee consumption,^{56,57,71} vitamin D intake,⁷² intake of tree nuts,⁷³ and intake of long-chain omega-3 PUFAs.⁷⁴

Physical Activity

• In a meta-analysis that included 76 699 participants and 13 871 incident cases of MetS, there was a negative linear relationship between leisure-time PA and the development of MetS.⁷⁵ With each 10 MET-h/wk of PA (equal to ≈150 min/wk of moderate-intensity PA), the risk of MetS was reduced by 10% (RR, 0.90 [95% CI, 0.86–0.94]).

• A meta-analysis that included 105 239 participants suggested that high levels of sedentary behavior were associated with a higher risk of MetS (OR, 1.71 [95% CI, 1.43–2.04]), independently of PA,

and the pattern of association was stronger in females (OR for females, 2.10 [95% CI, 1.06–4.18]; OR for males, 1.75 [95% CI, 1.41–2.18]).⁷⁶

- The following factors have been reported as being inversely associated with incident MetS, defined by 1 of the major definitions, in prospective or retrospective cohort studies: increased PA or physical fitness,⁷⁷ aerobic or resistance
- Each 1000-step/d increase was associated with lower odds of having MetS (OR, 0.90 [95% CI, 0.83–0.98]) in American males.⁸⁰ The long-term meeting of step-based guidelines or an increase in daily steps was associated with a reduced risk of MetS from 39% to 12% over 7 years of follow-up among older European females.⁸¹

Sleep

- The association between sleep duration and incident MetS appears U shaped, but compared with normal sleep duration (7–8 hours), only short duration of sleep was significantly associated with an increased risk of incident MetS (OR, 1.28 [95% CI, 1.07–1.53]); a long duration of sleep was not.⁸²

Blood Biomarkers

- In Chinese adults, greater high-sensitivity CRP levels were associated with a higher risk of MetS in females (OR, 4.82 [95% CI,

indicated that depression was a risk factor for MetS (OR, 1.22 [95% CI, 1.09–1.37]) and its components (WC:

OR, 1.08 [95% CI, 1.03–1.14]; hypertension: OR, 1.03 [95% CI, 1.02–1.04]; triglycerides: OR, 1.11 [95% CI, 1.06–1.16], and HDL-C: OR, 0.93 [95% CI, 0.89–0.98]).⁹⁷ Furthermore,

individuals with depression in the United States (OR, 1.46 [95% CI, 1.89–12.3] for highest versus lowest quartile) but not in males (OR, 3.15 [95% CI, 0.82–12.1]).⁸³

- Blood biomarkers⁸⁴ that were associated with incident MetS include higher triglyceride-glucose index (HR, 1.79 [95% CI, 1.61–2.00]; cutoff point, 8.518)⁸⁵; lower adiponectin (OR, 2.24 [95% CI, 1.11–4.52] comparing lowest versus highest quartile)⁸⁶; elevated CRP (OR, 1.23 [95% CI, 1.11–1.36] per 1-unit change in log-transformed plasma CRP)⁸⁷; ferritin (OR, 1.73 [95% CI, 1.54–1.95] comparing highest and lowest quartiles)⁸⁸; γ -glutamyltransferase (HR, 1.26 [95% CI, 1.18–1.35] per 1-SD increment log- γ -glutamyltransferase)⁸⁹; uric acid (RR, 1.30 [95% CI, 1.22–1.38] per 1-mg/dL increase)⁹⁰; lower total (HR, 0.48 [95% CI, 0.32–0.72] comparing highest and lowest quartiles) and indirect (HR, 0.52 [95% CI, 0.35–0.77] comparing highest and lowest quartiles) bilirubin⁹¹; and lower follicle-stimulating hormone in postmenopausal females (OR, 2.39 [95% CI, 1.05–5.46] comparing lowest and highest quartiles).⁹²

- individuals with 4 or 5 MetS components had an HR of incident depression of 1.16 (95% CI, 1.06–1.32) and 1.25 (95% CI, 1.10–1.54), respectively.⁹⁹
- There was also a bidirectional association between MetS and osteoarthritis. In a meta-analysis, osteoarthritis increased the odds of incident MetS in females (OR, 2.34 [95% CI, 1.54–3.56]) but not in males (OR, 0.86 [95% CI, 0.61–1.16]), and MetS increased the odds of incident osteoarthritis for both males and females (pooled OR, 1.45 [95% CI, 1.27–1.66]).¹⁰⁰ In a meta-analysis, infant outcomes such as LBW (pooled OR, 1.79 [95% CI, 1.39–2.31]) and PTB (pooled OR, 1.72 [95% CI, 1.12–2.65]) were associated with greater odds of MetS.¹⁰¹
 - A meta-analysis including a combined total of 18 295 preterm and 294 063 term-born adults showed that PTB was strongly associated with a number of components of MetS, including higher glucose (0.07 mmol/L [95% CI, 0.02–0.10]), fasting insulin (random mean difference, 16% [95% CI, 6%–26%]), and homeostasis model assessment of insulin resistance (random mean difference, 24% [95% CI, 0%–47%]) in adult life.¹⁰²
 - Among perimenopausal females (mean age, 55±5.4 years), >12 months of breastfeeding significantly reduced the odds of incident MetS in midlife (OR, 0.76 [95% CI, 0.60–0.95]).¹⁰³
 - In the National Health Insurance Service–National Sample Cohort in South Korea 2009 to 2015, the presence of MASLD was associated with a higher risk of incident MetS (HR, 2.10 [95% CI, 1.18–3.71]).¹⁰⁴ MASLD was an early predictor of metabolic dysfunction even in metabolically healthy populations.

Prevalent MetS

Diet

- In cross-sectional studies, prevalent MetS was directly associated with a high dietary inflammatory

Other

- Risk factors for incident MetS include smoking,^{93,94} childhood MetS,⁹⁵ childhood cancer, and obesity-index score,¹⁰⁵ high dietary acid load,¹⁰⁶ high insulin and lipid-related indices.⁹⁶
- There was a bidirectional association between MetS

load or insulin index diet,¹⁰⁷ a long-chain food supply (compared with a short-chain food supply),¹⁰⁸ excessive dietary calcium (>1200 mg/d) in males,¹⁰⁹ and inadequate energy intake among patients undergoing dialysis.¹¹⁰ A mendelian

- Prevalent MetS is inversely associated with total antioxidant capacity from diet and dietary supplements.¹¹¹ animal-based oils such as butter and ghee,¹¹² organic food consumption,¹¹³ and Mediterranean– Intervention for Neurodegenerative Delay diet, identified as a new dietary pattern that combines the Mediterranean and DASH diets.¹¹⁴

- Longer eating duration and late meal intake, higher energy consumption in the evening, and skipped breakfast (but not dinner) were associated with higher odds of MetS and its key components.¹¹⁵ Adults with a longer eating duration (>12 h) had a higher prevalence of abdominal obesity (IRR, 1.15 [95% CI, 1.03–1.28]) compared with those who ate their meals in a shorter eating duration (<12 h). Adults in the third tertile of the time of the last meal (mean, 10:03 pm) had a higher prevalence of abdominal obesity (IRR, 1.12 [95% CI, 1.01–1.25]) compared with adults in the first tertile. Another study showed that compared with the group with a lower proportion of energy intake in the evening, the group with the highest proportion of energy intake in the evening had an OR of 1.37 (95% CI, 1.17–1.61) for prevalent MetS.¹¹⁶ Individuals who skipped breakfast had increased odds of MetS of 1.22 (95% CI, 1.04–1.43) for men and 1.18 (95% CI, 1.02–1.35) for women.¹¹⁷
- Compared with persistent light drinkers, individuals who increased alcohol intake to heavy levels had an elevated risk of MetS (OR, 1.45 [95% CI, 1.09–1.92]).¹¹⁸ In contrast, heavy drinkers who became light drinkers had a reduced risk of MetS (OR, 0.61 [95% CI, 0.44–0.84]) compared with persistent heavy drinkers.

Physical Activity

- In cross-sectional studies, prevalent MetS was directly associated with low cardiorespiratory fitness¹¹⁹ and low levels of PA.^{120,121} Prevalent

interaction
seen in

Sleep

- Associations MetS were duration (7–significantly lent MetS hours and as were 1.02–1.21] 1.40] for >10
- In data from U-shaped MetS. Sleep ciated with 1.10–

MetS was inversely associated with “weekend warrior” and regular PA patterns,¹²² any length of moderate- to vigorous-intensity PA,¹²¹ and greater handgrip strength.^{1,123,124}

- Higher leisure-time PA was associated with a lower risk of MetS in a dose-response manner, whereas no associations were found between occupational PA and the risk of MetS.¹²⁵

- The relationship between PA and MetS might be moderated by lean muscle mass in males. Males and females with higher lean muscle mass had lower risk of MetS, regardless of PA. However, males with low lean muscle mass exhibited a U-shaped relationship between vigorous PA and MetS risk (0 h/wk versus 4–8 h/wk: OR, 2.1 [95% CI, 1.1–4.3]; >12 h/wk versus 4–8 h/wk: aOR, 4.3 [95% CI, 1.7–11.0]). No

Blood Biomarkers

• Blood biomarkers directly associated with prevalent as interleukin-6 and tumor necrosis factor- α ¹²⁸; retinol serum liver chemistries, including alanine transaminase,¹³¹ aspartate transaminase ratio, alkaline phosphatase,¹³² serum vitamin levels,¹³³ including retinol and α -tocopherol; serum thyrotropin in individuals with euthyroidism¹³⁴; and erythrocyte parameters¹³⁵ such as hemoglobin level and red blood cell distribution width. For example, participants with elevated serum CA 19-9 (≥ 37 U/mL) had an increased risk of prevalent MetS compared with those with serum CA 19-9 < 37 U/mL (OR, 2.10 [95% CI, 1.21–3.65]).¹³⁰

• In cross-sectional studies, prevalent MetS was inversely associated with anti-inflammatory cytokines (interleukin-10),¹²⁸ ghrelin,¹²⁸ adiponectin,¹²⁸ and aging protein such as klotho.¹³⁶

• Lower serum 25-hydroxyvitamin D level was associated with higher odd of MetS.^{119,137–139} For example, results from NHANES show that individuals with a 25-hydroxyvitamin D level < 30 nmol/L were almost 3 times more likely to have MetS (OR, 2.98 [95% CI, 2.14–4.16]) compared with those with 25-hydroxyvitamin D level > 75 nmol/L.

Other

• Prevalent MetS was also directly associated with elevated urine sodium¹⁴⁰ and high heavy metal exposure.¹⁴¹

• Current and former e-cigarette users were 30% (OR, 1.30 [95% CI, 1.13–1.50]) and 15% (OR, 1.15 [95% CI, 1.03–1.28]) more likely to have MetS than never e-cigarette users (48.5%, 40.2%, and 45.7%).

with MetS for current, former, and never e-cigarette users, respectively).¹⁴² The prevalence of MetS for dual users (using both combustible cigarette and e-cigarette) was 1.35-fold (95% CI, 1.15–1.58) higher than that for nonsmokers and 1.21-fold (95% CI, 1.00–1.46) higher than that for combustible cigarette-only users.

- In cross-sectional studies, prevalent MetS was inversely associated with the ratio of quency,¹⁴⁴ and substance use.¹⁴⁵
- A systematic review and meta-analysis found that adults in psychological high-stress groups had a higher chance of having MetS than those in the low-stress group (OR, 1.45 [95% CI, 1.21–1.74]).¹⁴⁶ Occupational stress showed the strongest association with MetS (OR, 1.69 [95% CI, 1.18–2.42]), whereas perceived general stress showed the weakest association (OR, 1.22 [95% CI, 1.02–1.46]).
- In NHANES 2005 to 2018, the odds of depression in patients with MetS was 1.37 in the fully adjusted model (95% CI, 1.17–1.60) after propensity score matching.¹⁴⁷ In addition, an elevation in MetS component count was associated with a significant linear elevation in the mean score of Patient Health Questionnaire-9 ($F=2.8356$, $P<0.001$).
- In Korea NHANES 2013 to 2017, among 24 695 participants, a higher density of physicians (2.71 per 1000 population versus 2.64 per 1000 population) was significantly associated with a lower prevalence of MetS (OR, 0.86 [95% CI, 0.76–0.98]).¹⁴⁸

females in households with higher food security (OR, 1.43 [95% CI, 1.13–1.80] and 1.71 [95% CI, 1.31–2.24], respectively).¹⁵¹

- In the HELENA study among 1037 European adolescents 12.5 to 17.5 years of age, those with mothers with low education had a higher MetS risk (β estimate for the MetS score, calculated as the sum of sex-

Social Determinants of Health/Health Equity

- In HCHS/SOL, SES was inversely associated with prevalent MetS among Hispanic/Latino adults of diverse ancestry groups.¹⁴⁹ Higher versus lower income, higher versus lower education level, and full-time employment status versus unemployed status were associated with a 4%, 3%, and 24% decreased odds of having MetS, respectively. The association with income was significant only among females and those with current health insurance.
- In the JHS, subjective measures of social status were independently associated with MetS severity among Black adults ($\beta=-0.05$, $P=0.0007$).¹⁵⁰ Education level (objective measure of social status) was also independently associated with MetS severity ($\beta=-0.19$, $P=0.0498$ for graduate/professional compared with below high school education). Subjective social status was a stronger predictor of MetS severity than subjective social status, particularly among women.
- In NHANES 2007 to 2014, females in households with low and very low food security were at increased risk for prevalent MetS compared with

who accumulated >3 disadvantages (defined as parents with low education, low family affluence, migrant origin, unemployed parents, or nontraditional families) had a higher MetS risk score compared with those who did not experience disadvantage (β estimate, 0.69 [95% CI, 0.08–1.31]).¹⁵²

- According to data from the Korean National Health and Nutrition Examination Survey (2016–2018), high SES was inversely associated with the prevalence of MetS after adjustment for covariates (OR, 0.67 [95% CI, 0.50–0.89]).¹⁵³
- Similar findings were reported around the world on the association of socioeconomic inequalities with MetS.^{154–156} In a Spanish working population, the prevalence of MetS by ATP III criteria among males was 8.01% for social class I (highest), 8.72% for social class II, and 9.82% for social class III (lowest; $P=0.004$); the values among females were 1.35%, 3.85%, and 4.6%, respectively. Individuals with no education or primary school education in the French West Indies had a higher risk of MetS (OR, 2.4 [95% CI, 1.3–4.4]) compared with those having equivalent to high school or higher than high school education.¹⁵⁵

Genetics and Family History

(See also Chapter 6 [Overweight and Obesity], Chapter 8 [High Blood Pressure], and Chapter 9 [Diabetes])

- The combined genetic heritability in self-identified Black individuals and White individuals for ATP III–defined MetS is estimated to be $\approx 25\%$.¹⁵⁷
- Genetic factors are associated with the individual components of MetS. In a candidate gene study of 3067 children, variants in the *FTO* gene were associated with MetS.¹⁵⁸ Several pleiotropic variants of genes of apolipoproteins (*APOE*, *APOC1*, *APOC3*, and *APOA5*), Wnt signaling pathway (*TCF7L2*), lipoproteins (*LPL*, *CETP*), mitochondrial proteins (*TOMM40*), gene transcription regulation (*PROX1*), cell proliferation (*DUSP9*), cAMP signaling (*ADCY5*), and oxidative LDL metabolism (*COLEC12*), as well as expression of liver-specific genes (*HNF1A*), have been identified

across various racial and could explain some of the MetS traits.^{159–162} A recent MetS components has genetic associations (6 loci in individuals, 3 loci in Europeans, 3 loci in Japanese in Mexican American interethnicity heterogeneity).¹⁶³

- The A allele of the *TNFα* (–308 polymorphic gene, which is levels of circulating tumor

been associated with higher prevalence of MetS in Egyptians.¹⁶⁴

- The minor G allele of the atrial natriuretic peptide genetic variant rs5068, which is associated with higher levels of circulating ANP, has been associated with lower prevalence of MetS in White people and Black people.^{165–167}
- SNPs of inflammatory genes (encoding interleukin-6, interleukin-1 β , and interleukin-10) and plasma fatty acids, as well as interactions

randomization analysis in MetS, including tein B, and proto-oncogene receptor.

Prevention and Awareness of

- Despite the high prevalence of recognition of MetS was that the average MetS 36.7 $\pm$ 18.8 of a possible score of 100.¹⁷⁵

among these SNPs, are differentially associated with odds of MetS.¹⁶⁸

- A UK Biobank study of 291 107 individuals performed GWASs for the clustering of MetS traits and found 3 loci associated with all 5 MetS components (near *LINC0112*, *C5orf67*, and *GIP*), of which *C5orf67* has been associated with individual MetS

Morbidity and Mortality

Adults

CVD Morbidity and Mortality

- MetS had been associated with incident AF,^{176,177} HF,¹⁷⁸ and PAD.¹⁷⁹ The HR was 1.38 (95% CI, 1.36–1.39) for incident AF and 2.50 (95% CI, 1.68–3.40) for incident HF. The RR for incident PAD was 1.76 (95% CI, 1.05–2.92).
- MetS was associated with CVD morbidity and mor-tality. A meta-analysis of 87 studies comprising 951 083 subjects showed that MetS increased the risk of CVD (summary RR, 2.35 [95% CI, 2.02–2.73]), with significantly increased risks (RRs ranging from 1.6–2.9) for all-cause mortality, CVD mortality, MI, and stroke, even for those with MetS but without diabetes.¹⁸⁰
 - components.¹⁶⁹
 - Recently, 90 novel loci (cumulative 94 loci) have been identified for MASLD.¹⁷⁰ A total of 8 com-mon genetic loci (*MTARC1*, *ADH1B*, *TRIB1*, *GPAM*, *MAST3*, *TM6SF2*, *APOE*, and *PNPLA3*)
 - In the HAPIEE study of 4257 participants 45 to have also been identified for association with hepatic ste-atosis, a leading risk factor for cardiometabolic

72 years of age with a mean follow-up of 11 years, MetS increased the risk of a first CVD event among males (HR, 1.53 [95% CI, 1.18–1.97]) and females (HR, 1.56 [95% CI, 1.14–2.15]).¹⁸¹

- In the RIVANA Study, a Mediterranean population-based cohort of 3976 participants, individuals with diseases.¹⁷¹ MetS had an HR of 1.32 (95% CI, 1.01–1.74)

- A comprehensive GWAS, using the continuous parameters of MetS components such as fasting glucose, HDL-C, SBP, triglycerides, and WC, uncovered the shared genetic architecture of each component with MetS. This study identified 235 genomic loci, of which 174 loci were novel.¹⁷² Among the loci identified, 53 (22.5%) overlapped with loci associated with ≥ 2 components of MetS.
- An epigenome-wide association study of MetS including 1187 individuals of European ancestry examining 468 809 methylation sites identified 12 sites associated with MetS and 33 sites asso-

ciated with at least 1 component of MetS.¹⁷³ The cg19693031 methylation site in *TXNIP* was prioritized as a strong candidate for linking the individual components of MetS.

- A proteomics-based study of MetS including 1921 participants with prevalent MetS identified 116 proteins associated with prevalent MetS.¹⁷⁴ Mendelian

a rate advancement period (indicating prematurity of cardiovascular events occurrence) of 3.23 years (95% CI, 0.03–6.42 years) for MACEs and an HR of 1.64 (95% CI, 1.03–2.60) with rate advancement periods of 3.73 years (95% CI, 0.02–7.45 years) for cardiovascular mortality.¹⁸²

• In the INTERHEART case-control study of 26 903 subjects from 52 countries, MetS was associated with an increased risk of MI, according to both the WHO (OR, 2.69 [95% CI, 2.45–2.95]) and IDF (OR, 2.20 [95% CI, 2.03–2.38]) definitions, with a PAR of 14.5% (95% CI, 12.7%–16.3%) and 16.8% (95% CI, 14.8%–18.8%), respectively.

Associations were similar across all regions and ethnic groups. In addition, the presence of ≥ 3 versus < 3 elevated risk factors was associated with an increased risk of MI (OR, 1.50 [95% CI, 1.24–1.81]). Similar results were observed when the IDF definition was used.¹⁸³

- In the Three-City Study, among 7612 participants ≥ 65 years of age who were followed up for 5.2 years, MetS was associated with an increased risk of total CHD (HR, 1.78 [95% CI, 1.39–2.28]) and fatal CHD (HR, 2.40 [95% CI, 1.41–4.09]); however, MetS was not associated with CHD risk beyond its individual components.¹⁸⁴
- Among 3414 patients with stable CVD and atherogenic dyslipidemia who were of MetS nor the number of MetS components was associated with cardiovascular outcomes, including coronary events, ischemic stroke, nonfatal MI, CAD death, or the composite end point.¹⁸⁵
- In patients with chest pain undergoing invasive coronary angiography, presence of MetS and increasing number of MetS factors were independently associated with obstructive CAD in females (OR, 1.92 [95% CI, 1.31–2.81]) but not in males (OR, 0.97 [95% CI, 0.61–1.55]).¹⁸⁶
- In a meta-analysis of 16 studies including 116 496 participants who were initially free of CVD, those with MetS had an increased risk of stroke (pooled RR, 1.70 [95% CI, 1.49–1.95]) compared with those without MetS.¹⁸⁷ The magnitude of the effect was stronger among females (RR, 1.83 [95% CI, 1.31–2.56]) than males (RR, 1.47 [95% CI, 1.22–1.78]). The risk was higher for ischemic stroke (RR, 2.12 [95% CI, 1.46–3.08]) than hemorrhagic stroke (RR, 1.48 [95% CI, 0.98–2.24]).
- In a combined analysis from the ARIC and JHS studies, among 13 141 White individuals and Black individuals with a mean follow-up of 18.6 years, risk of ischemic stroke increased consistently with MetS severity z score (HR, 1.75 [95% CI, 1.35–2.27]) for those above the 75th percentile compared with those below the 25th percentile. Risk was highest for White females (HR, 2.63 [95% CI, 1.70–4.07]), although there was no significant interaction by sex with increased risk of all-cause in-hospital mortality (OR, 5.99 [95% CI, 1.02–35.15]).¹⁹¹
- In a meta-analysis of 20 prospective cohort studies that included 57 202 adults ≥ 60 years of age, MetS was associated with an increased risk of all-cause mortality (RR, 1.20 [95% CI, 1.05–1.38] for males; RR, 1.22 [95% CI, 1.02–1.44] for females)

across the studies (all-cause mortality, $I^2=55.9\%$, $P=0.001$; CVD mortality, $I^2=58.1\%$, $P=0.008$). In subgroup analyses, the association of MetS with CVD and all-cause mortality varied by geographic location, sample size, and definition of MetS and with adjustment for frailty.

- In a recent meta-analysis of 13 cohort studies comprising 59 919 participants >60 years of age, MetS was significantly associated with all-cause mortality (RR, 1.27 [95% CI, 1.18–1.36]).¹⁹⁰
- From the Taiwan NHIRD including 119 843 subjects, after propensity score matching, subjects with 3 to 4 MetS components had a significantly higher risk of all-cause mortality (HR, 1.13 [95% CI, 1.08–1.17]) than those with only 1 to 2 MetS components.¹⁹³ In addition, 3 to 4 MetS components (versus 1–2) led to greater all-cause mortality among those <65 years of age (OR, 1.35 [95% CI, 1.25–1.45]) in males (OR, 1.06 [95% CI, 1.01–1.12]) and females (OR, 1.20 [95% CI, 1.13–1.27]), individuals with (OR, 1.13 [95% CI, 1.06–1.20]) or without (OR, 1.13 [95% CI, 1.08–1.19]) CHD, those without CKD history (OR, 1.13 [95% CI, 1.09–1.18]), aspirin users (OR, 1.24 [95% CI, 1.17–1.31]) and nonusers (OR, 1.06 [95% CI, 1.00–1.12]), users of nonsteroidal anti-inflammatory drugs (OR, 1.18 [95% CI, 1.13–1.23]), and users of statins (OR, 1.54 [95% CI, 1.43–1.66]).
- The impact of MetS on mortality had been shown to and race.¹⁸⁸
- In the ARIC study, among 13 168 participants with a median follow-up of 23.6 years, MetS was independently associated with an increased risk of SCD (HR, 1.70 [95% CI, 1.37–2.12]; $P<0.001$).¹⁸⁹ The risk of SCD varied according to the number be modified by objective sleep duration.¹⁹⁴ According of MetS components (HR, 1.31 per 1 additional component of the MetS [95% CI, 1.19–1.44]; $P<0.001$) independently of race or sex.
- In a recent meta-analysis of 13 cohort studies com-

to data from the Penn State Adult Cohort, a pro-spective population-based study of 1344 males and females followed up for 16.6 years, the HRs of all-cause and CVD mortality associated with MetS were 1.29 (95% CI, 0.89–1.87) and 1.49 (95% CI, 0.75–2.97) for individuals who slept ≥ 6 hours and 1.99 (95% CI, 1.53–2.59) and 2.10 (95% CI, 1.39–3.16) for individuals who slept < 6 hours.

prising 59 919 participants > 60 years of age, MetS was significantly associated with stroke recurrence (RR, 1.46 [95% CI, 1.07–1.97]).¹⁹⁰

All-Cause Mortality

Complications

Youths

- In an International Childhood

Cardiovascular Cohort

- In patients with impaired LV systolic function (EF $< 50\%$) who underwent CABG, MetS was associated

cohort studies (Cardiovascular Risk in Young Finns, Bogalusa Heart Study, Princeton Lipid Research

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Study, and Minnesota Insulin follow-up period of 22.3 years, overweight were associated adult MetS from 5 years of for type 2 diabetes was years of age (RR, 2.6 [95% basis of international cutoff tion of childhood MetS. Risk

subclinical CKM (stages 1–3) 80.94%, 85.95%, and 72.03%.

- A novel CVD risk prediction was recommended by the CVD in the context of CKM would serve a central role in risk-based primary prevention individuals with CKM syndrome

increased beginning at 11 years of age (RR, 2.44 [95% CI, 1.55–3.55]) with the same definition.

- Among 2798 adolescents 11 to 19 years of age in the Tehran Lipid and Glucose Study with a mean follow-up of 11.3 years, those with MetS in adolescence had a 2.8 times increased hazard of incident type 2 diabetes in adulthood (incidence rate, 33.78 per 10 000 person-years; HR, 2.82 [95% CI, 1.41– 5.64]) independently of baseline age and sex, adult BMI, and family history of diabetes.¹⁹⁵

- Among 1757 youths from the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study, those with MetS in youth and adulthood were at 3.4 times increased risk of high carotid IMT and 12.2 times increased risk of type 2 diabetes in adulthood compared with those without MetS at either time.

Adults whose MetS had resolved after their youth did not have an increased risk of having high IMT or type 2 diabetes.¹⁹⁶

An analysis of 5803 participants in 4 cohort studies (Cardiovascular Risk in Young Finns, Bogalusa Heart Study, Princeton Lipid Research Study, Insulin

- CKM syndrome was defined in an AHA presidential advisory in 2023 as a health disorder attributable to connections among obesity, diabetes, CKD, and CVD, including HF, AF, CHD, stroke,

MetS and Subclinical CVD

- In MESA, among 6603 adults 45 to 84 years of age (1686 [25%] with MetS without diabetes and 881 [13%] with diabetes), subclinical atherosclerosis prevalence and progression assessed by CAC were

more severe in people with MetS and diabetes than in those without these conditions, and the extent and progression of CAC were strong predictors of CHD and CVD events in these groups.^{200,201} There

appears to be a synergistic relationship among MetS, MASLD, and prevalence of CAC,²⁰² as well as a synergistic relationship with smoking.²⁰³

- Individuals with MetS have a higher degree of endothelial dysfunction than individuals with a similar burden of traditional cardiovascular risk factors.²⁰⁴ The OR for the association of MetS with peripheral endothelial dysfunction was 2.06 ($P=0.009$).

Furthermore, individuals with both MetS and diabetes have demonstrated increased microvascular and macrovascular dysfunction.²⁰⁵ MetS was associated with increased thrombosis, including increased resistance to aspirin²⁰⁶ and

and PAD. CKM syndrome includes those at risk for CVD and

1.61 [95% CI, 1.29–2.01]; $P<0.0001$).²⁰⁸ Both cardio-ankle vascular index (OR, 1.34 [95% CI, 1.20–1.50] per 1.0-unit increase) and carotid IMT (OR, 1.31 [95% CI, 1.22–1.41] per 0.1-mm increase) were positively associated with the pres-

those with existing CVD.¹⁹⁷ The advisory provided CKM syndrome staging that features the following: stage 0, no CKM risk factors; stage 1, excess or dysfunctional adiposity; stage 2, metabolic risk factors (hypertriglyceridemia, hypertension, diabetes, MetS) or moderate- to high-risk CKD; stage 3, sub-

ence of MetS.²⁰⁹

clinical CVD in CKM syndrome or risk equivalents (high predicted CVD risk or very high-risk CKD); and stage 4, clinical CVD in CKM syndrome (Chart

- In modern imaging studies using echocardiography, MRI, cardiac CT, and positron emission tomogra-phy, MetS was closely related to increased epicar-dial adipose tissues²¹⁰; increased visceral fat²¹¹; increased ascending aortic diameter²¹²; high-risk coronary plaque features, including increased necrotic core²¹³; impaired coronary flow reserve²¹⁴; abnormal indexes of LV strain²¹⁵; LV diastolic dys-
 10-3).¹⁹⁷
 RV function²¹⁶; LV dyssynchrony²¹⁷; and subclinical
- In the NHANES 2011 to 2018 database, among 5.45%, and 1.80%, respectively,
 individuals 20 to 44, 45 to 64, and ≥65 years of and risk factors and
 age, stage 0 CKM was present in 17.35%,

dysfunction.²¹⁸ For example, the epicardial adipose thickness was higher in patients with MetS than in those without MetS (difference in means, 1.15 mm [95% CI, 0.78–1.53]).²¹⁰

MetS and Non-CVD Complications

Diabetes

• In data from ARIC and JHS, MetS was associated with an increased risk of diabetes (HR, 4.36 [95% CI, 3.83–4.97]), although the association was attenuated after adjustment for the individual components of MetS.²¹⁹ However, use of a continuous sex- and race-specific MetS severity z score was associated with an increased risk of diabetes that was independent of individual MetS components, with increases in this score over time conferring additional risk for diabetes. Among White men and women, compared with below the 25th percentile of a MetS severity score, the risk of incident diabetes was 0.97 (95% CI, 0.62–1.53) for the 25th to 50th percentiles, 1.29

Cancer

- MetS was associated with increased risk of cancer (in particular breast, endometrial, prostate, pancreatic, hepatic, colorectal, and renal cancers)^{224–226} and gastroenteropancreatic neuroendocrine tumors.²²⁷ A nationwide cohort study conducted among Korean individuals studied the changes in MetS status and breast cancer risk and found that, compared with the sustained non-MetS group, the aHR for breast cancer was 1.11 (95% CI, 1.04–1.19) in the transition to MetS group, 1.05 (95% CI, 0.96–1.14) in the transition to non-MetS group, and 1.18 (95% CI, 1.12–1.25) in the sustained MetS group.²²⁸ Another large, nested, case-control study among participants 18 to 64 years of age in the IBM MarketScan Commercial Database (2006–2015) suggested that MetS was associated with increased risk of early-onset (diagnosed before 50 years of age) colorectal cancer (OR, 1.25 [95% CI, 1.09–1.43]).²²⁹
- MetS was linked to poorer cancer outcomes, including increased risk of recurrence and over-all mortality.^{230,231} In a meta-analysis of 24 studies that included 132 589 males with prostate cancer (17.4% with MetS), MetS was associated with worse oncological outcomes, including biochemical recurrence and more aggressive tumor features.²³² Among 94 555 females free of cancer at baseline in the prospective NIH-AARP cohort, MetS was associated with increased risk of breast cancer mortality (HR, 1.73 [95% CI, 1.09–2.75]), particularly among postmenopausal females (HR, 2.07 [95% CI, 1.32–3.25]).²³³
- In a meta-analysis of 17 prospective longitudinal studies that included 602 195 females and 15 945 cases of breast cancer, MetS was associated with increased risk of incident breast cancer in postmenopausal females (RR, 1.25 [95% CI, 1.12–1.39]) but significantly reduced breast cancer risk in premenopausal females (RR, 0.82 [95% CI, 0.76–0.89]).²³⁴ The association between MetS and increased risk of breast cancer was observed only among White females and Asian females, whereas and incident (OR, 2.75 [95% CI, 1.45–6.05]) post-transplantation diabetes.²²²
- In RENIS-T6, which included 1627 people repre-

- Among 633 Chinese adults without diabetes receiving a first renal transplantation, presence of pretransplantation MetS was an independent predictor of prevalent (OR, 1.28 [95% CI, 1.04–1.51])

there was no association in Black females.

- In data obtained from HCUP, hospitalized patients with a diagnosis of MetS and cancer had significantly increased odds of adverse health outcomes, including increased postsurgical complications (OR, 1.20 [95% CI, 1.03–1.39] and 1.22 [95% CI, 1.09–1.37] for patients with breast and prostate cancer, respectively).²³⁵ representative of the general population without baseline self-reported CKD, CVD, or diabetes, MetS was associated with a mean 0.30-mL/min per year (95% CI, 0.02–0.58) faster decline in glomerular filtration rate than in individuals without MetS during

- In 25 038 Black individuals and White individuals in the REGARDS study, MetS was associated with increased risk of cancer-related mortality (HR, 1.22 [95% CI, 1.03–1.45]).²²⁴ For those with all 5 MetS components present, the risk of cancer mortality follow-up.²²³

was 59% higher than for
ponent present (HR, 1.59
• In NHANES III, MetS was
cancer mortality (HR, 1.33
and breast cancer mortality
1.09–4.11).²³⁶

Gastrointestinal

- MASLD, a spectrum of liver
from isolated fatty liver to fatty
mation (nonalcoholic
esized to represent the
MetS. According to data from
2014, the overall prevalence
US adults was 21.9%.²³⁷ The
MASLD was estimated to be
sectional studies, an increase
MetS components was
nonalcoholic steatohepatitis
in MASLD in adults and
- MetS has been associated
tal adenomas,²⁴¹ acute
esophagus.²⁴³

Other

- Among 725 Chinese adults ≥ 90 years of age,
MetS was associated with prevalent
disability in activities of daily living (OR, 1.65
[95% CI, 1.10–3.21]) and instrumental
activities of daily living (OR, 2.09 [95%
CI, 1.17–4.32]).²⁴⁴
- In a cross-sectional analysis of data from the
PREDIMED-Plus multicenter randomized trial,
MetS was associated with adverse health-
related quality of life as measured by
the Short Form-36 in the aggregated physical
dimensions, body pain in females, and
general health in males; however, this
adverse association was absent for the psychologi-
cal dimensions of health-related quality of life.²⁴⁵
- MetS was associated with dementia²⁴⁶ (particu-
larly Alzheimer dementia²⁴⁷), cognitive decline,²⁴⁸
and lower cognitive performance in older adults
at risk for cognitive decline.²⁴⁹ For example, dur-
ing the mean follow-up of 4.9 years, the aHRs in

AD, and 1.38 (95% CI, 1.32–
dementia.

- MetS was associated with
sity and, in some but not all
of bone fractures, depending
MetS used, fracture site, and
with excess weight and MetS
lower transformed bone
centrations of bone alkaline
calcin, and carboxy-terminal
with the matched group,
male adolescents; thus, bone
tion may be affected.²⁵²
- In males, MetS had been
decreased sperm total count,
tion, sperm normal
motility, sperm vitality, and
increase in sperm DNA
chondrial membrane
ute to male infertility.²⁵³
- MetS and its components were
more severe infection with
risk for poor outcomes in

a non-MetS group who progressed to
having MetS compared with the
sustained non-MetS group were
1.11 (95% CI, 1.08–1.13) for total
dementia, 1.08 (95% CI,
1.05–1.11) for AD, and 1.20 (95% CI,
1.13–1.28) for vascular dementia.²⁴⁶
The aHRs in the improved group
(MetS to normal) compared with
the sustained normal group were 1.12
(95% CI, 1.10–1.15) for
total dementia, 1.10 (95% CI,
1.07–1.13) for AD, and 1.19 (95% CI,
1.12–1.27) for vascular
dementia. The aHRs in the sustained
group (MetS to MetS) compared with
the sustained normal
group were 1.18 (95% CI, 1.16–1.20)
for total dementia, 1.13 (95% CI,
1.11–1.15) for

Cost and Health Care Use

- The medical costs of subjects with MetS for 5 years were 2.16 times higher than for those without MetS (\$15 699 versus \$7274; $P<0.001$); medical costs were higher with a greater number of risk factors (\$2285, \$3154, \$4277, \$5888, \$7391, \$8466 for those with 0–6 MetS components; $P<0.001$).²⁵⁸• The presence of MetS increased the risk for post-operative complications, including prolonged hospital stay and risk for postsurgical complications (OR, 1.20 [95% CI, 1.03–1.09] and 1.22 [95% CI, 1.09–1.37] for patients with breast and prostate cancer with MetS undergoing tumor removal, respectively), blood transfusion, surgical site infection, and respiratory failure, across various surgical populations.^{235,259–261}

Global Burden of MetS

(See Chart 10-4)

- MetS has become hyperendemic around the world. Published evidence has described the prevalence of MetS in Aruba,²⁶² India,²⁶³ Bangladesh,²⁶⁴ Iran,^{265,266} Ghana,²⁶⁷ the Gaza Strip,²⁶⁸ Jordan,²⁶⁹ and Ethiopia,^{270,271} as well as many other countries. Chart 10-4 shows the prevalence of MetS by different definitions and by WHO region from a meta-analysis published in 2021.¹³
- Global prevalence of MetS in military personnel was estimated at 21% (95% CI, 17%–25%; N=37

studies: 15 in America, 13 in Europe, and 9 in Asia) between 2001 and 2017.²⁷²

- MetS among children and adolescents is an emerging public health challenge in low- to middle-income countries. In a meta-analysis including data from 76 studies with 142 142 children and adolescents residing in low- to middle-income countries, the pooled prevalence of MetS was 4.0% (IDF), 6.7% (ATP III), and 8.9% (de Ferranti et al criteria, respectively).²⁷³
- A systematic review synthesized the prevalence of MetS using data published between 2014 and 2019 according to different definitions in the pediatric population across the world.⁹

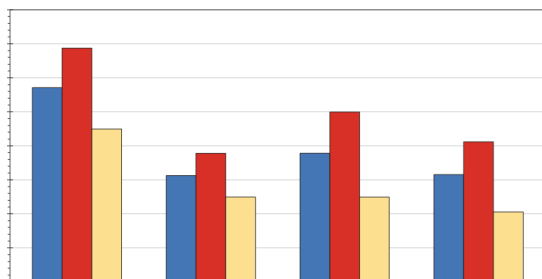
- The prevalence of MetS in Mexican adults according to the harmonized definition was 40.2% in 2006,

57.3% in 2012, 59.99% in 2016, and 56.31% in 2018 ($P_{\text{trend}} < 0.0001$).²⁷⁵

- The prevalence of MetS in Brazil was 28% in 2005 to 2009, 35% in 2010 to 2014, and 31% in 2015 to 2019.

The pooled prevalence was 34% in urban, 15% in rural, 28% in

According to the IDF, the prevalence of MetS was 3.1% to 5.4% in the United States, 2.1% in Canada, 0.3% to 0.9% in Colombia, 1.5% in Venezuela, 2.1% to 2.6% in Brazil, 9.5% in Chile, 0.4% to 2.7% in Europe, 3.8% in Spain, 1.9% in South Africa, 1.1% to 7.6% in China, 1.0 to 2.1% in Korea, 2.6% in Malaysia, 2.0% in Saudi Arabia, 8.4% in Iran, and 2.7% in Australia.



Asia and Middle East

- The prevalence of MetS among Chinese adults ≥ 20 years of age in 2015 to 2017 was 31.1%, with a significantly higher prevalence in women than in men (32.3% versus 30.0%).²⁷⁷ The highest prevalence was in participants ≥ 75 years of age (44.2%), and the lowest prevalence was in participants 20 to 44 years of age (23.3%). The prevalence in the north (35.9%) was higher than in the south (27.4%).
- In a meta-analysis of cross-sectional studies that assessed the prevalence of MetS in 15 Middle Eastern countries, the pooled prevalence estimate for MetS was 31.2% (95% CI, 28.4%–33.9%).

Latin America

- In a meta-analysis of 10 191 participants across 6 studies, the prevalence of MetS in Argentina was Pooled prevalence estimates ranged from a low of 27.5% (95% CI, 21.3%–34.1%), and the prevalence was higher in males than in females (29.4%)

23.6% in Kuwait to as high as 40.1% in the United Arab Emirates, depending on the time frame, coun-try studied, and definition of MetS used. There was high heterogeneity among the 61 included studies.²⁷⁸

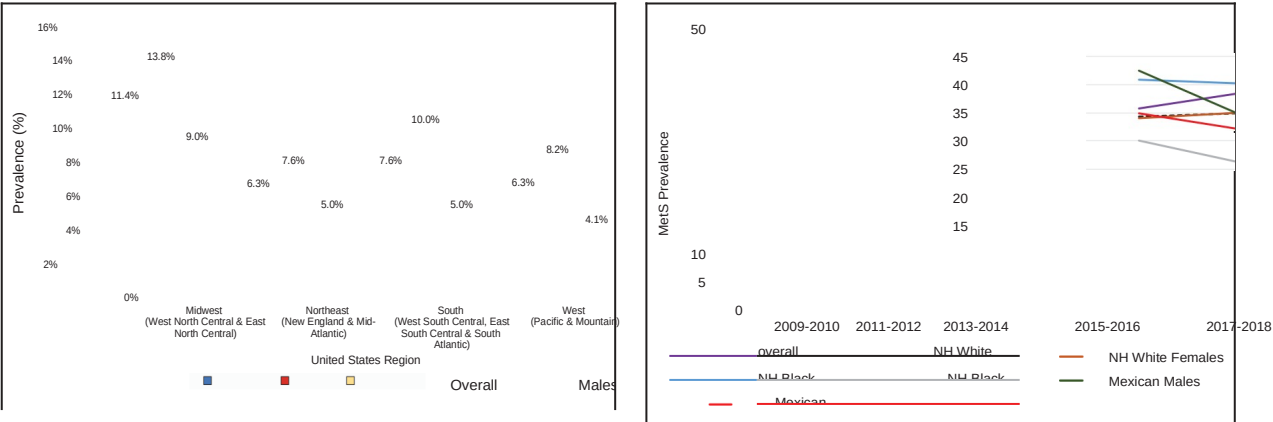


Chart 10-1. Prevalence of MetS by sex and US region among adolescents 12 to 19 years of age (NHANES 1999–2014).

MetS indicates metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.
Source: Data derived from DeBoer et al.²⁷⁹

Chart 10-2. Prevalence of MetS among US adults using the harmonized MetS criteria (NHANES 2009–2018).

MetS was defined using the criteria agreed to jointly by the IDF; the NHLBI; the AHA; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity.

AHA indicates American Heart Association; IDF, International Diabetes Federation; MetS, metabolic syndrome; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and NHLBI, National Heart, Lung, and Blood Institute.

Source: Data courtesy of Junxiu Liu using NHANES.²⁸⁰

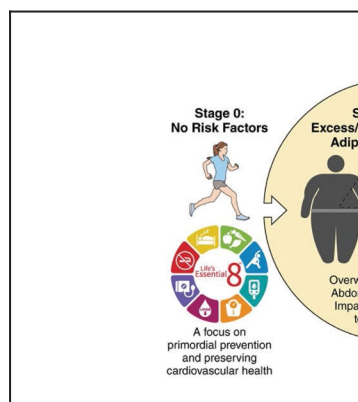


Chart 10-3. Stages of CKM syndrome.

The CKM staging construct reflects the progressive pathophysiology and increasing absolute CVD risk along the spectrum of CKM syndrome.

Stage 0 CKM includes individuals with normal weight, normal glucose, normal BP, normal lipids, normal kidney function, and no evidence of subclinical or clinical CVD; the focus in stage 0 CKM is primordial prevention and preserving CVH. Stage 1 CKM includes individuals with excess adipose tissue, dysfunctional adipose tissue, or both. Excess adiposity is identified by either weight or abdominal obesity, and dysfunctional adipose tissue is reflected by impaired glucose tolerance and hyperglycemia. Stage 2 includes individuals with metabolic risk factors (hypertriglyceridemia, hypertension, MetS, or type 2 diabetes), moderate- to high-risk CKD, or both. Although hypertension and CKD are usually downstream of metabolic risk factors, curved arrows represent individuals with nonmetabolic causes of these conditions; the risk implications and treatment approaches are similar. Stage 3 includes individuals with subclinical CVD with overlapping CKM risk factors (excess/dysfunctional adipose tissue, metabolic risk factors, or CKD) or those with the risk equivalents of very high-risk CKD or high predicted risk using the forthcoming CKM risk calculator. Stage 4 includes individuals with clinical CVD (CHD, HF, stroke, PAD, or Afib) overlapping with CKM risk factors.

Afib indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CKM, cardio-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; MetS, metabolic syndrome; and PAD, peripheral artery disease.

Source: Reprinted from Ndumele et al.¹⁹⁷ Copyright © 2023 American Heart Association, Inc.

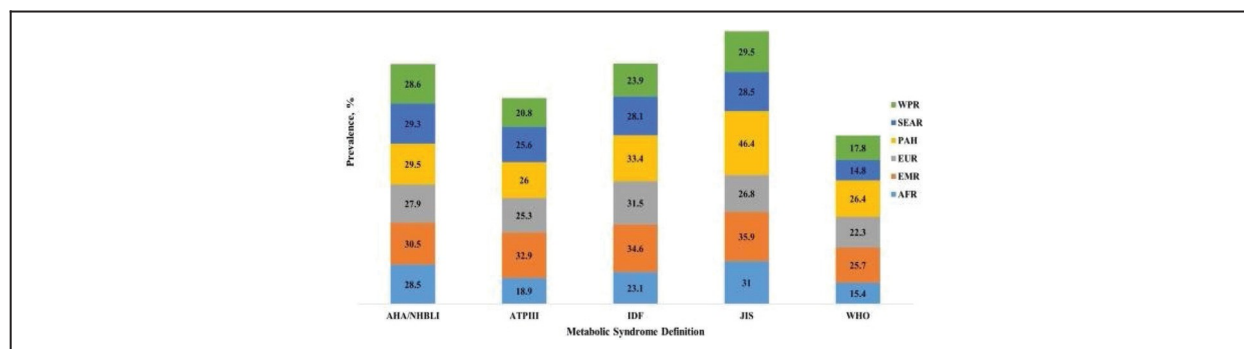


Chart 10-4. Meta-analysis prevalence of MetS, by different definitions and by WHO region.

AFR indicates Africa region; AHA, American Heart Association; ATP-III, Adult Treatment Panel III of the National Cholesterol Education Program; EMR, Eastern Mediterranean Region; EUR, European Region; IDF, International Diabetes Federation; JIS, Joint Interim Statement; MetS, metabolic syndrome; NHLBI, National Heart, Lung, and Blood Institute; PAH, Region of the Americas; SEAR, South-East Asia Region; WHO, World Health Organization; and WPR, Western Pacific Region.

REFERENCES

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. Harmonizing the meta-bolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644
2. Chirinos DA, Llabre MM, Goldberg R, Gellman M, Mendez A, Cai J, Sotres-Alvarez D, Daviglus M, Gallo LC, Schneiderman N. Defining abdominal obesity as a risk factor for coronary heart disease in the U.S.: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes Care*. 2020;43:1774–1780. doi: 10.2337/dc19-1855
3. Mendrick DL, Diehl AM, Topor LS, Dietert RR, Will Y, La Merrill MA, Bouret S, Varma V, Hastings KL, Schug TT, et al. Metabolic syndrome and associated diseases: from the bench to the clinic. *Toxicol Sci*. 2018;162:36–42. doi: 10.1093/toxsci/kfx233
15. Coello K, Vinberg M, Knop FK, Munkholm K. Metabolic disorder and their unaffected first-degree relatives. *Dev Med Child Neurol*. 2019;7:93. doi: 10.1080/10790268.2017.1423266
16. Thoenes 33. Gater DR Jr, Farkas GJ, Berg AS, Castillo C. Prevalence of metabolic syndrome in veterans with spinal cord injury. *J Spinal Cord Med*. 2018;42:86–93. doi: 10.1080/10790268.2017.1423266
17. Bielorai B, Pinhas-Hamiel O. Type 2 diabetes mellitus, the metabolic syndrome, and its components in adult survivors of acute lymphoblastic leukemia and hematopoietic stem cell transplantations. *Curr Diab Rep*. 2018;18:32. doi: 10.1007/s11892-018-0998-0
18. Masenga SK, Elijovich F, Koethe JR, Hamooya BM, Heimbürger DC, Munsaka SM, Laffer CL, Kirabo A. Hypertension and metabolic syndrome in persons with HIV. *Curr Hypertens Rep*. 2020;22:78. doi: 10.1007/s11906-020-01089-3
19. Ahmed MES, Elnaby HEHA, Hussein MAR, Abo-Ghabsha ME. Metabolic syndrome in patients with chronic obstructive pulmonary disease. *Egyptian J Chest Dis Tuberculosis*. 2020;69:316–322. doi: 10.4103/ejcdt.ejcdt_142_19
20. Oudin C, Berbis J, Bertrand Y, Vercasson C, Thomas F, Chastagner P, Ducassou S, Kanold J, Tabone MD, Paillard C, et al. Prevalence and characteristics of metabolic syndrome in adults from the French childhood leukemia survivors' cohort: a comparison with controls from the French population. *Haematologica*. 2018;103:645–654. doi: 10.3324/haematol.2017.176123
21. Fernandez-Armenteros JM, Gomez-Arbonex X, Buti-Soler M, Betriu-Bars A, Sanmartín-Novell V, Ortega-Bravo M, Martínez-Alonso M, Gari E, Portero-Otin M, Santamaria-Babi L, et al. Psoriasis, metabolic syndrome and cardiovascular risk factors: a population-based study. *J Eur Acad Dermatol Venereol*. 2019;33:128–135. doi: 10.1111/jdv.15159
22. Liu M, Huang Y, Huang Z, Huang Q, Guo X, Wang Y, Deng W, Huang Z, Li T. Prevalence of metabolic syndrome and its associated factors in Chinese patients with ankylosing spondylitis. *Diabetes Metab Syndr Obes*. 2019;12:477–484. doi: 10.2147/DMSO.S197745
23. Bhattacharya PK, Barman B, Jamil M, Bora K. Metabolic syndrome and atherogenic indices in rheumatoid arthritis and their relationship with disease activity: a hospital-based study from northeast India. *J Transl Internal Med*. 2020;8:99–105. doi: 10.2478/jtim-2020-0015
24. Simonienė D, Platukienė A, Prakupienė E, Radzeviciene L, Velickiene D. Insulin resistance in type 1 diabetes mellitus and its association with patient's micro- and macrovascular complications, sex hormones, and other clinical data. *Diabetes Ther*. 2020;11:161–174. doi: 10.1007/s13300-019-00729-5
25. Li X, Cao C, Tang X, Yan X, Zhou H, Liu J, Ji L, Yang X, Zhou Z. Prevalence of metabolic syndrome and its determinants in newly-diagnosed adult-onset diabetes in China: a multi-center, cross-sectional survey. *Front Endocrinol (Lausanne)*. 2019;10:661. doi: 10.3389/fendo.2019.00661
26. Kaiser K, Nielsen MF, Kalfia E, Dubietyte G, Lauszus FF. Metabolic syndrome in women with previous gestational diabetes. *Sci Rep*. 2021;11:11558. doi: 10.1038/s41598-021-90832-0
27. Ehrenthal DB, McNeil RB, Crenshaw EG, Bairey Merz CN, Grobman WA, Parker CB, Greenland P, Pemberton VL, Zee PC, Scifres CM, et al. Adverse pregnancy outcomes and future metabolic syndrome. *J Womens Health (Larchmt)*. 2023;32:932–941. doi: 10.1089/jwh.2023.0026
28. Kridin K, Solomon A, Tzur-Bitan D, Damiani G, Comaneshter D, Cohen AD. Acne keloidalis nuchae and the metabolic syndrome: a population-based study. *Am J Clin Dermatol*. 2020;21:733–739. doi: 10.1007/s40257-020-00541-z
29. Montero E, Molina A, Carasol M, Fernández-Meseguer A, Calvo-Bonacho E, Teresa García-Margallo M, Sanz M, Herrera D. The association between metabolic syndrome and periodontitis in Spain: results from the WORALTH (Workers' ORAL health) Study. *J Clin Periodontol*. 2021;48:38–50. doi: 10.1111/jcpe.13391
30. Gobin R, Tian D, Liu Q, Wang J. Periodontal diseases and the risk of metabolic syndrome: an updated systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2020;11:336. doi: 10.3389/fendo.2020.00336
31. Almobarak AO, Jervase A, Fadl AA, Garelnabi NIA, Hakem SA, Hussein TM, Ahmad AAA, El-Den Ahmed IS, Badi S, Ahmed MH. The prevalence of diabetes and metabolic syndrome and associated risk factors in Sudanese individuals with gallstones: a cross sectional survey. *Transl Hepatol*. 2020;5:14. doi: 10.21037/TGH.2019.10.09
32. Heyn PC, Tagawa A, Pan Z, Thomas S, Carollo JJ. Prevalence of metabolic syndrome and cardiovascular disease risk factors in adults with cerebral palsy. *Dev Med Child Neurol*. 2019;61:477–483. doi: 10.1111/dmcn.14148
33. Gater DR Jr, Farkas GJ, Berg AS, Castillo C. Prevalence of metabolic syndrome in veterans with spinal cord injury. *J Spinal Cord Med*. 2018;42:86–93. doi: 10.1080/10790268.2017.1423266
34. Dwivedi S, Purohit P, Nebhinani N, Sharma P. Effect of severity of opiate use on cardiometabolic profile of chronic opiate dependents of western Rajasthan. *Indian J Clin Biochem*. 2019;34:280–287. doi: 10.1016/j.itra.2019.10.009

35. Chen MS, Breavale BMJ. 54. Fabiani R, Naldini G, Chiavarini M. Dietary patterns and metabolic syndrome in adult subjects: a systematic review and meta-analysis. *Nutrients*. 2019;11:2056. doi: 10.3390/nu11092056

36. Hozawa and in small- 10.2302 55. Ushula TW, Mamun A, Darssan D, Wang WYS, Williams GM, Whitino SJ, Naiman JM. Dietary patterns and the risks of metabolic syndrome and insulin resistance among young adults: evidence from a longitudinal study. *Clin Nutr*. 2022;41:1523–1531. doi: 10.1016/j.clnu.2022.05.006

37. Robbins 10.1097 56. Kouvari M, Panagiotakos DB, Naumovski N, Chrysoschoou C, Georgousopoulou EN, Yannakoulia M, Tousoulis D, Pitsavos C. Dietary anti-inflammatory index, metabolic syndrome and transition in metabolic status: a gender-specific analysis of ATTICA prospective study. *Diabetes Res Clin Pract*. 2020;161:108031. doi: 10.1016/j.diabres.2020.108031

38. Moore JX, race/ 10 5888 57. Canto-Osorio F, Denova-Gutierrez E, Sánchez-Romero LM, Salmerón J, Barrientos-Gutierrez T. Dietary Inflammatory Index and metabolic syndrome in Mexican adult population. *Am J Clin Nutr*. 2020;112:373–380. doi: 10.1093/ajcn/nqaa135

39. Palmer MK, Toth PP. Trends in lipids, obesity, metabolic syndrome, and diabetes mellitus in the United States: an NHANES analysis (2003-2004 to 2013-2014). *Obesity (Silver Spring)*. 2019;27:309–314. doi:

58. Gallardo-Alfaro L, Bibiloni MM, Mascaró CM, Montemayor S, Ruiz-Canela M, Salas-Salvadó J, Corella D, Fitó M, Romaguera D, Vioque J, et al. Leisure-time physical activity, sedentary behaviour and diet quality are associated with metabolic syndrome severity: the PREDIMED-Plus study. *10.1002/oby.22370*
40. Zhang Y, Qi H, Hu C, Wang S, Zhu Y, Lin H, Lin L, Zhang J, Wang T, Zhao Z, et al. Association between early life famine exposure and risk of metabolic syndrome in later life. *J Diabetes*. 2022;14:685–694. doi: 10.1111/1753-0407.13319
41. Xu Y, Hua J, Wang J, Shen Y. Sleep duration is associated with metabolic syndrome in adolescents and children: a systematic review and meta-analysis. *J Clin Sleep Med*. 2023;19:1835–1843. doi: 10.5664/jcsm.10622
42. Mohite S, Wu H, Sharma S, Lavagnino L, Zeni CP, Currie TT, Soares JC, Pigott TA. Higher prevalence of metabolic syndrome in child- adolescent patients with bipolar disorder. *Clin Psychopharmacol Neurosci*.

- Nutrients*. 2020;12:1013. doi: 10.3390/nu12041013
59. Zhang X, Li X, Liu L, Hong F, Zhao H, Chen L, Zhang J, Jiang Y, Zhang J, Luo P. Dose-response association between sugar- and artificially sweetened beverage consumption and the risk of metabolic syndrome: a meta-analysis of population-based epidemiological studies. *Public Health Nutr*. 2021;24:3892–3904. doi: 10.1017/S1368980020003614
 60. Akter S, Akhter H, Chaudhury HS, Rahman MH, Gorski A, Hasan MN, Shin Y, Rahman MA, Nguyen MN, Choi TG, et al. Dietary carbohydrates: pathogenesis and potential therapeutic targets to obesity-associated metabolic syndrome. *Biofactors*. 2022;48:1036–1059. doi: 10.1002/biof.1886
 43. Gepstein V, Weiss R. Obesity as the main risk factor for metabolic syndrome in children. *Front Endocrinol (Lausanne)*. 2019;10:568. doi: 10.3389/fendo.2019.00568
 44. Li Y, Wang D, Wang Y, Zhao Y, Han L, Zhong L, Zhang Q, Speakman JR, Li M, Gao S. Impact of parental smoking on adipokine profiles and cardiometabolic risk factors in Chinese children. *Atherosclerosis*. 2020;301:23–29. doi: 10.1016/j.atherosclerosis.2020.03.023
 45. Zhang JS, Gui ZH, Zou ZY, Yang BY, Ma J, Jing J, Wang HJ, Luo JY, Zhang X, Luo CY, et al. Long-term exposure to ambient air pollution and metabolic syndrome in children and adolescents: a national cross-sectional study in China. *Environ Int*. 2021;148:106383. doi: 10.1016/j.envint.2021.106383
 46. Franks PW, Ekelund U, Brage S, Wong MY, Wareham NJ. Does the association of habitual physical activity with the metabolic syndrome differ by level of cardiorespiratory fitness? *Diabetes Care*. 2004;27:1187–1193. doi: 10.2337/diacare.27.5.1187
 47. Okuda M, Fujiwara A, Sasaki S. Added and free sugars intake and metabolic biomarkers in Japanese adolescents. *Nutrients*. 2020;12:2046. doi: 10.3390/nu12042046

61. Julibert A, Bibiloni MDM, Bouzas C, Martinez-Gonzalez MA, Salas-Salvado J, Corella D, Zomeno MD, Romaguera D, Vioque J, Alonso-Gomez AM, et al; PREDIMED-Plus Investigators. Total and subtypes of dietary fat intake and its association with components of the metabolic syndrome in a Mediterranean population at high cardiovascular risk. *Nutrients*. 2019;11:1493. doi: 10.3390/nu11071493
62. Kim Y, Je Y. Meat consumption and risk of metabolic syndrome: results from the Korean population and a meta-analysis of observational studies. *Nutrients*. 2018;10:390. doi: 10.3390/nu10040390
63. Luan D, Wang D, Campos H, Baylin A. Red meat consumption and metabolic syndrome in the Costa Rica Heart Study. *Eur J Nutr*. 2019;59:185–193. doi: 10.1007/s00394-019-01898-6
64. Kim H, Lee K, Rebholz CM, Kim J. Plant-based diets and incident metabolic syndrome: results from a South Korean prospective cohort study. *PLoS Med*. 2020;17:e1003371. doi: 10.1371/journal.pmed.1003371
65. Song YM, Lee K. Eating behavior and metabolic syndrome over time. *Eating Weight Disord*. 2019;25:545–552. doi: 10.1007/s40519-019-00640-9
66. Yoon C, Jacobs DR, Duprez DA, Neumark-Sztainer D, Steffen LM, Mason
48. Martinez Steele E, Juul F, Neri D, Rauber F, Monteiro CA. Dietary share of ultra-processed foods and metabolic syndrome in the US adult population. *Prev Med*. 2019;125:40–48. doi: 10.1016/j.ypmed.2019.05.004

- SM. Problematic eating behaviors and attitudes predict long-term incident metabolic syndrome and diabetes: the Coronary Artery Risk Development in Young Adults study. *Int J Eat Disord.* 2019;52:304–308.
49. Renninger M, Hansen BH, Steene-Johannessen J, Kriemler S, Froberg doi: 10.1002/eat.23020
K, Northstone K, Sardinha L, Anderssen SA, Andersen LB, Ekelund U; International Children's Accelerometry Database (ICAD) Collaborators. Associations between accelerometry measured physical activity and sedentary time and the metabolic syndrome: a meta-analysis of more than 6000 children and adolescents. *Pediatric Obesity.* 2020;15:e12578. doi:

67. Wei B, Liu Y, Lin X, Fang Y, Cui J, Wan J. Dietary fiber intake and risk of metabolic syndrome: a meta-analysis of observational studies. *Clin Nutr*. 2017;37:1935–1942. doi: 10.1016/j.clnu.2017.10.019
68. Franquesa M, Pujol-Busquets G, Garcia-Fernandez E, Rico L, Shamirian-Pulido L, Aguilar-Martinez A, Medina FX, Serra-Majem L, Bach-Faig A. Mediterranean diet and cardiometabolic risk: a systematic review. *Diabetol Metab Syndr*. 2019;11:40. doi: 10.1186/s13098-019-0435-9
50. Lin S, Tang L, Jiang R, Chen Y, Yang S, Li L, Li P. The relationship between aspartate aminotransferase to alanine aminotransferase ratio and metabolic syndrome in adolescents in northeast China. *Diabetes Metab Syndr Obes*. 2019;12:2387–2394. doi: 10.2147/DMSO.S217127
51. Xie S, Jiang R, Xu W, Chen Y, Tang L, Li L, Li P. The relationship between serum-free insulinlike growth factor-1 and metabolic syndrome in school adolescents of northeast China. *Diabetes Metab Syndr Obes*. 2019;12:305–313. doi: 10.2147/dmso.s195625
52. Sparrenberger K, Sbaraini M, Cureau FV, Teló GH, Bahia L, Schaan BD. Higher adiponectin concentrations are associated with reduced metabolic syndrome risk independently of weight status in Brazilian adolescents. *Diabetol Metab Syndr*. 2019;11:40. doi: 10.1186/s13098-019-0435-9
53. Gomez JAM, Moreno-Masclareño D, Rojo CEA, de la Peña GD. Association of total and high molecular weight adiponectin with components of metabolic syndrome in Mexican children. *J Clin Res Pediatr Endocrinol*. 2020;12:180–188. doi: 10.4274/jcrpe.galenos.2019.2019.0113

view through evidence-based answers to key clinical questions. *Nutrients*. 2019;11:655. doi: 10.3390/nu11030655

69. Lim M, Kim J. Association between fruit and vegetable consumption and risk of metabolic syndrome determined using the Korean Genome and Epidemiology Study (KoGES). *Eur J Nutr*. 2020;59:1667–1678. doi: 10.1007/s00394-019-02021-5

70. Hidayat K, Yu L-G, Yang J-R, Zhang X-Y, Zhou H, Shi Y-J, Liu B, Qin L-Q. The association between milk consumption and the metabolic syndrome: a cross-sectional study of the residents of Suzhou, China and a meta-analysis. *Br J Nutr*. 2020;123:1013–1023. doi: 10.1017/S0007114520000227

71. Koyama T, Maekawa M, Ozaki E, Kuriyama N, Uehara R. Daily consumption of coffee and eating bread at breakfast time is associated with lower visceral adipose tissue and with lower prevalence of both visceral obesity and metabolic syndrome in Japanese populations: a cross-sectional study. *Nutrients*. 2020;12:3090. doi: 10.3390/nu12103090

72. Lee K, Kim J. Serum vitamin D status and metabolic syndrome: a systematic review and dose-response meta-analysis. *Nutr Res Pract*. 2021;15:329–345. doi: 10.4162/nrp.2021.15.3.329
73. Zhang Y, Zhang DZ. Relationship between nut consumption and metabolic syndrome: a meta-analysis of observational studies. *J Am Coll Nutr*. 2019;38:499–505. doi: 10.1080/07315724.2018.1561341
74. Jang H, Park K. Omega-3 and omega-6 polyunsaturated fatty acids and metabolic syndrome: a systematic review and meta-analysis. *Clin Nutr*. 2020;39:765–773. doi: 10.1016/j.clnu.2019.03.032
75. Zhang D, Liu X, Liu Y, Sun X, Wang B, Ren Y, Zhao Y, Zhou J, Han C, Yin L, et al. Leisure-time physical activity and incident metabolic syndrome: a systematic review and dose-response meta-analysis of cohort studies. *Metabolism*. 2017;75:36–44. doi: 10.1016/j.metabol.2017.08.001
76. Wu J, Zhang H, Yan L, Shao J, Chen D, Cui N, Tan L, Fu Y, Xue E.
77. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, Liu S, Song Y. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4:e002014. doi: 10.1161/jaha.115.002014
78. Said MA, Abdelmoneim MA, Alibrahim MS, Kotb AAH. Aerobic training, resistance training, or their combination as a means to fight against excess weight and metabolic syndrome in obese students: which is the most effective modality? A randomized controlled trial. *Appl Physiol Nutr Metab*. 2019;14:1000–1008. doi: 10.1139/apnm-2018-0100
90. Yuan H, Yu C, Li X, Sun L, Zhu X, Zhao C, Zhang Z, Yang Z. Serum uric acid levels and risk of metabolic syndrome: a dose-response meta-analysis of prospective studies. *J Clin Endocrinol Metab*. 2015;100:4198–4207. doi: 10.1210/jc.2015-2527
91. Hao H, Guo H, Ma RL, Yan YZ, Hu YH, Ma JL, Zhang XH, Wang XP, Wang K, Mu LT, et al. Association of total bilirubin and indirect bilirubin content with metabolic syndrome among Kazakhs in Xinjiang. *BMC Endocr Disord*. 2020;20:110. doi: 10.1186/s12902-020-00563-y
92. Jung ES, Choi EK, Park BH, Chae SW. Serum follicle-stimulating hormone levels are associated with cardiometabolic risk factors in post-menopausal Korean women. *J Clin Med*. 2020;9:1161. doi: 10.3390/jcm9041161
93. Chen E, Burrows R, Correa P, Güichapani CG. 2021;46:952–963. doi: 10.1139/apnm-2020-0972
79. Kelley E, Imboden MT, Harber MP, Finch H, Kaminsky LA, Whaley MH. Cardiorespiratory fitness is inversely associated with clustering of metabolic syndrome risk factors: the Ball State Adult Fitness Program Longitudinal Lifestyle Study. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2:155–164. doi: 10.1016/j.mayocpiqo.2018.03.001
80. Sagawa N, Rockette-Wagner B, Azuma K, Ueshima H, Hisamatsu T, Takamiya T, El-Saed A, Miura K, Kriska A, Sekikawa A. Physical activity levels in American and Japanese men from the ERA-JUMP study and associations with metabolic syndrome. *J Sport Health Sci*. 2019;9:170–178.

with incidence of metabolic syndrome in 47 379 Korean adults. *J Diabetes*.

2019;11:402–409. doi: 10.1111/1753-0407.12868

95. Koskinen J, Magnussen CG, Sinaiko A, Woo J, Urbina E, Jacobs DR Jr, Steinberger J, Prineas R, Sabin MA, Burns T, et al. Childhood age and associations between childhood metabolic syndrome and adult risk for metabolic syndrome, type 2 diabetes mellitus and carotid intima media thickness: the International Childhood Cardiovascular Cohort Consortium. *J Am Heart Assoc*. 2017;6:e005632. doi: 10.1161/jaha.117.005632
96. Gui J, Li Y, Liu H, Guo LL, Li J, Lei Y, Li X, Sun L, Yang L, Yuan T, et al. Obesity- and lipid-related indices as a predictor of obesity metabolic syndrome in a national cohort study. *Front Public Health*. 2023;11:1073824. doi: 10.3389/fpubh.2023.1073824
97. Zhang M, Chen J, Yin Z, Wang L, Peng L. The association between depression and metabolic syndrome and its components: a bidirectional two-sample mendelian randomization study. *Transl Psychiatry*. 2021;11:633. doi: 10.1038/s41398-021-01759-z
98. Moradi Y, Albatineh AN, Mahmoodi H, Gheshlagh RG. The relationship between depression and risk of metabolic syndrome: a meta-analysis of observational studies. *Clin Diabetes Endocrinol*. 2021;7:4. doi: 10.1016/j.jshs.2019.09.007 10.1186/s40842-021-00117-8
81. Zajac-Gawlak I, Pelclova J, Groffik D, Pridalova M, Nawrat-Szoltysik A, Kroemeke A, Gaba A, Sadowska-Krepa E. Does physical activity lower the risk for metabolic syndrome: a longitudinal study

99. Jeon SW, Lim SW, Shin DW, Ryu S, Chang Y, Kim SY, Oh KS, Shin YC, Kim YH. Metabolic syndrome and incident depressive symptoms in young and middle-aged adults: a cohort study. *J Affect Disord.* 2019;246:643–651. doi: 10.1016/j.jad.2018.12.073
- 10.1186/s12877-020-01952-7
82. Xie J, Li Y, Zhang Y, Vgontzas AN, Basta M, Chen B, Xu C, Tang X. Sleep duration and metabolic syndrome: an updated systematic review and meta-analysis. *Sleep Med Rev.* 2021;59:101451. doi: 10.1016/j.smr.2021.101451
83. Hong GB, Gao PC, Chen YY, Xia Y, Ke XS, Shao XF, Xiong CX, Chen HS, Xiao H, Ning J, et al. High-sensitivity c-reactive protein leads to increased incident metabolic syndrome in women but not in men: a five-year follow-up study in a Chinese population. *Diabetes Metab Syndr Obes.* 2020;13:581–590. doi: 10.2147/DMSO.S241774
84. Cho Y, Lee SY. Useful biomarkers of metabolic syndrome. *Int J Environ Res Public Health.* 2022;19:15003. doi: 10.3390/ijerph192215003
85. Son DH, Lee HS, Lee YJ, Lee JH, Han JH. Comparison of triglyceride-

100. Liu SY, Zhu WT, Chen BW, Chen YH, Ni GX. Bidirectional association between metabolic syndrome and osteoarthritis: a meta-analysis of observational studies. *Diabetol Metab Syndr*. 2020;12:38. doi: 10.1186/s13098-020-00547-x
 101. Liao L, Deng Y, Zhao D. Association of low birth weight and premature birth with the risk of metabolic syndrome: a meta-analysis. *Front Pediatr*. 2020;8:405. doi: 10.3389/fped.2020.00405
 102. Markopoulou P, Papanikolaou E, Analytis A, Zoumakis E, Siahianidou T. Preterm birth as a risk factor for metabolic syndrome and cardiovascular disease in adult life: a systematic review and meta-analysis. *J Pediatr*. 2019;210:69–80.e5. doi: 10.1016/j.jpeds.2019.02.041
 103. Suliga E, Ciesla E, Gluszek-Osuch M, Lysek-Gladysinska M, Wawrzycka I, Gluszek S. Breastfeeding and prevalence of metabolic syndrome glucose index among perimenopausal women. *Nutrients*. 2020;12:2691. doi: 10.3390/nu12092691
- 10.1016/j.numecd.2021.11.017
86. Lindberg S, Jensen JS, Bjerre M, Frystyk J, Flyvbjerg A, Jeppesen J, Mogelvang R. Low adiponectin levels at baseline and decreasing adiponectin levels over 10 years of follow-up predict risk of the metabolic syndrome. *Diabetes Metab*. 2017;43:134–139. doi: 10.1016/j.diabet.2016.07.027
 87. Jeong H, Baek SY, Kim SW, Park EJ, Lee J, Kim H, Jeon CH. C reactive protein level as a marker for dyslipidaemia, diabetes and metabolic syndrome: results from the Korea National Health and Nutrition Examination Survey. *BMJ Open*. 2019;9:e029861. doi: 10.1136/bmjopen-2019-029861
 88. Abril-Ulloa V, Flores-Mateo G, Sola-Alberich R, Manuel-y-Keenoy B, Añija V. Ferritin levels and risk of metabolic syndrome: meta-analysis of observational studies. *BMC Public Health*. 2014;14:483. doi: 10.1186/1471-2458-14-483
 89. Lee DS, Evans JC, Robins SJ, Wilson PW, Albano I, Fox CS, Wang TJ, Benjamin EJ, D'Agostino RB, Vasan RS. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2007;27:127–133. doi: 10.1161/01.ATV.0000251993.20372.40

104. Yang S, Kwak S, Lee JH, Kang S, Lee SP. Nonalcoholic fatty liver disease is an early predictor of metabolic diseases in a metabolically healthy population. *PLoS One*. 2019;14:e0224626. doi: 10.1371/journal.pone.0224626
105. Aslani Z, Sadeghi O, Heidari-Beni M, Zahedi H, Baygi F, Shivappa N, Hébert JR, Moradi S, Sotoudeh G, Asayesh H, et al. Association of dietary inflammatory potential with cardiometabolic risk factors and diseases: a systematic review and dose–response meta-analysis of observational studies. *Diabetol Metab Syndr*. 2020;12:106. doi: 10.1186/s13098-020-00615-2
106. Arisawa K, Katsuura-Kamano S, Uemura H, Van Tien N, Hishida A, Tamura T, Kubo Y, Tsukamoto M, Tanaka K, Hara M, et al. Association of dietary acid load with the prevalence of metabolic syndrome among participants in baseline survey of the Japan Multi-Institutional Collaborative Cohort Study. *Nutrients*. 2020;12:1605. doi: 10.3390/nu12061605
107. Sadeghi O, Hasani H, Mozaffari-Khosravi H, Maleki V, Lotfi MH, Mirzaei M. Dietary Insulin Index and dietary insulin load in relation to metabolic syndrome: the Shahedieh Cohort Study. *J Acad Nutr Diet*. 2020;120:1672–1686.e4. doi: 10.1016/j.jand.2020.03.008

108. Santulli G, Pascale V, Finelli R, Visco V, Ciccirelli M, Illario M, Iaccarino G, et al. from short supply chain on metabolic. doi: 10.3390/ijcm8122061
109. Kim MK, Chon SJ, Noe EB, Roh YH, Yun BS, Seo SK. Associations of dietary syndrome and bone mineral density among KNHANES 2008-2011. *Osteoporos Int*. 10.1007/s00198-016-3717-1
110. Duong TV, Wong TC, Chen HH, Chen TW, KL, Liu HC, Lin ET, et al. Inadequate higher prevalence of metabolic syndrome in sis patients: a clinical observational study in *Nephrol*. 2018;19:236. doi: 10.1186/s12882-018-1041-z
111. Kim S, Song Y, Lee JE, Jun S, Shin S, Wie GA, Cho YH, Joung H. Total antioxidant capacity from dietary supplement decreases the likelihood
125. Seo MW, Eum Y, Jung HC. Leisure factor against metabolic syndrome 2023;23:2449. doi: 10.1186/s12889-126. Yean BB, Dedic D, Buddeen CA, K, Cooke BR, Lim EM, Mulrennan S. ous physical activity with risk of mass, and no interaction of physical D with metabolic syndrome risk. *Intern* 10.1111/imi.14379
127. Fan L, Hao Z, Gao L, Qi M, Feng S. sleep duration and metabolic (Baltimore). 2020;99:e18753. doi:
128. Srikanthan K, Fekih A, Visweswar H of having metabolic syndrome in Korean adults. *Nutrients*. 2017;9:1055. doi:

- view of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the West Virginian population. *Int J Med Sci.* 2016;13:25–38. doi: 10.7150/ijms.13800
129. Klisic A, Kavaric N, Soldatovic I, Ninic A, Kotur-Stevuljevic J. Retinol-cystatin binding protein 4 better correlates with metabolic syndrome than 112. Ahmadi E, Abdollahzad H, Pasdar Y, Rezaeian S, Moludi J, Nachvak SM, Mostafai R. Relationship between the consumption of milk-based oils in-cluding butter and kermanshah ghee with metabolic syndrome: Ravansar Non-Communicable Disease Cohort Study. *Diabetes Metab Syndr Obes.*

- C. *J Lab Med*. 2019;43:29–34. doi: 10.1515/labmed-2018-0325
130. Du R, Cheng D, Lin L, Sun J, Peng K, Xu Y, Xu M, Chen Y, Bi Y, Wang W, et al. Association between serum CA 19-9 and metabolic syndrome: a cross-sectional study. *J Diabetes*. 2017;9:1040–1047. doi: 10.1007/s00394-017-1520-1
 113. Baudry J, Lelong H, Adriouch S, Julia C, Alles B, Hercberg S, Touvier M, Lairon D, Galan P, Kesse-Guyot E. Association between organic food consumption and metabolic syndrome: cross-sectional results from the NutriNet-Sante study. *Eur J Nutr*. 2018;57:2477–2488. doi: 10.1007/s00394-017-1520-1
 114. Mohammadpour S, Ghorbaninejad P, Janbozorgi N, Shab-Bidar S. Associations between adherence to MIND diet and metabolic syndrome and general and abdominal obesity: a cross-sectional study. *Diabetol Metab Syndr*. 2020;12:101. doi: 10.1186/s13098-020-00611-6
 115. Bernardes da Cunha N, Teixeira GP, Madalena Rinaldi AE, Azeredo CM, Crispim CA. Late meal intake is associated with abdominal obesity and metabolic disorders related to metabolic syndrome: a chrononutrition approach using data from NHANES 2015-2018. *Clin Nutr*. 2023;42:1798–1805. doi: 10.1016/j.clnu.2023.08.005
 116. Jeong S, Lee H, Jung S, Kim JY, Park S. Higher energy consumption in the evening is associated with increased odds of obesity and metabolic syndrome: findings from the 2016-2018 Korea National Health and Nutrition Examination Survey (7th KNHANES). *Epidemiol Health*. 2023;45:e2023087. doi: 10.4178/epih.e2023087
 117. Park H, Shin D, Lee KW. Association of main meal frequency and skipping with metabolic syndrome in Korean adults: a cross-sectional study. *Nutr J*. 2023;22:24. doi: 10.1186/s12937-023-00852-x
 118. Choi S, Kim K, Lee JK, Choi JY, Shin A, Park SK, Kang D, Park SM. Association between change in alcohol consumption and metabolic syndrome: analysis from the Health Examinees Study. *Diabetes Metab J*. 2019;43:615–626. doi: 10.4093/dmj.2018.0128
 119. Farrell SW, Leonard D, Barlow CE, Willis BL, Pavlovic A, Defina LF, Haskell WL. Cardiorespiratory fitness, serum vitamin D, and prevalence of metabolic syndrome in men. *Med Sci Sports Exer*. 2021;53:68–73. doi: 10.1249/MSS.0000000000002445
 120. Aljuhani O, Alkahtani S, Alhussain M, Smith L, Habib SS. Associations of physical activity and sedentary time with metabolic syndrome in Saudi adult males. *Risk Manag Healthc Policy*. 2020;13:1839–1847. doi: 10.1111/1753-0407.12523

131. Chen Y-F, Lin Y-A, Yeh W-C, Tsao Y-C, Li W-C, Fang W-C, Chen IJ, Chen J-Y. The association between metabolic syndrome and elevated alanine aminotransferase levels in an Indigenous population in northern Taiwan: a community-based and cross-sectional study. *Evid Based Complement Alternat Med*. 2020;2020:6612447. doi: 10.1155/2020/6612447

132. Gaeini Z, Bahadoran Z, Mirmiran P, Azizi F. The association between liver function tests and some metabolic outcomes: Tehran Lipid and Glucose Study. *Hepatitis Monthly*. 2020;20:1–10. doi: 10.5812/hepatmon.98535

133. Kim T, Kang J. Association between serum retinol and α -tocopherol levels and metabolic syndrome in Korean general population: analysis of population-based nationally representative data. *Nutrients*. 2020;12:1689. doi: 10.3390/nu12061689

134. Li M, Zhang X, Zhou X, Han X, Zhang R, Fu Z, Wang L, Gao Y, Li Y, Ji L. The association between serum thyrotropin within the reference range and metabolic syndrome in a community-based Chinese population. *Diabetes Metab Syndr Obes*. 2020;13:2001–2011. doi: 10.2147/DMSO.S252154

135. Huang LL, Dou DM, Liu N, Wang XX, Fu LY, Wu X, Wang P. Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China: a cross sectional study. *BMJ Open*. 2018;8:e019792. doi: 10.1136/bmjopen-2017-019792

136. Yuguang L, Chang Y, Chen N, Zhao Y, Zhang X, Song W, Lu J, Liu X. Serum klotho as a novel biomarker for metabolic syndrome: findings from a large national cohort. *Front Endocrinol (Lausanne)*. 2024;15:1295927. doi: 10.3389/fendo.2024.1295927

137. Ganji V, Tangpricha V, Zhang X. Serum vitamin D concentration ≥ 75 nmol/L is related to decreased cardiometabolic and inflammatory biomarkers, metabolic syndrome, and diabetes; and increased cardiorespiratory fitness in US adults. *Nutrients*. 2020;12:730. doi: 10.3390/nu12030730

138. Liu L, Cao Z, Lu F, Liu Y, Lv Y, Qu Y, Gu H, Li C, Cai J, Ji S, et al. Vitamin D deficiency and metabolic syndrome in elderly Chinese individuals: evidence from CLHLS. *Nutr Metab (Lond)*. 2020;17:58. doi: 10.1186/s12986-020-00479-3

139. Pott-Junior H, Nascimento CMC, Costa-Guarisco LP, Gomes GAO, Gramani-Say K, Orlandi FS, Gratão ACM, Orlandi AAS, Pavarini SCI, 10.2147/RMHP.S267575

121. Colpitts BH, Smith S, Bouchard DR, Boudreau J, Sénéchal M. Are diabetes and metabolic syndrome simultaneously? *Transl Sports Med*. 2020;4:231–240. phys-i-cal activity and sedentary behavior patterns contributing to

- Vasilceac FA, et al. Vitamin D deficient older adults are more prone to have metabolic syndrome, but not to a greater number of metabolic syndrome parameters. *Nutrients*. 2020;12:748. doi: 10.3390/nu12030748
doi: 10.1002/tsm2.216
122. Xiao J, Chu M, Shen H, Ren W, Li Z, Hua T, Xu H, Liang Y, Gao Y, Zhuang X. Relationship of "weekend warrior" and regular physical activity patterns with metabolic syndrome and its associated diseases among Chinese rural adults. *J Sports Sci*. 2018;36:1963–1971. doi: 10.1080/02640414.2018.1428883
123. Churilla JR, Summerlin M, Richardson MR, Boltz AJ. Mean combined relative grip strength and metabolic syndrome: 2011-2014 National Health and Nutrition Examination Survey. *J Strength Cond Res*. 2020;34:995–1000. doi: 10.1519/JSC.0000000000003515
124. Merchant RA, Chan YH, Lim JY, Emorley J. Prevalence of metabolic syn-
140. Naser AM, Rahman M, Unicomb L, Doza S, Selim S, Chaity M, Luby

Anand S, Staimez L, Clasen TF, et al. Past sodium intake, contemporary so-dium intake, and cardiometabolic health in southwest coastal Bangladesh. *J Am Heart Assoc.* 2020;9:e014978. doi: 10.1161/JAHA.119.014978 141. Xu P, Liu A, Li F, Tinkov AA, Liu L, Zhou JC. Associations between metabol- ic syndrome and four heavy metals: a systematic review and meta-analysis. *Environ Pollut.* 2021;273:116480. doi: 10.1016/j.envpol.2021.116480 142. Cai J, Bidulescu A. Associations between e-cigarette use or dual use of e- cigarette and combustible cigarette and metabolic syndrome: results from the National Health and Nutrition Examination Survey (NHANES). *Ann Epidemiol.* 2023;85:93–99.e2. doi: 10.1016/j.annepidem.2023.05.009 143. Ramírez-Vélez R, Garcia-Hermoso A, Prieto-Benavides DH, Correa-Bautista JE, Quino-Ávila AC, Rubio-Barreto CM, González-Ruíz K, Carrillo HA, Correa-Rodríguez M, González-Jiménez E, et al. 10.2147/DMSO.S260544 Muscle

- mass to visceral fat ratio is an important predictor of the metabolic syndrome in college students. *Br J Nutr*. 2019;121:330–339. doi: 10.1017/S0007114518003392
144. Hruska B, Pressman SD, Bendinskas K, Gump BB. Vacation frequency is associated with metabolic syndrome and symptoms. *Psychol Health*. 2020;35:1–15. doi: 10.1080/08870446.2019.1628962
145. Patnaik Kuppili P, Vengadavaradan A, Bharadwaj B. Metabolic syndrome and substance use: a narrative review. *Asian J Psychiatr*. 2019;43:111–120. doi: 10.1016/j.ajp.2019.05.022
146. Kuo WC, Bratzke LC, Oakley LD, Kuo F, Wang H, Brown RL. The association between psychological stress and metabolic syndrome: a systematic review and meta-analysis. *Obes Rev*. 2019;20:1651–1664. with metabolic syndrome components in the Moroccan population. *Curr Res Transl Med*. 2017;65:121–125. doi: 10.1016/j.retram.2017.08.001
162. Carty CL, Bhattacharjee S, Haessler J, Cheng I, Hindorff LA, Aroda V, Carlson CS, Hsu CN, Wilkens L, Liu S, et al. Analysis of metabolic syndrome components in >15 000 African Americans identifies pleiotropic variants: results from the Population Architecture Using Genomics and Epidemiology Study. *Circ Cardiovasc Genet*. 2014;7:505–513. doi: 10.1161/CIRCGENETICS.113.000386
163. Wan JY, Goodman DL, Willems EL, Freedland
147. Zhang L, Zhou Q, Shao LH, Hu XQ, Wen J, Xia J. Association of metabolic syndrome with depression in US adults: a nationwide cross-sectional study using propensity score-based analysis. *Front Public Health*.

164. Ghareeb D, Abdelazem AS, Hussein EM, Al-Karamany AS. Association of TNF- α -308 G>A (rs1800629) polymorphism with susceptibility of metabolic syndrome. *J Diabetes Metab Disord*. 2021;20:209–215. doi: 10.1007/s40200-021-00732-3
148. Han KT, Kim SJ. Regional factors associated with the prevalence of meta-bolic syndrome: focusing on the role of healthcare providers. *Health Soc Care Commun*. 2021;29:104–112. doi: 10.1111/hsc.13073
149. Khambaty T, Schneiderman N, Llabre MM, Elfassy T, Moncrieft AE, Daviglius

165. Cannone V, Cefalu AB, Noto D, Scott CG, Bailey KR, Cavera G, Pagano M, Sapienza M, Aversa MR, Burnett JC Jr. The atrial natriuretic peptide genetic variant rs5068 is associated with a favorable cardiometabolic phenotype in a Mediterranean population. *Diabetes Care*. 2013;36:2850–2856. doi: 10.2337/dc12-2337
- M, Talavera GA, Isasi CR, Gallo LC, Reina SA, et al. Elucidating the multidimensionality of socioeconomic status in relation to metabolic syndrome in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Int J Behav Med*. 2020;27:188–199. doi: 10.1007/s12529-020-09847-y
150. Cardel MI, Guo Y, Sims M, Dulin A, Miller D, Chi X, Pavea G, DeBoer MD, Gurka MJ. Objective and subjective socioeconomic status associated with metabolic syndrome severity among African American adults in Jackson Heart Study. *Psychoneuroendocrinology*. 2020;117:104686. doi: 10.1016/j.psyneuen.2020.104686
151. Park SH, Strauss SM. Food insecurity as a predictor of metabolic syndrome in U.S. female adults. *Public Health Nurs*. 2020;37:663–670. doi: 10.1016/j.puhe.2020.05.001

166. Cannone V, Cabassi A, Volpi R, Burnett JC Jr. Atrial natriuretic peptide: a molecular target of novel therapeutic approaches to cardio-metabolic disease. *Int J Mol Sci.* 2019;20:3265. doi: 10.3390/ijms20133265 167. Cannone V, Scott CG, Decker PA, Larson NB, Palmas W, Taylor KD, Wang TJ, Gupta DK, Bielinski SJ, Burnett JC Jr. A favorable cardiometabolic profile is associated with the G allele of the genetic variant rs5068 in African Americans: the Multi-Ethnic Study of Atherosclerosis (MESA). *PLoS One.* 2017;12:e0189858. doi: 10.1371/journal.pone.0189858
168. Maintinguer Norde M, Oki E, Ferreira Carioca AA, Teixeira Damasceno NR, Fisberg RM, Lobo Marchioni DM, Rogero MM. Influence of IL1B, IL6 and IL10 gene variants and plasma fatty acid interaction on metabolic. Socioeconomically disadvantaged groups and metabolic syndrome in European adolescents: the HELENA study. *J Adolesc Health.*
152. Iguacel I, Bornhorst C, Michels N, Breidenassel C, Dallongeville J, Gonzalez-Gross M, Gottrand F, Kafatos A, Karaglan E, Kersting M, et

bolic syndrome risk in a cross-sectional population-based study. *Clin Nutr*.

2018;37:659–666. doi: 10.1016/j.clnu.2017.02.009

169. Lind L. Genetic determinants of clustering of cardiometabolic risk factors in U.K. Biobank. *Metab Syndr Relat Disord*. 2020;18:121–127. doi: 10.1089/met.2019.0096
153. Chung J, Choi H, Jung J, Kong MG. Association between socioeconomic status and metabolic syndrome in Korean adults: data from the Korean National Health and Nutrition Examination Survey. *CardioMetabolic Syndr J*. 2021;68:146–154. doi: 10.1016/j.jadohealth.2020.05.027
154. Abbate M, Pericas J, Yanez AM, Lopez-Gonzalez AA, De Pedro-Gomez J, Aguilo A, Morales-Asencio JM, Bennasar-Veny M. Socioeconomic inequalities in metabolic syndrome by age and gender in a Spanish work-ing population. *Int J Environ Res Public Health*. 2021;18:10333. doi: 10.51789/cmsj.2021.1.e16

170. Miao Z, Garske KM, Pan DZ, Koka A, Kaminska D, Mannisto V, Sinsheimer JS, Pihlajamaki J, Pajukanta P. Identification of 90 NAFLD GWAS loci and establishment of NAFLD PRS and causal role of NAFLD in coronary artery disease. *HGG Adv.* 2022;3:100056. doi: 10.1016/j.xhgg.2021.100056
171. Haas ME, Pirruccello JP, Friedman SN, Wang M, Emdin CA, Ajmera VH, Simon TG, Homburger JR, Guo X, Budoff M, et al. Machine learning enables new insights into genetic contributions to liver fat accumulation. *Cell Genom.* 2021;1:100066. doi: 10.1016/j.xgen.2021.100066
- 10.3390/ijerph181910333
155. Colombet Z, Perignon M, Salanave B, Landais E, Martin-Prevel Y, Alles B, Drogue S, Amiot MJ, Mejean C. Socioeconomic inequalities in metabolic syndrome in the French West Indies. *BMC Public Health.* 2019;19:1620. doi: 10.1186/s12889-019-7970-z
156. Ying X, Yang S, Li S, Su M, Wang N, Chen Y, Jiang Q, Fu C. Prevalences of metabolic syndrome and its sex-specific association with socioeco-nomic status in rural China: a cross-sectional study. *BMC Public Health.*
172. Walree ES, Jansen IE, Bell NY, Savage JE, de Leeuw C, Nieuwdorp M, 2021;21:2033. doi: 10.1186/s12889-021-12074-z
157. Musani SK, Martin LJ, Woo JG, Olivier M, Gurka MJ, DeBoer MD. Heritability of the severity of the metabolic syndrome in Whites and Blacks in 3 large cohorts. *Circ Cardiovasc Genet.* 2017;10:e001621. doi: 10.1161/CIRCGENETICS.116.001621
158. Nagrani R, Foraita R, Gianfagna F, Iacoviello L, Marild S, Michels N, Molnar

- van der Sluis S, Posthuma D. Disentangling genetic risks for metabolic syndrome. *Diabetes*. 2022;71:2447–2457. doi: 10.2337/db22-0478 173.
- Nuotio ML, Pervjakova N, Joensuu A, Karhunen V, Hiekkalinna T, Milani L, Kettunen J, Järvelin MR, Jousilahti P, Metspalu A, et al. An epigenome-wide association study of metabolic syndrome and its components. *Sci Rep*. 2020;10:20567. doi: 10.1038/s41598-020-77506-z
174. Elhadad MA, Wilson R, Zaghlool SB, Huth C, Gieger C, Grallert H, Graumann J, Rathmann W, Koenig W, Sinner MF, et al. Metabolic syndrome and the plasma proteome: from association to causation. *Cardiovasc Diabetol*. 2021;20:111. doi: 10.1186/s12933-021-01299-2
175. Wang Q, Chair SY, Wong EM, Taylor-Piliae RE, Qiu XCH, Li XM. Metabolic syndrome knowledge among adults with cardiometabolic risk factors: a cross-sectional study. *Int J Environ Res Public Health*. 2019;16:159. doi: 10.3390/ijerph16010159
- D, Moreno L, Russo P, Veidebaum T, et al. Common genetic variation in obesity, lipid transfer genes and risk of metabolic syndrome: results from IDEFICS/I.Family study and meta-analysis. *Sci Rep*. 2020;10:7189. doi: 10.1038/s41598-020-64031-2
159. Lin E, Kuo PH, Liu YL, Yang AC, Tsai SJ. Detection of susceptibility loci on APOA5 and COLEC12 associated with metabolic syndrome using a genome-wide association study in a Taiwanese population. *Oncotarget*. 2017;8:93349–93359. doi: 10.18632/oncotarget.20967
160. Morjane I, Kefi R, Charoute H, Lakbakbi El Yaagoubi F, Hechmi M, Saile R, Abdelhak S, Barakat A. Association study of HNF1A polymorphisms with metabolic syndrome in the Moroccan population. *Diabetes Metab Syndr*. 2017;11(suppl 2):S853–S857. doi: 10.1016/j.dsx.2017.07.005
161. Lakbakbi El Yaagoubi F, Charoute H, Morjane I, Sefri H, Rouba H, Ainahi A, Kandil M, Benrahma H, Barakat A. Association analysis of genetic variants

176. Choe WS, Choi EK, Han KD, Lee EJ, Lee SR, Cha MJ, Oh S. Association of metabolic syndrome and chronic kidney disease with atrial fibrillation: a nationwide population-based study in Korea. *Diabetes Res Clin Pract*. 2019;148:14–22. doi: 10.1016/j.diabres.2018.12.004
177. Wang Z, Wang B, Li X, Zhang S, Wu S, Xia Y. Metabolic syndrome, high-sensitivity C-reactive protein levels and the risk of new-onset atrial fibrillation: results from the Kailuan Study. *Nutr Metab Cardiovasc Dis*. 2021;31:102–109. doi: 10.1016/j.numecd.2020.06.026
178. Perrone-Filardi P, Paolillo S, Costanzo P, Savarese G, Trimarco B, Bonow RO. The role of metabolic syndrome in heart failure. *Eur Heart J*. 2015;36:2630–2634. doi: 10.1093/eurheartj/ehv350
179. Vidula H, Liu K, Criqui MH, Szklo M, Allison M, Sibley C, Ouyang P, Tracy RP, Chan C, McDermott MM. Metabolic syndrome and incident peripheral

- artery disease: the Multi-Ethnic Study of 2015;243:198–203. doi:
180. Mottillo S, Filion KB, Genest J, Joseph L, Schiffrin EL, Eisenberg MJ. The metabolic risk a systematic review and meta-2010;56:1113–1132. doi:
181. Jasiukaitienė V, Lukšienė D, Tamošiūnas A. The impact of metabolic syndrome and the first event of cardiovascular disease: in Lithuanian urban population. *Medicina* 10.3390/medicina56010018
182. Guembe MJ, Fernandez-Lazaro CI, Savon-C. Investigators RS. Risk for cardiovascular metabolic syndrome and its components: a 13-year prospective study in the RIVANA cohort. *Cardiovasc Diabetol*. 2020;19:195. doi: 10.1186/s12933-020-01166-6
183. Mente A, Yusuf S, Islam S, McQueen MJ, Tanomsup S, Onen CL, Rangarajan S, Gerstein HC, Anand SS; INTERHEART Investigators. Metabolic syndrome and risk of acute myocardial infarction a case-control study of 26,903 subjects from 52 countries. *J Am Coll Cardiol*. 2010;55:2390–2398. doi: 10.1016/j.jacc.2009.12.053
184. Rachas A, Raffaitin C, Barberger-Gateau P, Helmer C, Ritchie K, Tzourio C, Amouyel P, Ducimetiere P, Empiana JP. Clinical usefulness of the metabolic syndrome for the risk of coronary heart disease does not exceed the sum of its individual components in older men and women: the Three-City (3C) Study. *Heart*. 2012;98:650–655. doi: 10.1136/heartjnl-2011-301185
185. Lyubarova R, Robinson JG, Miller M, Simmons DL, Xu P, Abramson BL, Elam MB, Brown TM, McBride R, Fleg JL, et al; Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) Investigators. Metabolic syndrome cluster does not provide incremental prognostic information in patients with stable cardiovascular disease: a post hoc analysis of the AIM-HIGH trial. *J Clin Lipidol*. 2017;11:1201–1211. doi: 10.1016/j.jacl.2017.06.017
186. Lee HS, Kim H-L, Kim M-A, Oh S, Kim M, Tehran Lipid and Glucose Study. 10.1186/s13098-020-00608-1
196. Mannussen CG, Koskinen J, Juonala MA, Thomson R, Schmidt MD. the metabolic syndrome in youth that led with a normalization of high carotid 2 diabetes mellitus risk: the Bogalusa in Young Finns studies. *J Am Coll* 10.1016/j.jacc.2012.05.056
197. Ndumele CE, Ranaaswami J, Chow Coresh J, Mathew RO, Baker-Smith of the American Heart Association. health: a presidential advisory from Park SM, Yoon HJ, Byun YS, Park SM, Shin MS, et al. Sex difference in the association between metabolic syndrome and obstructive coronary artery disease: analysis of data from the KoRean wOmen's chest pain rEgistry (KoROSE). *J Womens Health (Larchmt)*. 2020;29:1500–1506. doi: 10.1089/jwh.2020.8488
187. Li X, Li X, Lin H, Fu X, Lin W, Li M, Zeng X, Gao Q. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies. *J Clin Neurosci*. 2017;40:34–38. doi: 10.1016/j.jocn.2017.01.018
188. DeBoer MD, Filipp SL, Sims M, Musani SK, Gurka MJ. Risk of ischemic stroke increases over the spectrum of metabolic syndrome severity. *Stroke*. 2020;51:2548–2552. doi: 10.1161/STROKEAHA.120.028944
189. Hess PL, Al-Khalidi HR, Friedman DJ, Mulder H, Kucharska-Newton A, Rosamond WR, Lopes RD, Gersh BJ, Mark DB, Curtis LH, et al. The metabolic syndrome and risk of sudden cardiac death: the Atherosclerosis Risk in Communities study. *J Am Heart Assoc*. 2017;6:e006103. doi:

- lished correction appears in *Circulation*. 2024;149:e1023]. *Circulation*. 2023;148:1606–1635. doi: 10.1161/CIR.0000000000001184
198. Minhas AMK, Mathew RO, Sperling LS, Nambi V, Virani SS, Navaneethan SD, Shapiro MD, Abramov D. Prevalence of the cardiovascular-kidney-metabolic syndrome in the United States. *J Am Coll Cardiol*. 2024;83:1824–1826. doi: 10.1016/j.jacc.2024.03.368
199. Khan SS, Coresh J, Pencina MJ, Ndumele CE, Rangaswami J, Chow SL, Palaniappan LP, Sperling LS, Virani SS, Ho JE, et al; on behalf of the American Heart Association. Novel prediction equations for absolute risk assessment of total cardiovascular disease incorporating cardiovascular-kidney-metabolic health: a scientific statement from the American Heart Association. *Circulation*. 2023;148:1982–2004. doi: 10.1161/CIR.0000000000001191
200. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, Szklo M, Barr RG, Wong ND. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care*. 2011;34:2285–2290. doi: 10.2337/dc11-0816
201. Wong ND, Nelson JC, Granston T, Bertoni AG, Blumenthal RS, Carr JJ, Guerci A, Jacobs DR Jr, Kronmal R, Liu K, et al. Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study. *JACC Cardiovasc Imaging*. 2012;5:358–366. doi: 10.1016/j.jcmg.2011.12.015
202. Al Rifai M, Silverman MG, Nasir K, Budoff MJ, Blankstein R, Szklo M, Katz R, Blumenthal RS, Blaha MJ. The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2015;239:629–633. doi: 10.1016/j.atherosclerosis.2015.02.011
203. Lee YA, Kang SG, Song SW, Rho JS, Kim EK. Association between metabolic syndrome, smoking status and coronary artery calcification. *PLoS One*. 2015;10:e0122430. doi: 10.1371/journal.pone.0122430
204. Taher R, Sara JD, Heidari B, Toya T, Lerman LO, Lerman A. Metabolic syndrome is associated with peripheral endothelial dysfunction amongst men. *Diabetes Metab Syndr Obes*. 2019;12:1035–1045. doi: 10.1161/jaha.117.006103
190. Zhang F, Liu L, Zhang C, Ji S, Mei Z, Li T. Association of metabolic syndrome and its components with risk of stroke recurrence and mortality: a meta-analysis. *Neurology*. 2021;97:e695–e705. doi: 10.1212/WNL.00000000000012415
191. Chen S, Li J, Li Q, Qiu Z, Wu X, Chen L. Metabolic syndrome increases operative mortality in patients with impaired left ventricular systolic function who undergo coronary artery bypass grafting: a retrospective observational study. *BMC Cardiovasc Disord*. 2019;19:25. doi: 10.1186/s12872-019-1004-8
192. Ju SY, Lee JY, Kim DH. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-analysis of prospective cohort studies. *Medicine (Baltimore)*. 2017;96:e8491. doi: 10.1097/md.0000000000008491
193. Chung KC, Juang SE, Chen HH, Cheng KC, Wu KL, Song LC, Lee KC. Association between metabolic syndrome and colorectal cancer incidence and all-cause mortality: a hospital-based observational study. *BMC Gastroenterol*. 2022;22:453. doi: 10.1186/s12876-022-02505-5
194. Fernandez-Mendoza J, He F, LaGrotte C, Vgontzas AN, Liao D, Bixler

205. Walther G, Obert P, Dutheil F, Chapier R, Lesourd B, Naughton G, Courteix D, Vinet A. Metabolic syndrome individuals with and without type 2 diabetes mellitus present generalized vascular dysfunction: cross-sectional study. *Arterioscler Thromb Vasc Biol.* 2015;35:1022–1029. doi: 10.1161/ATVBAHA.114.304591
206. Smith JP, Haddad EV, Taylor MB, Oram D, Blakemore D, Chen Q, Boutaud O, Oates JA. Suboptimal inhibition of platelet cyclooxygenase-1 by aspirin in metabolic syndrome. *Hypertension.* 2012;59:719–725. doi: 10.1161/HYPERTENSIONAHA.111.181404
207. Feldman L, Tubach F, Juliard JM, Himbert D, Ducrocq G, Sorbets E, Triantafyllou K, Kerner A, Abergel H, Huisse MG, et al. Impact of diabetes mellitus and metabolic syndrome on acute and chronic on-clopidogrel platelet reactivity in patients with stable coronary artery disease undergoing drug-eluting stent placement. *Am Heart J.* 2014;168:940–947. doi: 10.1016/j.ahj.2014.08.014
208. Cuspidi C, Sala C, Tadic M, Gherbesi E, Grassi G, Mancia G. Association of metabolic syndrome with carotid thickening and plaque in the general population: a meta-analysis. *J Clin Hypertens (Greenwich).* 2018;20:4–10. doi: 10.1111/jch.13138
- EO. Impact of the metabolic syndrome on mortality is modified by objective short sleep duration. *J Am Heart Assoc.* 2017;6:e005479. doi: 10.1161/jaha.117.005479
- MK, Azizi F, Hadaegh F. Adolescent metabolic syndrome and its composition.
195. Asghari G, Hasheminia M, Heidari A, Mirmiran P, Guity K, Shahrzad

209. Sugiura T, Dohi Y, Takagi Y, Yoshikane N, Ito M, Suzuki K, Nagami T, Iwase M, Seo Y, Ohte N. Relationships of obesity-related indices and metabolic syndrome with subclinical atherosclerosis in middle-aged un-treated Japanese workers. *J Atheroscler Thromb*. 2020;27:342–352. doi: 10.5551/jat.50633

210. Pierdomenico SD, Pierdomenico AM, Cuccurullo F, Iacobellis G. Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome. *Am J Cardiol*. 2013;111:73–78. doi: 10.1016/j.amjcard.2012.08.044
211. van der Meer RW, Lamb HJ, Smit JW, de Roos A. MR imaging evaluation of cardiovascular risk in metabolic syndrome. *Radiology*. 2012;264:21–37. doi: 10.1148/radiol.12110772
212. Chun H. Ascending aortic diameter and metabolic syndrome in Korean men. *J Investig Med*. 2017;65:1125–1130. doi: 10.1136/jim-2016-000367
213. Marso SP, Mercado N, Maehara A, Weisz G, Mintz GS, McPherson J, Schiele F, Dudek D, Fahy M, Xu K, et al. Plaque composition and clinical outcomes in acute coronary syndrome patients with metabolic syndrome. *J Nucl Med*. 2011;52:1369–1377. doi: 10.2967/jnumed.110.082883
215. Canon-Montanez W, Santos ABS, Nunes LA, Pires JCG, Freire CMV, Chen H, Zheng X, Zong X, Li Z, Li N, Hur J, Fritz CD, Chapman W Jr, Nickel KB, Tipping A, et al. Metabolic syndrome, metabolic comorbid conditions and risk of early-onset colorectal cancer. *Gut*. 2021;70:1147–1154. doi: 10.1136/gutjnl-2020-321661
230. Watanabe J, Kakehi E, Kotani K, Kayaba K, Nakamura Y, Ishikawa S. Metabolic syndrome is a risk factor for cancer mortality in the general Japanese population: the Jichi Medical School Cohort Study. *Diabetol Metab Syndr*. 2019;11:3. doi: 10.1186/s13098-018-0398-2
231. Liu Y, Wang L, Liu H, Li C, He J. The prognostic significance of metabolic syndrome and a related

233. Dibaba DT, Ogunsina K, Braithwaite D, Akinyemiju T. Metabolic syn-drome and risk of breast cancer mortality by menopause, obe-sity, and subtype. *Breast Cancer Res Treat*. 2018;174:209–218. doi: 10.1007/s10549-018-5056-8
- Ribeiro ALP, Mill JG, Bessel M, Duncan BB, Schmidt MI, et al. Central obe-sity is the key component in the association of metabolic syndrome with left ventricular global longitudinal strain impairment. *Rev Esp Cardiol (Engl Ed)*. 2018;71:524–530. doi: 10.1016/j.rec.2017.10.008
216. Aksoy S, Durmus G, Ozcan S, Toprak E, Gurkan U, Oz D, Canga Y, Karatas B, Duman D. Is left ventricular diastolic dysfunction independent from pres- ence of hypertension in metabolic syndrome? An echocardiographic study. *J Cardiol*. 2014;64:194–198. doi: 10.1016/j.jjcc.2014.01.002
217. Crendal E, Walther G, Dutheil F, Courteix D, Lesourd B, Chapier R, Naughton G, Vinet A, Obert P. Left ventricular myocardial dyssynchrony is already present in nondiabetic patients with metabolic syndrome. *Can J Cardiol*. 2014;30:320–324. doi: 10.1016/j.cjca.2013.10.019
218. Tadic M, Cuspidi C, Sljivic A, Andric A, Ivanovic B, Scepanovic R, Ilic I, Jozika L, Marjanovic T, Celic V. Effects of the metabolic syndrome on right heart mechanics and function. *Can J Cardiol*. 2014;30:325–331. doi: 10.1016/j.cjca.2013.12.006
219. Gurka MJ, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Cardel M, Pearson TA, DeBoer MD. Independent associations between a meta-bolic syndrome severity score and future diabetes by sex and race: the

234. Li Y, Liu T, Ivan C, Huang J, Shen DY, Kavanagh JJ, Bast RC Jr., Fu S, Hu W, Sood AK. Corrigendum: enhanced cytotoxic effects of combined valproic acid and the aurora kinase inhibitor VE465 on gynecologic cancer cells. *Front Oncol.* 2018;8:9. doi: 10.3389/fonc.2018.00009
235. Akinyemiju T, Sakhuja S, Vin-Raviv N. In-hospital mortality and post-surgical complications among cancer patients with metabolic syndrome. *Obes Surg.* 2018;28:683–692. doi: 10.1007/s11695-017-2900-6
236. Gathirua-Mwangi WG, Song Y, Monahan PO, Champion VL, Zollinger TW. Associations of metabolic syndrome and C-reactive protein with mortality from total cancer, obesity-linked cancers and breast cancer among women in NHANES III. *Int J Cancer.* 2018;143:535–542. doi: 10.1002/ijc.31344
237. Wong RJ, Liu B, Bhuket T. Significant burden of nonalcoholic fatty liver disease with advanced fibrosis in the US: a cross-sectional analysis of 2011-2014 National Health and Nutrition Examination Survey. *Aliment Pharmacol Ther.* 2017;46:974–980. doi: 10.1111/apt.14327
238. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016;64:73–84. doi: 10.1002/hep.28431
- Atherosclerosis Risk in Communities Study and Jackson Heart Study. *Diabetologia.* 2017;60:1261–1270. doi: 10.1007/s00125-017-4267-6
220. Huh JH, Ahn SG, Kim YI, Go T, Sung KC, Choi JH, Koh KK, Kim JY. Impact of longitudinal changes in metabolic syndrome status over 2 years on 10-

239. Ting YW, Wong SW, Anuar Zaini A, Mohamed R, Jalaludin MY. Metabolic syndrome is associated with advanced liver fibrosis among pediatric patients with non-alcoholic fatty liver disease. *Front Pediatr*. 2019;7:491. doi: 10.3389/fped.2019.00491
- year incident diabetes mellitus. *Diabetes Metab J*. 2019;43:530–538. doi: 10.4093/dmj.2018.0111
221. Lee MK, Han K, Kim MK, Koh ES, Kim ES, Nam GE, Kwon HS. tween alcohol consumption and metabolic syndrome in predicting severe Changes in metabolic syndrome and its components and the risk of liver disease in the general population. *Hepatology*. 2018;67:2141–2149. doi: 10.1002/hep.29631
- 10.1038/s41598-020-59203-z
222. Cai R, Wu M, Xing Y. Pretransplant metabolic syndrome and its compo-nents predict post-transplantation diabetes mellitus in Chinese patients receiving a first renal transplant. *Ther Clin Risk Manag*. 2019;15:497–503.

241. Milano A, Bianco MA, Buri L, Cipolletta L, Grossi E, Rotondano G, Tessari F, Efthymakis K, Neri M. Metabolic syndrome is a risk factor for colorectal adenoma and cancer: a study in a White population using the harmonized criteria. *Ther Adv Gastroenterol*. 2019;12:175628481986783. doi: 10.2147/TCRM.S190185
- 10.1177/1756284819867839

242. Niknam R, Moradi J, Jahanshahi KA, Mahmoudi L, Ejtehad F. Association between metabolic syndrome and its components with severity of acute pancreatitis. *Diabetes Metab Syndr Obes.* 2020;13:1289–1296. doi: 10.2147/DMSO.S249128
224. Akinyemiju T, Moore JX, Judd S, Lakoski S, Goodman M, Safford MM, Pisu M. Metabolic dysregulation and cancer mortality in a national cohort of Blacks and Whites. *BMC Cancer.* 2017;17:856. doi:

243. Di J, Cheng Y, Chang D, Liu Y. A meta-analysis of the impact of obesity, metabolic syndrome, insulin resistance, and microbiome on the diagnosis of Barrett's esophagus. *Dig Dis*. 2019;38:165–177. doi: 10.1186/s12885-017-3807-2
225. Esmaeili ES, Asadollahi K, Delpisheh A, Sayehmiri K, Azizi H. Metabolic syndrome and risk of colorectal cancer: a case-control study. *Int J Cancer Manag*. 2019;12:e84627. doi: 10.5812/ijcm.84627
226. Zhao P, Xia N, Zhang H, Deng T. The metabolic syndrome is a risk factor for breast cancer: a systematic review and meta-analysis. *Obesity Facts*. 2020;13:384–396. doi: 10.1159/000507554
227. Santos AP, Santos AC, Castro C, Raposo L, Pereira SS, Torres I, Henrique R, Cardoso H, Monteiro MP. Visceral obesity and metabolic syndrome are associated with well-differentiated gastroenteropancreatic neuroendocrine tumors. *Cancers*. 2018;10:293. doi: 10.3390/cancers10090293
228. Choi IY, Chun S, Shin DW, Han K, Jeon KH, Yu J, Chae BJ, Suh M, Park YM. Changes in metabolic syndrome status and breast cancer risk: a nationwide cohort study. *Cancers (Basel)*. 2021;13:1177. doi: 10.3390/cancers13051177

244. Yang M, Xu H, Yang L, Jiang J, Dong B. Metabolic syndrome and disability in Chinese nonagenarians and centenarians. *Aging Clin Exp Res*. 2018;30:943–949. doi: 10.1007/s40520-017-0877-6
245. Marcos-Delgado A, Lopez-Garcia E, Martinez-Gonzalez MA, Salas-Salvado J, Corella D, Fito M, Romaguera D, Vioque J, Alonso-Gomez AM, Warnberg J, et al. Health-related quality of life in individuals with metabolic syndrome: a cross-sectional study. *Semergen*. 2020;46:524–537. doi: 10.1016/j.semerg.2020.03.003
246. Lee JE, Shin DW, Han K, Kim D, Yoo JE, Lee J, Kim S, Son KY, Cho B, Kim MJ. Changes in metabolic syndrome status and risk of dementia. *J Clin Med*. 2020;9:122. doi: 10.3390/jcm9010122
247. Kim YJ, Kim SM, Jeong DH, Lee SK, Ahn ME, Ryu OH. Associations between metabolic syndrome and type of dementia: analysis based on the National Health Insurance Service database of Gangwon province in South Korea. *Diabetol Metab Syndr*. 2021;13:4. doi: 10.1186/s13098-020-00620-5

248. Lee EY, Lee SJ, Kim KM, Yun YM, Song Y, Youm Y, Kim CO. Association of hydroxyvitamin D with cognitive impairment. *Geriatr Gerontol Int*. 2017;17:1069–1075.
249. Lai MMY, Ames DJ, Cox KL, Ellis KA, P. Cvarto EV, Szeke C, Martins R, et al. function and clustered cardiovascular risk adults at risk of cognitive decline. *J Nutr*. doi: 10.1007/s12603-020-1333-4
250. Yang L, Lv X, Wei D, Yue F, Guo J, Zhang risk of bone fractures: a meta-analysis of 2016;84:52–56. doi: 10.1371/journal.pone.0129116
251. Muka T, Traianoska K, Kieffe-de Jong JC, A, Dehghan A, Zillikens MC, Franco OH, Rivadeneira F. The association between metabolic syndrome, bone mineral density, hip bone geometry and fracture risk: the Rotterdam study. *PLoS One*. 2015;10:e0129116. doi: 10.1371/journal.pone.0129116
252. Nobrega da Silva V, Goldberg TBL, Silva CC, Kurokawa CS, Fiorelli LNM, Rizzo A, Corrente JE. Impact of metabolic syndrome and its components on bone remodeling in adolescents. *PLoS One*. 2021;16:e0253892. doi: 10.1371/journal.pone.0253892
265. Bakhshayeshkaram M, Heydari ST, J. Dabhanmanesh MH, Lankarani drome and determinants of its 5-year longitudinal follow-up study. *J* 10.4103/jrms.JRMS 884 19
266. Fatahi A, Doosti-Irani A, Cheranhi Z. bolic syndrome in Iran: a systematic *Med*. 2020;11:64. doi: 10.1186/s13098-019-0423-0
267. Annani-Akollor ME, Laino EF, Osei H, Anto EO. Prevalence of metabolic plasma glucose and HbA1c as the non-diabetic population in Ghana. 1110 1186/s13098-019-0423-0
253. Zhao L, Pang A. Effects of metabolic syndrome on semen quality and circulating sex hormones: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2020;11:428. doi: 10.3389/fendo.2020.00428
254. Bansal R, Gubbi S, Muniyappa R. Metabolic syndrome and COVID 19: endocrine-immune-vascular interactions shapes clinical course.

268. Jamee AS, Aboyans V, Magne J, Preux PM, Lacroix P. The epidemic of the metabolic syndrome among the Palestinians in the Gaza Strip. *Diabetes Metab Syndr Obes.* 2019;12:2201–2208. doi: 10.2147/DMSO.S207781
269. Ajlouni K, Khader Y, Alyousfi M, Al Nsour M, Batieha A, Jaddou H. Metabolic syndrome amongst adults in Jordan: prevalence, trend, and its association with socio-demographic characteristics. *Diabetol Metab Syndr.* 2020;12:100. doi: 1210.1186/s13098-020-00610-7
270. Motuma A, Gobena T, Roba KT, Berhane Y, Worku A. Metabolic syndrome among working adults in eastern Ethiopia. *Diabetes Metab Syndr Obes.* 2020;13:4941–4951. doi: 10.2147/DMSO.S283270
271. Ambachew S, Endalamaw A, Worede A, Tegegne Y, Melku M, Biadgo B. The Prevalence of metabolic syndrome in Ethiopian population: a systematic review and meta-analysis. *J Obes.* 2020;2020:2701309. doi: 10.1155/2020/2701309
255. Mechanick JL, Rosenson RS, Pinney SP, Mancini DM, Narula J, Fuster V. Coronavirus and cardiometabolic syndrome: JACC focus seminar. *J Am Coll Cardiol.* 2020;76:2024–2035. doi: 10.1016/j.jacc.2020.07.069
256. Costa FF, Rosário WR, Ribeiro Farias AC, de Souza RG, Duarte Gondim RS, Barroso WA. Metabolic syndrome and COVID-19: An update on the associated comorbidities and proposed therapies. *Diabetes Metab Syndr.* 2020;14:809–814. doi: 10.1016/j.dsx.2020.06.016
257. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol.* 2020;109:531–538. doi: 10.1007/s00392-020-01626-9
258. Yoo JS, Choe EY, Kim YM, Kim SH, Won YJ. Predictive costs in medical care for Koreans with metabolic syndrome from 2009 to 2013 based on the National Health Insurance claims dataset. *Korean J Intern Med.* 2020;35:936–945. doi: 10.3904/kjim.2016.343
259. He X, Fei Q, Sun T. Metabolic syndrome increases risk for perioperative outcomes following posterior lumbar interbody fusion. *Medicine (Baltimore).* 2020;99:e21786. doi: 10.1097/md.00000000000021786
260. Chen X, Zhang W, Sun X, Shi M, Xu L, Cai Y, Chen W, Mao C, Shen X. Metabolic syndrome predicts postoperative complications after gastrectomy in gastric cancer patients: development of an individualized usable nomogram and rating model. *Cancer Med.* 2020;9:7116–7124. doi: 10.1097/md.00000000000021786

272. Baygi F, Herttua K, Jensen OC, Djalalinia S, Mahdavi Ghorabi A, Asayesh H, Qorbani M. Global prevalence of cardiometabolic risk factors in the military population: a systematic review and meta-analysis. *BMC Endocr Disord*. 2020;20:8. doi: 10.1186/s12902-020-0489-6
273. Bitew ZW, Alemu A, Ayele EG, Tenaw Z, Alebel A, Worku T. Metabolic syndrome among children and adolescents in low and middle income countries: a systematic review and meta-analysis. *Diabetol Metab Syndr*. 2020;12:93. doi: 10.1186/s13098-020-00601-8
274. Diaz A, Espeche W, March C, Flores R, Parodi R, Genesio MA, Sabio R, Poppe S. Prevalence of metabolic syndrome in Argentina in the last 25 years: systematic review of population observational studies [in Spanish]. *Hipertens Riesgo Vasc*. 2018;35:64–69. doi: 10.1016/j.hipert.2017.08.003
275. Rojas-Martinez R, Aguilar-Salinas CA, Romero-Martinez M, Castro-Porras L, Gomez-Velasco D, Mehta R. Trends in the prevalence of metabolic syndrome and its components in Mexican adults, 2006-2018. *Salud Publica Mex*. 2021;63:713–724. doi: 10.21149/12835
276. de Siqueira Valadares LT, de Souza LSB, Salgado Junior VA, de Freitas Bonomo L, de Macedo LR, Silva M. Prevalence of metabolic syndrome in Brazilian adults in the last 10 years: a systematic review and meta-analysis. *BMC Public Health*. 2022;22:327. doi: 10.1186/s12889-022-12753-5
277. Yao F, Bo Y, Zhao L, Li Y, Ju L, Fang H, Piao W, Yu D, Lao X. Prevalence and influencing factors of metabolic syndrome among adults in China from 2013 to 2018. *Front Public Health*. 2022;10:895732. doi: 10.3389/fpubh.2022.895732
261. Guofeng C, Chen Y, Rong W, Ruiyu L, Kunzheng W. Patients with metabolic syndrome have a greater rate of complications after arthroplasty. *Bone Joint Res*. 2020;9:120–129. doi: 10.1302/2046-3758.93.BJR-2019-0138.R1
262. Ramdass PVAK, Ford T, Sidhu T, Ogbonnia CF, Gomez A. Prevalence of metabolic syndrome and obesity among adults in Aruba. *Int Public Health J*. 2022;17:1000000. doi: 10.3390/ijph17010000

2015 to 2017. *Nutrients*. 2021;13:4475. doi: 10.3390/nu13124475 278. Ansari-Moghaddam A, Adineh HA, Zareban I, Kalan Farmanfarma KH. Prevalence of metabolic syndrome and population attributable risk for cardiovascular, stroke, and coronary heart diseases as well as myocardial infarction and all-cause mortality in middle-east: sys-2020;12:75–82.

263. Mini GK, Sarma PS, Thankappan KR. Overweight, the major determinant of metabolic syndrome among industrial workers in Kerala, India: results of a cross-sectional study. *Diabetes Metab Syndr*. 2018;13:3025–3030. doi: 10.1016/j.dsx.2018.07.009

264. Chowdhury MZI, Anik AM, Farhana Z, Bristi PD, Abu Al Mamun BM, thematic review & meta-analysis. *Obes Med*. 2019;14:100086. doi: Uddin MJ, Fatema J, Akter T, Tani TA, Rahman M, et al. Prevalence of metabolic syndrome in Bangladesh: a systematic review and meta-analysis of the stud-

- 10.1016/j.obmed.2019.100086
279. DeBoer MD, Filipp SL, Gurka MJ. Geographical variation in the prevalence of obesity and metabolic syndrome among US adolescents. *Pediatr Obes*. 2019;14:e12483. doi: 10.1111/ijpo.12483
280. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2024.
- ies. *BMC Public Health*. 2018;18:308. doi: 10.1186/s12889-018-5209-z

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Circulation.2025;151:e41–e660. DOI: 10.1161/CIR.0000000000001303

11. ADVERSE PREGNANCY OUTCOMES

See Tables 11-1 and 11-2 and Charts 11-1 through 11-8

[Click here to return to the](#)

APOs include gestational hypertension, preeclampsia, gestational diabetes, PTB, delivery of an infant who is SGA, pregnancy loss (eg, miscarriage or stillbirth), and placental abruption. The processes leading to these interrelated disorders reflect a response to the “stress test” of pregnancy, and they are associated with risk of poor future CVH outcomes in females and offspring, including CHD, stroke, and HF. Furthermore, growing rates of pregnancy-related morbidity and mortality in the United States are attributed predominantly to CVD. Because of this, the AHA has recognized the importance of raising awareness about these disorders in comprehensive CVH promotion and CVD prevention in birthing people. Furthermore,

Kawasaki Disease] for pregnancy-related risk factors for congenital HD).

Classification of APOs

• HDP

- Gestational hypertension: Gestational hypertension is de novo hypertension that develops after week 20 of pregnancy without protein in the urine or evidence of end-organ involvement.

- Hypertension after week 20 of pregnancy, most often de novo, with protein in the urine or other evidence of end-organ involvement is defined as preeclampsia and may progress to the convulsive phase or eclampsia.
- Chronic (ie, prepregnancy) hypertension is hypertension that is present before week 20 of pregnancy; note that preeclampsia/eclampsia can develop on top of chronic hypertension.
- The threshold for treatment of BP differs in pregnant and nonpregnant individuals. The American College of Obstetricians and Gynecologists defines HDP as a BP of $\geq 140/90$ mm Hg in pregnancy. In contrast, the AHA and ACC adopted a lower threshold for hypertension diagnosis in nonpregnant adults of $\geq 130/80$ mm Hg in 2017. In a retrospective cohort study, lowering the BP threshold to diagnose gestational hypertension would increase the prevalence from 6.0% to 13.8% in a sample of 137 398 females from an integrated health system between 2009 and 2014.⁴
- Gestational diabetes: De novo diabetes that develops after week 20 of pregnancy is considered gestational diabetes. Gestational diabetes often initially resolves after delivery but is strongly associated with future type 2 diabetes risk.⁵
- PTB: PTB includes spontaneous or indicated delivery before 37 weeks' gestation.
- Infant with SGA: An infant with a birth weight ≤ 10 th percentile for gestational age is considered to be SGA. SGA is called intrauterine growth restriction during gestation.

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- LBW is defined as a birth weight of <2500 g as per the WHO.⁶
- Pregnancy loss: Spontaneous loss of an intrauterine pregnancy is classified as pregnancy loss and is further categorized according to gestational age at which loss occurs.
 - Stillbirth: loss occurs at ≥ 20 weeks' gestational age; also called late fetal death and intrauterine fetal demise
 - Miscarriage: loss occurs before 20 weeks' gestational age; also called spontaneous abortion

- Placental abruption: Placental
tissue separation of a normally
attached placenta from the uterus before

Any APO

Incidence

- APOs (including HDP, gestational
diabetes, and SGA at birth) occur in
increasingly globally.⁷

Risk Factors (Including Social Determinants) (See Chart 11-1)

- According to a meta-analysis of individual partici-
pant data from 265 270 females from 39
European, North American, and Oceanic
cohort studies, the risk of any APO was
greater with higher categories of
prepregnancy BMI and greater degree of ges-
tational weight gain, with an aOR of 2.51 (95%
CI, 2.31–2.74) for females with prepregnancy
obesity and high (≥ 1.0 SD) gestational
weight gain (Chart 11-1).⁸
- A meta-analysis of 17 403 participants from 30
cross-sectional or case-control studies exam-
ined risk factors for PTB in Ethiopia (PTB preva-
lence is 11% in Ethiopia).⁹ This study showed
that pregnancy-induced hypertension (aOR, 5.11
[95% CI, 3.73–7.01]), living with HIV
(aOR, 4.74 [95% CI, 2.79–8.05]), rural
residence (aOR, 2.35 [95% CI, 1.56–
3.55]), premature rupture of membrane (aOR,
5.36 [95% CI, 3.76–7.64]), history of abortion
(aOR, 2.92 [95% CI, 1.91–4.47]),
multiple pregnancies (aOR, 3.60
[95% CI, 2.49–5.19]), and anemia dur-
ing pregnancy (aOR, 3.41 [95% CI, 2.1–5.56])
were associated with PTB.
- In 24 369 females from 12 studies (case-control,
cohort, and cross-sectional) in sub-Saharan

≥ 6 d/wk (OR 0.97 [95% CI,
protective for APOs.
overweight (OR, 1.42 [95%
1 obesity (OR, 1.68 [95% CI,
stage 2 or higher obesity (OR
2.18]) were associated with a
Avoiding harmful alcohol
PA were not independently
risk of adverse pregnancy
adjustment for other health

Africa, chronic hypertension (OR from
5 studies ranged from 2.2–10.5),
overweight (OR from 3 studies
ranged from 1.4–7.0), obesity (OR
from 5 studies ranged from 1.8–3.9),
diabetes (OR from 1 study was 5.4
[95% CI, 1.1–27.0]), and alcohol use
(OR from 1 study was 4.0 [95% CI,
1.8–8.8]) were significantly
associated with a high risk of
preeclampsia.¹⁰

Prevention

- In 15 509 females with 27 135
pregnancies from NHANES
(mean maternal age, 35.1 years; 35.8%
of pregnancies with ≥ 1 APO), most
healthy lifestyle factors
(defined as BMI 18.5–24.9 kg/m²,
nonsmoking, ≥ 150 min/wk of
moderate-to vigorous-intensity
PA, healthy eating [top 40% of DASH
score], no or low to moderate
alcohol intake [< 15 g/d], and use
of multivitamins) were independently
associated with lower risk of
APOs.¹¹ High-quality diet (highest
versus lowest quartile of DASH score,
0.85 [95% CI, 0.78–0.93]) and
multivitamin supplementation

healthy lifestyle factors had a PAR of 19% (95% CI, 13%–26%) with APOs.

- According to 21 systematic reviews and meta-analyses, and 54 RCTs, exercise interventions were more effective than standard prenatal care in decreasing gestational diabetes and gestational hypertension incidence by 39% and 47%, respectively.¹² Exercise interventions are particularly effective when they are supervised, have a low to moderate intensity level, and are initiated during the first trimester of pregnancy.

Pregnancy-Related Complications: Mortality and CVD

Pregnancy-Related Mortality

(See Chart 11-2)

- The pregnancy-related mortality rate was 32.9 per 100 000 live births in 2021.¹³ Maternal or pregnancy-related mortality is defined by the WHO as death while pregnant or within 42 days of the end of pregnancy; late maternal or pregnancy-related deaths occurring between 43 days and 1 year are not included as part of the definition.
- Maternal mortality rates have risen for all racial and ethnic groups since 2018. In 2021, maternal death rate per 100 000 live births was highest in NH Black females (69.9), followed by Hispanic females (28.0) and NH White females (26.6; Chart 11-2).¹³ • Pregnancy-related mortality rates were higher in older age groups for females ≥40 years of age compared with females <25 years of age (138.5 versus 20.4 per 100 000 live births) in 2021.¹³ • In a study of 712 284 birthing people in the Korean National Health Service, being the below the 25th percentile for income was associated with a higher mortality within 6 weeks of delivery (aOR, 2.42 [95% CI, 1.65–3.53]) and within 1 year (aOR, 1.83 [95% CI, 1.47–2.28]).¹⁴
- Between 1999 and 2019 in the United States, median-state pregnancy-related mortality increased in all racial and ethnic groups, although disparities were seen.¹⁵ Median mortality rates per 100 000 live births ranged from 14.0 (IQR, 5.7–23.9) to 49.2 (IQR, 14.4–88.0) among the American Indian and Alaska Native population; 26.7 (IQR, 18.3–32.9) to 55.4 (IQR, 31.6–74.5) among the Black population; 9.6 (IQR, 5.7–12.6) to 20.9 (IQR, 12.1–32.8)

among the Asian, Native Hawaiian, or Other Pacific Islander population; 9.6 (IQR, 6.9–11.6) to 19.1 (IQR, 11.6–24.9) among the Hispanic population; and 9.4 (IQR, 7.4–11.4) to 26.3 (IQR, 20.3–33.3) among the White population.

In each year between 1999 and 2019, the Black population had the high-est median rate,

whereas the American Indian and Alaska Native population had the largest increase in these rates. In 2019, pregnancy-related and highest in the South (94.2 [IQR, 45.4–193.4]).• From 2017 to 2019, the maternal mortality rate was lowest (14.0 deaths per 100 000 live births) for women living in large fringe metro

also elevated risks of hypertension among females who experienced extremely preterm (22–27 weeks' gestation; HR, 2.23 [95% CI, 1.98–2.5]) and mod-erately preterm (28–33 weeks' gestation; HR, 1.85 [95% CI, 1.74–1.97]) deliveries.

- Among 48 113 participants from the WHI, 13 482 (28.8%) reported ≥1 APOs (defined as HDP, gesta-tional counties and highest (26.1 deaths per 100 000 live births) for women living in noncore counties (ie, those not in

without APOs (1758 [5.8%]), and each APO was individually independently associated with future ASCVD (gestational diabetes: aOR, 1.32 [95% CI, 1.02–1.67]; LBW: aOR, 1.25 [95% CI, 1.12–1.39]; PTB: aOR, 1.23 [95% CI, 1.10–1.36]; HDP: aOR, 1.38 [95% CI, 1.19–1.58]; except for high birth proximity to a metro core).¹⁶ Cardiovascular maternal deaths (eg, from cardiomyopathy, arrhythmia, and congenital HD) are the most common cause of maternal or pregnancy-related mortality in high-income countries. In the United States, these accounted for 26.6% of maternal deaths from 2017 to 2019; HDP contributed an additional 6.3% of maternal deaths.¹⁷ In low- to middle-income countries, the second leading cause of death is HDP, accounting for 14% of maternal deaths.¹⁸

Long-Term Mortality

- The Collaborative Perinatal Project was a prospective cohort of 48 197 pregnant females at 12 US clinical centers during the years 1959 to 1966 (45% were Black females and 46% were White females).¹⁹

After a median of 52 years after pregnancy, the following APOs were associated with all-cause mortality: preterm spontaneous labor (HR, 1.07 [95% CI, 1.03–1.1]); premature

rupture of membranes (HR, 1.44 [95% CI, 0.97–1.22]); gestational hypertension (HR, 1.23 [95% CI, 1.05–1.44]); preeclampsia (HR, 1.32 [95% CI, 0.99–1.32]) and preeclampsia or eclampsia (HR, 1.32 [95% CI, 1.00–1.30]) compared with normotension; and gestational glucose (HR, 1.14 [95% CI, 1.00–1.30]) compared with normoglycemia. Preterm induced labor was associated with greater mortality risk among Black participants (HR, 1.64 [95% CI, 1.10–2.46]) compared with White participants (HR, 1.29 [95% CI, 0.97–1.73]).

1.23 [95% CI, 1.05–1.44]; preeclampsia (HR, 1.32 [95% CI, 0.99–1.32]) and preeclampsia or eclampsia (HR, 1.32 [95% CI, 1.00–1.30]) compared with normotension; and gestational glucose (HR, 1.14 [95% CI, 1.00–1.30]) compared with normoglycemia. associated with greater mortality risk among Black participants (HR, 1.64 [95% CI, 1.10–2.46]) compared with White participants (HR, 1.29 [95% CI, 0.97–1.73]).

Associations With Cardiovascular Risk Factors and CVD

- A cohort study of 2 195 989 Swedish females demonstrated a higher risk of hypertension within 10 years among those who had preterm delivery (gestational age <37 weeks; HR, 1.67 [95% CI, 1.61–1.74]) compared with those with full-term delivery (39–41 weeks' gestation).²⁰ There were

- In a study of 10 292 females in the WHI with APO data and adjudicated HF outcomes, only HDP was significantly associated with HF (aOR, 1.75 [95% CI, 1.22–2.50]) and HFpEF (aOR, 2.06 [95% CI, 1.29–3.27]).²² In mediation analyses, hypertension explained 24% (95% CI, 12%–73%), CHD explained 23% (95% CI, 11%–68%), and BMI explained 20% (95% CI, 10%–64%) of the association between HDP and HF.
- In a registry of 26 024 menopausal women from Japan (4.6% had HDP), the aOR for the combined 6 CVD categories (angina/MI, cerebral infarction, cerebral hemorrhage, SAH, HF, and aneurysm/ aortic dissection) was higher for those with HDP history and hypertension (OR, 4.11 [95% CI, 3.16–5.35]) compared with those with only hypertension (OR, 2.30 [95% CI, 2.02–2.63]) or only HDP (OR, 1.61 [95% CI, 1.03–2.53]).²³

Hypertensive Disorders of Pregnancy

Incidence, Prevalence, and Secular Trends

(See Charts 11-3 and 11-4)

- Rates of overall HDP are increasing. During 2017 to 2019, the prevalence of HDP among delivery hospitalizations increased from 13.3% to 15.9% (Chart 11-3). The highest prevalence was among females 35 to 44 and 45 to 55 years of age (18% and 31%, respectively) and those who were Black (20.9%) or American Indian and Alaska Native (16.4%).
- There is substantial geographic heterogeneity in rates of HDP across the United States (Chart 11-4). In 2019, the highest rate of HDP was observed in Louisiana at 116 per 1000 live births.
- Among 51 685 525 live births between 2007 and 2019, age-standardized HDP rates doubled (38.4 [95% CI, 38.2–38.6] to 77.8 [95% CI, 77.5–78.1] per 1000 live births).²⁴ An inflection point was observed in 2014, with an acceleration in the

rate of increase of HDP (from CI, 3.6%/v–4.7%/v) before [95% CI, 8.1%/v–10.1%/v] PTB and LBW increased occurring in the same rates of APOs were higher in and in older age groups. increases were seen across ethnic groups.

and conception by assisted (1.8 [95% CI, 1.6–2.1]). The nulliparity (32.3% [95% CI, 22.0%–25.6%]) and (22.8% [95% CI, 19.6%–

Weight Gain

- A review of 54 studies of >30 the obese weight category

Risk Factors (Including Social Determinants)

- Among 2304 female-newborn dyads in the multinational HAPO study, lower CVH (based on 5 metrics: BMI, BP, cholesterol, glucose, and smoking) at 28 weeks' gestation was associated with higher risk of preeclampsia; aRRs were 3.13 (95% CI, 1.39–7.06), 5.34 (95% CI, 2.44–11.70), and 9.30 (95% CI, 3.95–21.86) for females with ≥ 1 intermediate, 1 poor, or ≥ 2 poor (versus all ideal) CVH metrics during pregnancy, respectively.²⁵ Conversely, each 1-point higher (more favorable) CVH score was associated with 33% lower risk for preeclampsia (aRR, 0.67 [95% CI, 0.61–0.73]).
- Among 7633 pregnant females recruited between 12 and 20 weeks' gestation in the Ottawa and Kingston Birth Cohort from 2002 to 2009, risk factors for gestational hypertension and preeclampsia were studied and compared. Risk factors for gestational hypertension and preeclampsia were largely similar; aRRs for gestational hypertension and preeclampsia for overweight were 1.80 (95% CI, 1.35–2.41) and 1.93 (95% CI, 1.37–2.70), respectively; for obesity, 2.81 (95% CI, 2.07–3.81) and 3.38 (95% CI, 2.40–4.76); for nulliparity, 2.59 (95% CI, 1.90–3.52) and 2.78 (95% CI, 2.00–3.86); for preeclampsia in previous pregnancy, 14.09 (95% CI, 9.28–21.40) and 6.35 (95% CI,

3.69–10.94); for diabetes, 3.24 (95% CI, 1.17–8.97) and 3.76 (95% CI, 1.62–8.71); and for twin birth, 4.82 (95% CI, 1.47–15.83) and 10.25 (95% CI, 5.48–19.15).²⁶ In a meta-analysis of 25 356 688 pregnancies from 92 studies published between 2000 and 2015, the following factors at ≤ 16 weeks' gestation were associated with significantly elevated risks for preeclampsia (reported as pooled unadjusted RR): >35 years of age (versus <35 years of age; 1.2 [95% CI, 1.1–1.3]); prior preeclampsia (8.4 [95% CI, 7.1–9.9]); chronic hypertension (5.1 [95% CI, 4.0–6.5]); prepregnancy diabetes (3.7 [95% CI, 3.1–4.3]); prepregnancy obesity (BMI >30 kg/m² versus <30 kg/m²; 2.8 [95% CI, 2.6–3.1]); prior stillbirth (2.4 [95% CI, 1.7–3.4]); multifetal pregnancy (2.9 [95% CI, 2.6–3.1]); nulliparity (2.1 [95% CI, 1.9–2.4]); CKD (1.8 [95% CI, 1.5–2.1]); systemic lupus erythematosus (2.5 [95% CI, 1.0–6.3]); antiphospholipid antibody syndrome (2.8 [95% CI, 1.8–4.3]);

cies showed that gestational weight gain less than recommended (by the current Institute of Medicine and the American College of Obstetricians and Gynecologists guidelines²⁸) compared with weight gain within the guidelines was associated with higher odds of having an SGA neonate (OR, 1.30 [95% CI, 1.17–1.45]) and lower odds for pre-eclampsia (OR, 0.71 [95% CI, 0.63–0.79]).²⁹

- In a meta-analysis of 13 studies including 156 170 singleton pregnancies in females who delivered at term, higher-than-recommended gestational weight gain per the 2009 National Academy of Medicine (Institute of Medicine) guidelines³⁰ (12.5–18 kg for underweight [BMI <18.5 kg/m²], 11.5–16 kg for normal weight [BMI, 18.5–24.9 kg/m²], 7.0–11.5 kg for overweight [BMI, 25.0–29.9 kg/m²], and 5.0–9.0 kg for obese [BMI >30.0 kg/m²]) was associated with higher risks for overall HDP (OR, 1.79 [95% CI, 1.61–1.99]), gestational hypertension (OR, 1.67 [95% CI, 1.43–1.95]), and preeclampsia (OR, 1.92 [95% CI, 1.36–2.72]).³¹
- Among 8296 nulliparous females in the nuMoM2b study, higher HDP risks were observed for excess weight gain in midpregnancy (from 5–13 to 16–21 weeks' gestation; aIRR, 1.16 [95% CI, 1.01–1.35]) and late pregnancy (from 16–21 to 22–29 weeks' gestation; aIRR, 1.19 [95% CI, 1.02–1.40]) but not in early pregnancy (from prepregnancy to 5–13 weeks' gestation; aIRR, 0.95 [95% CI, 0.83–1.08]).³²• A meta-analysis of 61 studies showed that inter-pregnancy weight gain was associated with HDP (OR, 1.46 [95% CI, 1.12–1.91]; *I*₂=94.9%) and preeclampsia (OR, 1.92 [95% CI, 1.55–2.37]; *I*₂=93.6%).³³ In a meta-analysis of 12 studies, interpregnancy weight gain was associated with increased HDP risk; each 1-kg/m² increase in BMI from the start of one pregnancy to the next was associated with a 31% increase in OR for HDP (95% CI, 11%–53%).³⁴

Blood Pressure

- Among 586 females with a mean age of 28.5 years (SD, 4.5 years) followed up from preconception through early pregnancy, each 2-mm Hg higher mean arterial pressure during preconception was associated with a higher risk of HDP (aRR, 1.08 [95% CI, 1.01–1.14]); in addition, each 2-mm Hg

increase in mean arterial pressure from preconception to 4 weeks' gestation was associated with a higher risk of preeclampsia (aRR, 1.13 [95% CI, 1.02–1.25]), and each 2-mm Hg increase in mean arterial pressure from preconception to 20 weeks' gestation was associated with a higher risk of HDP (aRR, 1.14 [95% CI, 1.06–1.22]) and higher risk of preeclampsia (aRR, 1.20 [95% CI, 1.08–1.33]). Among females who had chronic hypertension before 23 weeks, a more intensive antihypertensive strategy targeting a BP of <140/90 mm Hg compared with a strategy of no treatment unless BP was severely elevated ($\geq 160/105$ mm Hg) demonstrated an 18% reduction in the composite outcome of preeclampsia with severe features, PTB before 35 weeks, placental abruption, or fetal/neonatal death (aRR, 0.82 [95% CI, 0.74–0.92]).³⁶ In this same trial, targeting a BP of <140/90 mm Hg was also associated with reduced risk of developing any preeclampsia (RR, 0.79 [95% CI, 0.69–0.89]), with no increased risk in an SGA infant.

- In a retrospective cohort of 174 925 nulliparous women from Kaiser Permanente Northern California hospitals in 2009 to 2019 with measured BP trajectories in early pregnancy (≈ 4 measurements at ≤ 20 weeks' gestation), the low-increasing, moderate-stable, and elevated-stable groups had higher odds for preeclampsia/eclampsia (OR, 3.25 [95% CI, 2.7–3.9]; OR, 5.3 [95% CI, 4.5–6.3]; and OR, 9.2

during pregnancy (reported at 25 weeks' gestation) was associated with risk for HDP; females with >3.5 g/d sodium intake had 54% (95% CI, 16%–104%) higher risk for gestational hypertension and 20% (95% CI, 1%–42%) higher risk for preeclampsia compared with females with <2.8 g/d sodium intake.³⁹

- Among 8259 pregnant females in the [95% CI, 7.7–11.1], respectively) and for gestational hypertension (OR, 6.4 [95% CI, 4.9–8.3]; OR, 13.6 [95% CI, 10.5–17.7]; and (OR, 30.2 [95% CI, 23.2–39.4], respectively) compared with the reference group with ultralow-declining BP trajectory.³⁷ The highest odds for preeclampsia/eclampsia were seen among Black women, followed by Hispanic women and Asian women, for all BP trajectories ($P_{\text{interaction}} < 0.01$). As an example, the aOR for the elevated stable trajectory was 9.1 (95% CI, 6.4–13.1) for Black females, 8.4 (95% CI, 6.0–11.8) for Hispanic females, and 7.4 (95% CI, 5.2–10.5) for Asian females (referent White females with ultralow-declining BP).

Diet and Exercise

- Among 8507 females in the multiancestry (25% NH White, 47% Black, 28% Hispanic) Boston Birth Cohort, a greater adherence to a Mediterranean-style diet was associated with a 22% lower odds of preeclampsia (aOR, 0.78 [95% CI, 0.64–0.96] for the highest compared with lowest adherence of diet score).³⁸
- Among 62 774 females with singleton pregnancies in the Danish National Birth Cohort, sodium intake

females in the lowest quartile (poorest quality) of the HEI-2010 compared with 20.3% for females in the highest quartile (aRR, 1.16 [95% CI, 1.02–1.31]).⁴⁰

Race and Ethnicity

- In the nuMoM2b study, greater acculturation (defined as born in the United States with high English proficiency versus born or not born in the United States with low proficiency in English or use of Spanish as the preferred language) was associated with higher risk of preeclampsia or eclampsia (aOR, 1.31 [95% CI, 1.03–1.67]) and gestational hypertension (aOR, 1.48 [95% CI, 1.22–1.79]).
- In a nationwide sample spanning 15 years (2004– 2019), among females with preeclampsia, Black females with high income (defined as 75th–100th percentile based on the median US income) still had worse maternal outcomes at delivery such as PPCM (aOR, 1.47 [95% CI, 1.16–1.86]), stroke (aOR, 2.05 [95% CI, 1.54–2.74]), HF (aOR, 1.63 [95% CI, 1.34–1.99]), cardiac arrhythmias (aOR, 1.43 [95% CI, 1.31–1.58]), and VTE (aOR, 2.37 [95% CI, 1.54–3.65]) compared with White females of low income (<25th percentile [ranging from <\$36 000 in 2002 to <\$48 000 in 2018]).⁴¹
- In a study of hospital discharge records among 45 204 Black California-born primiparous mothers (born 1982–1997) and their infants (born 1997–2011), early childhood and adulthood neighborhoods were categorized as deprived, mixed, or privileged based on the Index of Concentration at the Extremes (a measure of concentrated racial and economic segregation), yielding 9 life-course trajectories. Women living in deprived neighborhoods had the highest odds of HDP (mixed effect logistic regression, unadjusted OR, 1.26 [95% CI, 1.13– 1.40]) compared with women living in privileged neighborhoods.⁴² Among 2697 NH Black women in the Boston Birth Cohort (1998–2016), 40.5% were foreign born. Foreign-born women who had <10 years of residence in the United States had lower odds of preeclampsia than those who were born in the US (OR, 0.73 [95% CI, 0.55–0.97]).⁴³ The odds of preeclampsia in foreign-born women with duration of US residence ≥10 years was similar to that of US-born women.

Other

- Among SDB was sion 2 1.30– after AHI ≥ 5 (aRR, 1.32 [95% CI, 1.26–1.40]), preeclampsia (aOR, 1.52 [95% CI, 1.44–1.60]), and eclampsia (aOR, 1.81 [95% CI, 1.26–2.61]).⁵² Maternal depression, bipolar disorder, and mood disorder were not associated with any HDP.

Genetics/Family History

- In a meta-analysis (PM2.5) 1.24–
- In an who serum late for the glycerid ated [95% levels [95%
- In a ciation studied. tutions had 19 were (8.1% 2.52]) COVID-
- Similarly, in sample year (n=46 (aOR, females
- Other US autoim tosus increas deliveri indepen [95% moarap amona lupus dent CI.
- Among 9 097 355 pregnant women in the HCUP NIS data from 2004 through 2014, anxiety was associated with increased odds of gestational hypertension (aOR, 1.32 [95% CI, 1.26–1.40]), preeclampsia (aOR, 1.52 [95% CI, 1.44–1.60]), and eclampsia (aOR, 1.81 [95% CI, 1.26–2.61]).⁵² Maternal depression, bipolar disorder, and mood disorder were not associated with any HDP.
- There is evidence of intergenerational transmission of HDP risk. According to multigenerational birth records for 17 302 nulliparous females in the Aberdeen Intergenerational Cohort, being born of a pregnancy complicated by preeclampsia or gestational hypertension was associated with higher risk for preeclampsia (aRR ratio, 2.55 [95% CI, 1.87–3.47] and 1.44 [95% CI, 1.23–1.69], respectively) and gestational hypertension (aRR ratio, 1.37 [95% CI, 1.09–1.71] and 1.36 [95% CI, 1.24–1.49], respectively).^{32,53}
- Maternal, paternal, and fetal genomes may influence preeclampsia. Using the population-based Swedish Birth and Multi-Generation Registries of 244 564 sibling pairs, 1 study reported that $\approx 50\%$ of the variance in preeclampsia was attributed to genetic factors and that maternal genomes contributed more to preeclampsia liability than fetal or paternal genomes.⁵⁴ Specifically, 35% of the variance in liability of preeclampsia was attributable to maternal genetic effects, 20% to fetal genetic effects (maternal and paternal genetic effects), 13% to the couple effect, and $<1\%$ to shared sibling environment.
- Many genetic risk factors for HDP may overlap with traditional CVD risk factors, most notably BP and anthropometry phenotypes. According to data from the UK Biobank, GRSs for SBP (aOR per 1 SD, 1.22 [95% CI, 1.17–1.27]), DBP (aOR per 1 SD, 1.22 [95% CI, 1.17–1.26]), and BMI (aOR per 1 SD, 1.06 [95% CI, 1.02–1.10]) were significantly associated with HDP risk, whereas GRSs for heart rate, type 2 diabetes, smoking, and LDL-C were not associated.⁵⁵
- Analysis of genetic instruments related to BP-lowering pathways suggested that nitric oxide signaling might be particularly relevant for HDP risk (*GUCY1A3* SNP was associated with an aOR of 0.21 per 5-mm Hg lowering of SBP versus PRS for SBP: aOR, 0.65 per 5-mm Hg lowering of SBP: $P_{\text{heterogeneity}}=0.037$).⁵⁵
- In a nationwide analysis between 2016 and 2019, pregnant females from rural areas were at greater risk for maternal ICU admission (RR, 1.14 [95% CI, 1.04–1.20]) and maternal mortality (RR, 1.93 [1.71–2.17]) compared with their counterparts from urban areas.⁵¹

Genetic Variants

• Large GWASs of preeclampsia and maternal hypertension during pregnancy are beginning to emerge. For example, a European consortium of 16 743 women with prior preeclampsia and 15 200 women with preeclampsia or other maternal hypertension

during pregnancy identified 19 loci.⁵⁶ Seven of the 13 novel loci were previously identified in BP GWASs.

Prevention Breastfeeding

- Among 3598 participants from the Avon Longitudinal Study of Parents and Children cohort, after a mean follow-up of 18 years after delivery, breastfeeding for 6 to 9 months among females with HDP was associated with significant reductions in DBP (−4.87 mm Hg [95% CI, −7.86 to −1.88]), mean arterial pressure (−4.61 mm Hg [95% CI, −7.45 to −1.77]), and LDL-C (−0.40 mmol/L [95% CI, −0.62 to −0.17 mmol/L]).⁶²

Other

improve identification of pregnant women eligible for low-dose aspirin after 12 weeks' gestation to reduce preeclampsia risk. The sensitivity and positive predictive value of major risk factors to identify preeclampsia/eclampsia for low-dose aspirin eligibility were 17.5% and 12.8%, respectively. However, including women at the top 10% of a GRS composed of SBP and preeclampsia loci increased sensitivity to 30.4%, although a decline in the positive predictive value (11%) was noted.

- The role of variants associated with preeclampsia risk factors (eg, hypertension and BMI) in preeclampsia is supported by a study of 498 preeclampsia cases. An increasing burden of risk alleles for elevated DBP and BMI was associated with an increased risk of preeclampsia (OR for DBP, 1.11 [95% CI, 1.01–1.21]; OR for BMI, 1.10 [95% CI, 1.00–1.20]).⁵⁸

ischemic stroke (OR, 1.27 [95% CI, 1.12–1.44]).⁶¹ Associations with CAD were partly attenuated in mediation analyses that accounted for SBP (direct effect OR, 1.10 [95% CI, 1.02–1.18]) and type 2 diabetes (direct effect OR, 1.16 [95% CI, 1.04–1.29]).

- *TTN* variants, present in DCM and PPCM, are enriched in patients with preeclampsia, suggesting a shared genetic architecture. In a study of 181 primarily White females with preeclampsia, the prevalence of loss-of-function variants in cardiomyopathy genes was higher in preeclampsia cases compared with controls (5.5% versus 2.5%; $P=0.014$), with most variants found in the *TTN* gene (see Chapter 22 [Cardiomyopathy and Heart Failure]).⁵⁹

- Motivated by high disease heterogeneity and prior evidence suggesting increased risk in high-altitude regions, a study of $N=883$ families in the Peruvian Andes was performed. This study identified associations between preeclampsia and a fetal locus containing clotting factor genes *PROZ*, *F7*, and *F10*.⁶⁰ Genetic data have also been used to examine whether HDPs increase later-life CVD risk.

Specifically, univariate mendelian randomization demonstrated that HDPs were positively associated with CAD (OR, 1.24 [95% CI, 1.08–1.43]) and

Lifestyle Modifications

- PA is recommended for pregnant females without obstetrical or medical complications.^{63–65} Several reviews of the literature that supported these guidelines indicate that PA (600 MET-min/wk of moderate-intensity exercise) during pregnancy can decrease the odds of HDP by 25%.⁶⁶
- Aerobic exercise for ≈30 to 60 minutes 2 to 7 times/wk during pregnancy was associated with a significantly lower risk of gestational hypertension in a systematic review from 17 trials including 5075 pregnant females (RR, 0.70 [95% CI, 0.53–0.83] for HDP).⁶⁷
- A meta-analysis of 20 studies up to 2019 showed the effectiveness of lifestyle intervention and bariatric surgery on reduced risk of HDP (OR, 0.45 [95% CI, 0.32–0.63]), gestational hypertension (OR, 0.61 [95% CI, 0.44–0.85]), and preeclampsia (OR, 0.67 [95% CI, 0.51–0.88]).⁶⁸

Aspirin

- Low-dose aspirin started in early pregnancy reduces risk for some APOs among higher-risk females. A 2021 meta-analysis by the US Preventive Services Task Force reported a lower risk of preeclampsia (RR, 0.85 [95% CI, 0.75–0.95]), perinatal mortality (RR, 0.79 [95% CI, 0.66–0.96]), PTB <37 weeks (RR, 0.80 [95% CI, 0.67–0.95]), and fetal growth restriction (RR, 0.82 [95% CI, 0.68–0.99]) and no significant increase in bleeding-related harms.⁶⁹
- Specific aspirin dose and preeclampsia prevention were studied in 23 randomized trials (32 370 females). Females assigned at random to 150 mg experienced a 62% reduction in risk of preterm preeclampsia (RR, 0.38 [95% CI, 0.20–0.72]).⁷⁰ Aspirin doses <150 mg produced no significant reductions. The number of pregnant females needed to treat with 150 mg aspirin to prevent 1 case of

preeclampsia was 39 (95% a maximum 30% reduction in age preeclampsia at all

Complications: Maternal CVD

- In an analysis of 65 286 425 from January 1, 1998, through females with HDP had a pared with those without HDP $P<0.0001$).⁷¹ A significant ethnicity was observed with of stroke in Black females 1.86–2.30]) and Hispanic CI, 1.98–2.43]) compared with NH
- On the basis of data on 1.3 abstracted between 1997 and Practice Research Datalink in females with preeclampsia hypertension (HR, 4.47 [95% various CVD subtypes 1.53–2.35]; atherosclerotic CI, 1.54–1.81]; HF: HR, 2.13 AF: HR, 1.73 [95% CI, 1.38–cular mortality: HR, 2.12 [95% a median of 9.25 years (IQR,
- In a 1980 to 2004 national cohort Norway, in 508 422 females at first birth, preeclampsia significantly higher risk for HF 1.50–2.68]) compared with median 11.8 years of follow-
- In an analysis from the Nurses' ing >60 000 parous was associated with a 63% dent CVD (HR, 1.63 [95% CI, greater risk for preeclampsia 1.42–2.10]) than for 1.41 [95% CI, 1.03–1.93]).⁷⁴ relationship, with HRs of 1.48 and 2.28 (95% CI, 1.70–3.07) ≥ 2 HDP, respectively, viduals without a history of sis suggested that 64% (95% the increased risk of CVD explained by traditional CVD subsequent development of hypercholesterolemia, diabetes, and changes in

Complications: Offspring Morbidity and Mortality

- A meta-analysis of 40 studies showed that offspring (at <10 years of age) of mothers with preeclampsia had increased SBP (mean difference, 2.2 mm Hg

4.19%),⁷⁶ during a median maternal HDP was associated 1.26 [95% CI, 1.18–1.34]) mortality in offspring.⁷⁷ maternal preeclampsia. sion was also elevated (OR, 1.38]. OR, 2.88 [95% CI, [95% CI, 0.98–1.28], respectively).

Gestational Diabetes

Incidence, Prevalence, and (See Chart 11-5)

- The pooled global tational diabetes in 2021 was This ranged from 7.1% in Caribbean to 27.6% in the Africa. The standardized diabetes in low-, middle- and was 12.7%, 9.2%, and 14.2%,
- In a meta-analysis of 254 pregnant women between weighted prevalence of 24 European countries was (95% CI, 10.0%–11.8%;
- The US national prevalence of was 8.3% in 2021, an according to birth data from gestational diabetes rose age: In 2021, the rate for was almost 6 times as high <20 years of age (15.6%
- The prevalence of gestational est in NH Asian females American Indian or Alaska Native Hawaiian or Other (10.6%), Hispanic females females (7.0%), and NH Black
- The prevalence of gestational with each adiposity category among females with females with obesity (Chart
- Temporal trends in gestational estimated from a serial cross- of NCHS data for 12 610 235 years of age with singleton 2011 to 2019 in the United [95% CI, 1.28–3.12]) and DBP (mean difference, 1.41 mm Hg [95% CI, 0.3–2.52]) compared with

years [SD, 5.8 years]).⁸¹ Gestational diabetes rates increased across all races and ethnicities from 47.6 to 63.5 per 1000 live births from 2011 to 2019, a mean annual percent change of 3.7% (95% CI, 2.8%–4.6%) per year.

- Of the participants, the following were race-specific

control subjects.⁷⁵

gestational diabetes rates: Hispanic/Latina, 66.6

- Among 2 437 718 individuals born in Denmark from 1978 to 2018 (102 095 of their mothers had HDP,

per 1000 live births (95% CI, 65.6–67.7; RR, 1.15 [95% CI, 1.13–1.18]); NH Asian/Pacific Islander,

102.7 per 1000 live births (95% CI, 100.7–104.7; RR, 1.78 [95% CI, 1.74–1.82]); NH Black, 55.7 per 1000 live births (95% CI, 54.5–57.0; RR, 0.97 [95% CI, 0.94–0.99]); and NH White, 57.7 per 1000 live births (95% CI, 57.2–58.3; referent group).

- Gestational diabetes rates were highest in Asian Indian participants, 129.1 per 1000 live births (95% CI, 100.7–104.7; RR, 2.24 [95% CI, 2.15–2.33]).
individuals at 75.8 per 1000 live births (95% CI, 71.8–79.9; RR, 1.31 [95% CI, 1.24–1.39]).

Risk Factors (Including Social Determinants)

- In an individual participant data meta-analysis of 265 270 births from 39 cohorts in Europe, North America, and Australia, higher prepregnancy BMI (OR per 1-kg/m² higher BMI, 1.12 [95% CI, 1.12–1.13]) and higher gestational weight gain (OR per 1-SD higher gestational weight gain, 1.14 [95% CI, 1.10–1.18]) were associated with higher risks of gestational diabetes.⁸ Approximately 42.8% of gestational diabetes cases were estimated as attributable to prepregnancy overweight (OR, 2.22 [95% CI, 2.06–2.40]) or obesity (OR, 4.59 [95% CI, 4.22–4.99]).
- In the nuMoM2b study, among 782 nulliparous females in the early second trimester with objec-

- Among 8 574 264 females 15 to 44 years of age at first live singleton birth in the United States, 1 747 066 (20%) were born outside the United States.⁸⁵ In females born outside the United States, gestational diabetes rates were higher than in females born in the United States (70.3 versus 53.2 per 1000 live births; rate ratio, 1.32 [95% CI, 1.31–1.33]).

tively measured sleep for 5 to 7 nights, short sleep duration (<7 h/night average; present in 27.9%) and late sleep midpoint (>5 am average; present in 18.9%) were significantly associated with risk for gestational diabetes (aOR, 2.06 [95% CI, 1.01–4.19] and 2.37 [95% CI, 1.13–4.97], respectively) independently of age, race and ethnicity, employment schedule, BMI, and snoring.⁸²

- In a cohort of 595 pregnant females in 4 US areas (Chicago, IL; Schuylkill County, Pennsylvania; Pittsburgh, PA; and San Antonio, TX), perceived discrimination (self-reported as based on sex, race, income level or social status, age, and physical appearance) was associated with the development of gestational diabetes. Gestational diabetes occurred in 12.8% of females in the top quartile of a self-reported discrimination scale versus 7.0% in all others (aOR, 2.11 [95% CI, 1.03–4.22] adjusted for age, income, parity, race and ethnicity, and study site); 22.6% of this association was statistically

those born in the United States).

Genetics/Family History

- Although gestational diabetes is thought to be heritable, heritability estimates from twin or familial clustering studies are not available. Korean females with gestational diabetes had a greater parental history of type 2 diabetes compared with pregnant females with normal glucose tolerance (30.1% versus 13.2%; $P<0.001$).⁸⁶ Gestational diabetes and type 2 diabetes also demonstrate high levels of genetic correlation ($r_g=0.71$).
- Reflecting the hypothesis that gestational diabetes and diabetes have a shared genetic architecture, the majority of gestational diabetes genetic studies have examined variants previously mapped for type 2 diabetes. For example, a meta-analysis of 23 studies examined the relevance of 100 type 2 diabetes variants that were reported by a minimum of 2 studies for gestational diabetes. This meta-analysis identified significant associations for gestational diabetes with 16 variants in 8 loci (in or near *IGF2BP2*, *CDKAL1*, *GLIS3*, *CDKN2A/2B*, *HHEX/IDE*, *TCF7L2*, *MTNR1B*, and *HNF1A*).⁸⁷
- An early GWAS of gestational diabetes in the FinnGen cohort and UK Biobank participants of European ancestry identified 4 maternal loci: *GCKR*, *HLA*, *TCF7L2*, and *MTNR1B*. All of these maternal loci are known to affect type 2 diabetes as well.⁸⁸ Similarly, in a multi-ancestry GWAS of $n=5485$ females with gestational diabetes and $n=347\,856$ females without gestational diabetes that also included UK Biobank participants, 5 gestational diabetes loci were identified: *MTNR1B*, *TCF7L2*, *CDKAL1*, *CDKN2A/2B*, and *HKDC1*. *HKDC1* was the only locus without evidence pointing to a shared pathophysiology between gestational diabetes and type 2 diabetes.⁸⁹ mediated by obesity.⁸³
- A systematic review of 17 studies demonstrated that individuals with gestational diabetes had statistically significant differences in the diversity of gut microbes.⁸⁴ Six prospective studies found that microbiota change during pregnancy is associated with risk of gestational diabetes. There was considerable heterogeneity in the type of microbiota change evaluated in these 6 studies.

- Recently, a large GWAS of gestational diabetes (N=12 332 cases) was published in FinnGen Finnish participants.⁹⁰ By identifying 13 loci, 9 of which were new, this GWAS approximately tripled the number of gestational diabetes loci. Findings suggests that the genetic architecture of gestational diabetes includes 2 distinct categories. The first category overlaps type 2 diabetes and

includes *GCKR* and *TCF7L2*. *Complications: Offspring Morbidity*

includes *ESR1* and possibility of different actions pregnancy.

- GRSs composed of diabetes loci diabetes. In a case-control with gestational diabetes and out gestational diabetes from Health Study II and the Cohort, a weighted GRS of 8

associated with diabetes was associated with gestational diabetes (OR for highest GRS quartile compared with lowest, 1.53 [95% CI, 1.34–1.74]).⁹¹

Similarly, among the US-based nuMoM2b cohort, compared with the general population, participants with a high diabetes GRS and low PA levels had

- In a meta-analysis of 24 tive studies, offspringes in utero had higher SBP mm Hg [95% CI, 0.57–2.94], difference, 0.11 [95% CI, (SMD, 0.43 [95% CI, 0.08–those not exposed to
- Among 2 432 000 live-born genital HD in the Danish higher odds of a gestational diabetes diagnosis (OR, 3.4 [95% CI, 2.3–5.3]). In contrast, compared with the general population, participants with a low

during 1977 to 2016, in utero exposure to gesta-tional diabetes was associated with higher risk for CVD during up to 40 years of follow-up (aOR, 1.19 [95% CI, 1.07–1.32]).⁹⁷ Findings were similar when a sibship design was used (ie, comparing gesta-tional diabetes–exposed with unexposed siblings) and when controlling for maternal prepregnancy BMI and paternal diabetes status.

diabetes GRS and high PA levels had a lower odds of a gestational diabetes diagnosis (OR, 0.5 [95% CI, 0.3–0.9]).⁹²

Preterm Birth

Incidence, Prevalence, and Secular Trends

- Association of diabetes GRSs with gestational diabetes is consistent in other ancestries; in a study of 832 South Asian females from the START and UK Biobank cohorts, a diabetes GRS optimized to South Asian ancestry was associated with gesta-tional diabetes (OR, 2.51 [95% CI, 1.82–3.47]; $P=1.75\times10^{-8}$; and OR, 2.66 [95% CI, 1.51–4.63]; $P=0.0006$, respectively, for the top 25% of GRSs compared with the bottom 75%).⁹³

Prevention

- A meta-analysis of 35 randomized trials showed that exercise interventions during pregnancy decrease the incidence of developing gestational diabetes (pooled OR, 0.61 [95% CI, 0.51–0.74]), particularly when they are supervised, have a low to moderate intensity level, and are initiated during the first trimester of pregnancy.¹²
- A meta-analysis of 7 trials with 1647 participants

showed that probiotics did not lower the risk of gesta-tional diabetes compared with placebo (mean RR, 0.80 [95% CI, 0.54–1.20]).⁹⁴ Furthermore, in 4 of these studies, probiotics increased the risk of pre-eclampsia compared with placebo (RR, 1.85 [95% CI, 1.04–3.29]).

Complications: Maternal Cardiovascular Risk

Factors and CVD

- In a meta-analysis of 20 studies that included 1 332 373 individuals, the RR for diabetes was estimated as 10 times higher (95% CI, 7.14–12.67) in females with a history of gestational diabetes compared with females without gestational diabetes.⁹⁵

- An analysis of all birth certificates for singleton births registered in the United States from 2014 to 2022 showed that PTB and early-term birth rates rose from 2014 to 2022 (by 12% and 20%, respectively), whereas full/late and postterm births declined (by 6% and 28%, respectively).⁹⁸ Similar trends were noted across maternal age and race and Hispanic-origin groups. The largest increase was observed for births at 37 weeks (42%).
- Among all singleton deliveries at a single US tertiary care center, compared with the overall PTB rate before the COVID-19 pandemic (11.1% among 17 687 deliveries from January 1, 2018–January 31, 2020), the rate was significantly lower during the pandemic (10.1% among 5396 deliveries from April 1, 2020–October 27, 2020; $P=0.039$ for comparison); spontaneous PTB rates also decreased during the pandemic (from 5.7% to 5.0%; $P=0.074$). However, decreases in spontaneous PTB occurred only among females from more advantaged neighborhoods (versus less advantaged neighborhoods; from 4.4% to 3.8% versus from 7.2% to 7.4%), White females (versus Black females; from 5.6% to 4.7% versus from 6.6% to 7.1%), and females receiving care from clinics that do not (versus do) provide prenatal care to those eligible for medical assistance (from 5.5% to 4.8% versus from 6.3% to 6.7%).⁹⁹

Risk Factors

- In a meta-analysis of studies reported between December 2019 and June 2020, maternal COVID-19 infection (versus no COVID-19 infection) was associated with higher prevalence and odds of

PTB (10.8% versus 6.0%; OR, 3.0 [95% CI, 1.15–7.85]).¹⁰⁰ In another US study using a surveillance database, among 4442 pregnant females with COVID-19 from March to October 2020, the PTB rate was 12.9%; this was higher than the rate in the general population in 2019 (10.2%).¹⁰¹

- Among 1482 nulliparous low-risk females at <20 weeks' gestation (who received placebo in a trial of low-dose aspirin to prevent even with mild stage 1 hypertension (SBP from 130–135 mm Hg or DBP from 80–85 mm Hg; 4.2% versus 1.1%; RR, 3.79 [95% CI, 1.28–

for each 5.6° C increase in weekly mean temperature.¹⁰⁵ Similarly, in a meta-analysis of 47 studies including international populations, the odds of PTB were 1.05 times higher (95% CI, 1.03–1.07) per 1° C increase in environmental temperature and were 1.16 times higher (95% CI, 1.10–1.23) during heat waves (defined in this analysis

11.20]; adjusted for age, race, and prepregnancy BMI: RR, 3.98 [95% CI, 1.36–11.70]).¹⁰²

- In a meta-analysis of 6 studies, objectively mea-

green space or greater environmental greenness (based on a standardized measure commonly used to indicate the presence and level of green space: the normalized difference vegetation index) within a 100-m buffer were associated with a lower risk for PTB (pooled standardized OR, 0.98 [95% CI, 0.97–0.99]).¹⁰⁸

of PTB, with an aOR of 1.6 (95% CI, 1.2–2.2).¹⁰³• 1.31–3.43]), maternal personality disorder (OR, 2.98 [95% CI, 1.38–6.44]), SDB (OR, 2.32 [95% CI, 1.87–2.89]), prior induced termination of pregnancy with vacuum aspiration (OR, 1.20 [95% CI, 1.13–1.27]), low gestational weight gain (OR, 1.64 [95% CI, 1.55–1.74]), and interpregnancy interval after miscarriage <6 months (OR, 0.79 [95% CI, 0.73–0.84]).¹⁰⁴

In an umbrella review of 85 eligible meta-analyses including 1480 primary studies providing data on 166 associations for the risk of PTB, the following 7 risk factors provided robust evidence for their association with PTB: amphetamine exposure (random-effects OR, 4.11 [95% CI, 1.8–9.37]), isolated single umbilical artery (OR, 2.12 [95% CI,

Environmental Exposures

Social Determinants of Health and Health Equity in PTB

- In a meta-analysis of 13 studies of 9299 females, increased odds of PTB (pooled OR, 1.40 [95% CI, 1.17–1.68]).¹⁰⁹
- Among infants born to females who were evicted in Georgia from 2000 to 2016, eviction during gestation (versus infants born to females who experienced an eviction before they were pregnant) was associated with 1.14% (95% CI, 0.21%–2.06%) higher rate of PTB after covariate adjustment (crude rate, 15.28% versus 13.36%, respectively).¹¹⁰
- In a cohort of 3801 females with 9075 live singleton births, latent class analysis revealed a stress/anxiety/depression class that was associated with increased risk for PTB (OR, 1.87 [95% CI, 1.20–2.30]).¹¹¹
- In a systematic review of studies examining air pollution, significant associations were found with PTB for 19 of 24 studies (examining a total of >7 million births). The risk was higher by a median of 11.5% (range, 2.0%–19.0%) for whole-pregnancy PM_{2.5} exposure per IQR higher exposure,¹⁰⁵ and risk was greater among NH Black females compared with NH White females. In a study of >14 000 mothers in California, the risk of PTB associated with increasing temperature was numerically but not statistically higher among Black mothers (24.6% [95% CI, 1.0%–55.3%]) and Hispanic mothers (17.4% [95% CI, 3.0%–35.0%]) compared with Asian mothers (7.3% [95% CI, –11.3% to 31.0%]) or White mothers (7.3% [95% CI, –6.8% to 22.1%]; $P=0.56$, 0.64, and 1.0, respectively, with White mothers as refer-

- In a study from data from the California Office of Statewide Health Planning and Development, 2794 females with unstable housing were propensity score matched with 2318 control subjects.¹¹² Females with unstable housing had higher odds of PTB (OR, 1.2 [95% CI, 1.0–1.4]; $P<0.05$) and preterm labor (OR, 1.4 [95% CI, 1.2–1.6]; $P<0.001$). • A retrospective study of US Vital Statistics data in 2018 showed that a county-level Maternal Vulnerability Index (a composite measure of 43 area-level indicators categorized into 6 themes reflecting physical, social, and health care landscapes) was associated with PTB (OR, 1.07 [95% CI, 1.01–1.13]).¹¹³ In adjusted analyses of PTB categories (extreme [gestational age ≤ 28 weeks], very preterm group).¹⁰⁶ [gestational age 29–31 weeks], moderate [gestational age 32–33 weeks], and late preterm [gestational age 34–36 weeks]).
- In a systematic review, 4 of 5 studies (>800 000 births) examining heat demonstrated that risk for PTB was higher by a median of 15.8% (range, 10.0–21.5%).

tional age 32-33 weeks], and late [gestational age 34-36 weeks]), Maternal Vulnerability Index had the greatest association with extreme PTB (aOR, 1.18 [95% CI, 1.07–1.29]).

9.0%–22.0%) for whole-pregnancy

Genetics/Family History

- There is evidence of of PTB risk.¹¹⁴ For example, maternal genetic effects on 15% to 40%, although these include effects of the fetal factors were estimated to the variation in gestational negligible to small genetic for the maternal contribution.¹¹⁵
- A maternal GWAS (43 568 females of European ancestry) of gestational duration (n=68 732) and spontaneous PTB (n=98 370) identified 15 loci for gestational duration and 4 loci for spontaneous PTB.¹¹⁶ Consistent with previous GWASs, the *EBF1* and *EEFSEC* loci were associated with gestational duration and spontaneous PTB,¹¹⁷ whereas associations with *GC*, *RHAG*, *WNT3A*, and *GNAQ* were novel. Genes at identified loci

Race and Ethnicity

- Among 9470 nulliparous NH White, 13.8% NH Black, 4.0% Asian, 5.0% other), PTB of NH White females, 12.3% (OR versus NH White 1.32–1.93), 8.1% of Hispanic [95% CI, 0.82–1.23], and (OR, 0.77 [95% CI, 0.51– among NH Black females was have previously established roles in uterine development, maternal nutrition, and vascular control. Despite its large size, the relatively small number of identified loci, particularly for spontaneous PTB, highlights the challenges associated with charac-

by adjustment for age, BMI, smoking, and medical comorbidities (aOR, 1.31 [95% CI, 1.06–1.63]) and, separately, for perceived social support (aOR, 1.35 [95% CI, 1.06–1.72]). The OR for the association of low perceived social support (lowest quartile of support) with PTB was 1.21 (95% CI, 1.01–1.44). • Examination of state Medicaid expansion noted an association with improvement in relative disparities between Black people and White people in rates of PTB among states that expanded compared with those that did not. Difference-in-difference models between 2011 and 2016 estimated a decline of –0.43 percentage points (95% CI, –0.84 to –0.002) for PTB for Black infants compared with

terizing the genetic architecture underlying parturition timing.

- A large maternal GWAS of gestational duration (n=195 555) and preterm delivery (n=18 797) in women of European ancestry identified 22 and 7 loci, respectively.¹¹⁸ Effect sizes for gestational duration were very small, increasing gestation by 7 to 27 hours per coded allele. It is interesting

White infants.¹²¹

- Black race–White race disparities in PTB are that 15 of the 22 loci identified for gestational duration acted through the maternal genome, whereas 7 loci acted through the maternal and

also present among females of high SES; among 2 170 686 singleton live births in the United States from 2015 to 2017 to college-educated females with private insurance who were not receiving WIC benefits, PTB rates for females who identified as NH White, multiracial NH White/Black, and NH Black were 5.5% versus 6.1% versus 9.9%, respectively, for PTB at <37 weeks' gestation and 0.2% versus 0.4% versus 1.2% for PTB at <28 weeks' gestation.¹²²

fetal genomes. Only 2 loci for gestational duration acted through the fetal genome. The genetic architecture governing gestational duration and preterm delivery also showed strong inverse correlation ($r_g = -0.62$). Last, GRS for gestational duration explained 2.2% of trait variance. For pre-term delivery, the GRS showed modest discrimina-

Complications: Maternal CVD and Mortality

- Among 57 904 females in the Nurses' Health Study with type 2 diabetes, increased risk of hypertension (HR, 1.11 [95% CI, 1.06–1.17]; median follow-up, 28 years), type 2 diabetes (HR, 1.17 [95% CI, 1.03–1.33]; median $P=2.2\times10^{-9}$), and higher birth weight (15 g/cm [95% CI, 13.7–16.3]; $P=1.5\times10^{-111}$).¹¹⁹ Genetically determined maternal BMI was associated with higher birth weight (15.6 g/[kg/m²] [95% CI, 13.5–17.7]; $P=1.0\times10^{-47}$) but not gestational duration or PTB risk.
- An international study that evaluated genetic scores known to be associated with adult height, BMI, BP, blood glucose, and type 2 diabetes in 10 734 female-infant duos of European ancestry found that taller genetic maternal height was associated with longer gestational duration (0.14 d/cm [95% CI, 0.10–0.18]; $P=2.2\times10^{-12}$), lower PTB risk (OR, 0.7/cm [95% CI, 0.96–0.98];

follow-up, 32 years), and hyperlipidemia (HR, 1.07 [95% CI, 1.03–1.11]; median follow-up, 26 years).¹²³• In a meta-analysis of 14 studies, females with a history of PTB (<37 weeks' gestation) had a 63% (95% CI, 1.39%–1.93%) higher risk of CVD compared with females with no history of PTB.¹²⁴

- Among 2 189 477 females with a singleton delivery in 1973 to 2015, risk of all-cause mortality was higher among those mothers with PTB (<37 weeks' gestational age) with an aHR of 1.73 (95% CI, 1.61–1.87) in the 10 years after delivery; a dose-dependent relationship was observed with higher risk based on delivery at earlier gestational ages

(extremely preterm, 22–27 weeks: 2.20 [95% CI, 1.63–2.96]; very preterm, 28–33 weeks: 2.28 [95% CI, 2.01–2.58]; late preterm, 34–36 weeks: 1.52 [95% CI, 1.39–1.67]; early term, 37–38 weeks: 1.19 [95% CI, 1.12–1.27]) compared with full-term delivery between 39 and 41 weeks.¹²⁵

Complications: Offspring Morbidity and Mortality •

In a meta-analysis of 4 cohort studies, having

MetS in childhood and adulthood (pooled OR, 1.72 [95% CI, 1.12–2.65]).¹²⁶

- In analyses of Swedish national birth register data (>2 million–>4 million individuals), gestational age at birth was inversely associated with the risks for type 1 diabetes (aHR, 1.21 [95% CI, 1.14–1.28] at <18 years of age and 1.24 [95% CI, 1.13–1.37] at 18–43 years of age), type 2 diabetes (aHR, 1.26 [95% CI, 1.01–1.58] at <18 years of age and 1.49 [95% CI, 1.31–1.68] at 18–43 years of age), hypertension (aHR, 1.24 [95% CI, 1.15–1.34] at <18 years of age, 1.28 [95% CI, 1.21–1.36] at 18–29 years of age, and 1.25 [95% CI, 1.18–1.31] at 30–43 years of age), and lipid disorders (aHR, 1.23 [95% CI, 1.16–1.29] at 0–44 years of age) among individuals born preterm compared with those born term.

- In cosibling analyses, associations remained significant for type 1 and 2 diabetes but were largely attenuated for hypertension and lipid disorders (suggesting that shared familial genetic and lifestyle risk factors for PTB and hypertension or lipid disorders accounted

age (aHR, 1.42 [95% CI, 1.19–1.71]) compared with individuals born full term. A dose-dependent relationship with prematurity was observed with further stratification in the group 18 to 43 years of age with highest risk for HF among those born extremely preterm (22–27 weeks; HR, 4.72 [95% CI, 2.75–4.27]).¹³²

for much of their associations).^{127–129} • Among participants in the WHI study, being born preterm was associated with incident hypertension (53.2% versus 51%; HR, 1.10 [95% CI, 1.03–1.19]; $P=0.008$) and early-onset hypertension (<50 years of age; 14.7% versus 11.7%; OR, 1.31 [95% CI, 1.15–1.48]; $P<0.0001$).¹³⁰

Offspring Cardiac Remodeling and HF

- In a 2020 meta-analysis of 32 studies, individuals born preterm had higher LV mass (increase compared with control subjects, 0.71 g/m² [95% CI, 0.20–1.22] per year from childhood), smaller LV diastolic dimension (percent WMD in young adulthood, –4.9%; $P=0.006$), lower LV stroke volume index (percent WMD in young adulthood, –8.2%; $P<0.001$), poorer LV diastolic function (e' percent WMD in childhood/young adulthood, –5.9%; $P<0.001$), and poorer RV systolic function (longitudinal strain percent WMD, –14.3%; $P<0.001$) compared with term-born individuals.¹³¹
- In a study of 4 193 069 individuals born in Sweden during 1973 through 2014, PTB was associated with higher risk of HF at <1 year of age (aHR, 4.49 [95% CI, 3.86–5.22]), 1 to 17 years of age (aHR,

Swedish Birth Registry from 1973 to 1994 followed up through 2015 (maximum, 43 years of age), gestational age at birth was inversely associated with risk for premature CHD (aHR at 30–43 years of age versus full-term [39–41 weeks] births: for pre-term [<37 weeks], 1.53 [95% CI, 1.20–1.94]; for early term [37–38 weeks], 1.19 [95% CI, 1.01–1.40]).¹³³ Cosibling analyses supported an association that was independent of familial shared genetic and environmental factors.

- Among 4 296 814 singleton live births in Sweden during 1973 to 2015 with up to 45 years of follow-up, gestational age at birth was inversely associated with mortality at 0 to 45 years of age, with an aHR of 0.78 (95% CI, 0.78–0.78) per 1-week-longer gestation.¹³⁴ Relative to full-term birth (39–41 weeks), PTB (<37 weeks) and early-term birth (37–38 weeks) were associated with mortality (aHR, 5.01 [95% CI, 4.88–5.15] and 1.34 [95% CI, 1.30–1.37], respectively), and earlier gestations were associated with even higher risks (eg, <28 weeks; aHR, 66.14 [95% CI, 63.09–69.34]). The HRs for mortality were highest in infancy (aHR for preterm, 17.15 [95% CI, 16.50–17.82]) and weakened at subsequent age intervals but remained significantly elevated through 30 to 45 years of age (aHR for preterm, 1.28 [95% CI, 1.14–1.43]).

LBW or SGA Delivery

Incidence, Prevalence, and Secular Trends

(See Chart 11-6)

- The percentage of infants born LBW (<2500 grams or 5 lb 8 ounces) rose 3% in 2021 (8.52% versus 8.24% in 2020).¹³⁵ Prevalence of LBW by race is shown in Chart 11-6.

Risk Factors (Including Social Determinants)

- Among 1482 nulliparous low-risk females at <20 weeks' gestation (who received placebo in a trial of low-dose aspirin to prevent preeclampsia), risks for SGA delivery were elevated even for mild stage 1 hypertension (SBP of 130–135 mm Hg or DBP of 80–85 mm Hg; 10.2% versus 5.6%; adjusted for age, race, and prepregnancy BMI: RR, 2.16 [95% CI, 1.12–4.16]) by the 2017 Hypertension Clinical Practice Guidelines.¹⁰² 3.42, [95% CI, 2.75–4.27]), and 18 to 43

• In an individual participant data *Environmental Exposures*

265 270 births from 39 America, and Australia. weight BMI (BMI <18.5 kg/m²; CI, 1.58–1.76) was for SGA delivery.⁸ Females pregnancy BMI and low had the highest odds for SGA (CI, 2.75–3.54), but risks were gestational weight gain was

with normal weight (1.81 [95% CI, 1.73–1.89]) and overweight (1.23 [95% CI, 1.14–1.33]) but not females with obesity.

- Among 8259 pregnant females in the nuMoM2b cohort, periconceptional dietary quality was associated with risks for SGA (birth weight <10th percentile for gestational age) and LBW (<2500 g). The SGA and LBW rates were 12.8% and

- In a systematic review of studies of air pollution, found with LBW for 25 of 29 total of >18 million births) in
- The median risk was 10.8% (36.0%) for whole-pregnancy IOR greater exposure (eq. 6 whole-pregnancy median of 6.45 µg/m³) of PM_{2.5}

7.7%, respectively, for females in the lowest quartile (poorest quality) of the HEI-2010 compared with 9.5% and 5.4% for females in the highest quartile (aRR, 1.24 [95% CI, 1.02–1.51] and 1.32 [95% CI, 1.02–1.71],

risk was higher by 3% for each 5-km closer proximity to a solid waste plant.¹⁰⁵

- In a systematic review examining heat, 3 of 3 studies (2.7 million births) demonstrated that the median risk for LBW was 31.0% higher (range, 13.0%–49.0%) for whole-pregnancy heat exposure per 5.6° C higher weekly mean temperature, and in 1 study, whole-pregnancy ambient local temperature >95th percentile was associated with an RR of 2.49 (95% CI, 2.20–2.83).¹⁰⁵
- In a meta-analysis of 5 studies, more favorable environmental characteristics such as greater access to green space or greater environmental greenness respectively).⁴⁰
 - Among 3435 females in a health system with routine urine toxicology screening at the first prenatal visit, cannabis exposure (detected in 8.2% of females) was associated with SGA delivery, with an aRR of 1.69 (95% CI, 1.22–2.34) after adjustment for maternal race and ethnicity, prepregnancy BMI, age, and cigarette smoking. In stratified analyses, the aRR for SGA associated with cannabis exposure was 1.42 (95% CI, 0.32–2.15) in females who did not also smoke cigarettes and 2.38 (95% CI, 1.35–4.19) in females who also smoked cigarettes during pregnancy.¹³⁶
 - In a study of 156 278 nulliparous females in Ontario, Canada, with singleton pregnancies between January 2011 and December 2018, the associations between prepregnancy HbA1c, glucose, lipids, and alanine aminotransferase and SGA were studied.¹³⁷ There were 19 367 SGA infants. Females with SGA infants had lower pregravid fasting glu-

(based on a standardized measure commonly used to indicate the presence and level of green space: the normalized difference vegetation index) within a 100- to 500-m buffer were associated with lower risk for LBW or SGA infants (pooled standardized OR, 0.94 [95% CI, 0.92–0.97]).¹⁰⁸

Social Determinants of Health/Health Equity

- In a meta-analysis of 3 studies of 1588 participants from the United States and Australia, racial discrimination was associated with increased odds of SGA (OR 1.23 [95% CI, 0.76–1.99]).¹⁰⁹
- Among infants born to females who were evicted in Georgia from 2000 to 2016, eviction during gestation (versus infants born to females who experienced an eviction before they were pregnant) was associated with a 0.88% (95% CI, 0.23%–1.54%) higher rate of LBW (<2500 g) after covariate adjustment (crude rate, 11.59% versus 10.24%, respectively).¹¹⁰
 - cose (4.69 mmol/L versus 4.73 mmol/L), random glucose (4.86 mmol/L versus 4.89 mmol/L), and triglyceride (0.99 mmol/L versus 1.02 mmol/L) levels than those without SGA infants. Therefore, prepregnancy cardiometabolic biomarkers were not associated with the development of SGA.
- In an individual participant data meta-analysis from the International Prediction of Pregnancy Complications Network of studies on pregnancy complications of 94 studies of 53 countries and 4 539 640 pregnancies, being SGA was more likely among babies born to Black/African mothers compared with White mothers globally (OR, 1.39 [95%

• Among 9470 nulliparous pregnant females in the nuMoM2b study (60.4% NH White, 13.8% NH Black, 16.7% Hispanic, 4.0% Asian, 5.0% other), NH White females were least likely to experience SGA delivery (8.6%), whereas higher rates were seen among Hispanic females (11.7%; OR, 1.41 [95% CI, 1.18–1.69]), Asian females (16.4%; OR, 2.08 [95% CI, 1.56–2.77]), and NH Black females (17.2%; OR, 2.21 [95% CI, 1.86–2.62]).¹²⁰ These differences remained essentially unchanged after adjustment for age, BMI, smoking, medical comor-bidities, or psychosocial burden (including depres-
CI, 1.13–1.72]).¹³⁸ sion, anxiety, experienced racism,

social support, or resilience), although lower social support was independently associated with SGA delivery (OR, 1.20 [95% CI, 1.03–1.40] for the low-est quartile of perceived social support compared with the upper 3 quartiles).

- Among >23 million singleton live births in the United States, the excess risks of were partly mediated by the adequacy of prenatal care: 13%, 12%, and 10% for intrauterine growth restriction and 7%, 6%, and 5% for SGA among Black females, Hispanic females, and females of other race and ethnicity, respectively, compared with White females.¹³⁹

Genetics/Family History

- Birth weight shows evidence of intergenerational transmission, which may extend across 3 generations.¹⁴⁰ For example, a study using population-based Swedish Multi-Generation and Medical Birth Registers that included 2 193 142 births reported that females whose full sisters had a child born SGA had an elevated risk of having a child born SGA (OR, 1.8 [95% CI, 1.7–1.9]). For brothers, the corresponding risk of SGA was 1.3 (95% CI, 1.2–1.4).

This study also reported that 37% of the liability in SGA was explained by fetal genetic effects, whereas maternal genetic effects explained only 9% of SGA liability.¹⁴¹

- Few SGA GWASs have been published. However, genetic risk factors for SGA share similarities in the genetic architecture of birth weight and maternal SBP.¹⁴² In a study of N=11 951 infants and N=5182 mothers of European ancestry, each decile increase in the fetal PRS for higher

- In data from 11 110 females in the prospectively collected Västerbotten Intervention Program and population-based registries in Sweden, LBW was associated with 10-year risk of CVD (HR, 1.95 [95% CI, 1.38–2.75]) at 50 years of age. However, this association did not persist by 60

Complications: Offspring Morbidity and Mortality

- In a meta-analysis of 6 cohort studies, LBW was associated with higher risk for MetS in either childhood or adulthood (pooled OR, 1.79

birth weight was associated with a lower odds of SGA (OR, 0.75 [95% CI, 0.71–0.80]). This effect was similar in magnitude to the association for maternal PRS and SGA (OR, 0.81 [95% CI, 0.75–0.88]). Last, an SBP maternal PRS also was associated with increased SGA odds (OR, 1.15 [95% CI, 1.04–1.27]).

Complications: Maternal CVD

- There is limited weak evidence for a relationship between infant birth weight and maternal CVD, which may be attributable in part to heterogeneity in definitions of LBW and SGA. In a meta-analysis examining 4 studies that defined LBW (<2500 g at term), females with a history of an infant with LBW had no difference in risk for CVD (OR, 1.29 [95% intrinsic CI, 0.91–1.83]). Across 7 studies (3 of which defined SGA as 1–2 SD from the mean and 4 defined it as <10th percentile of weight for gestational age), a trend was observed of higher risk of CVD (OR, 1.29 [95% intrinsic CI, 0.91–1.83]), but there was significant between-study heterogeneity.¹²⁴

- Among 4 193 069 individuals born in Sweden during 1973 to 2014, SGA birth (weight <10th percentile for gestational age) was associated with risk for type 2 diabetes; aHRs were 1.61 (95% CI, 1.38–1.89) at <18 years of age and 1.79 (95% CI, 1.65–1.93) at 18 to 43 years of age.¹²⁷
- A 2018 meta-analysis of 49 studies with 4 053 367 participants found a J-shaped association between birth weight and adult type 2 diabetes, with the lowest risk in the 3.5- to 4-kg category.¹⁴⁴ The pooled HRs were 0.78 (95% CI, 0.70–0.87) per 1-kg higher birth weight, 1.45 (95% CI, 1.33–1.59) for <2.5 kg (versus >2.5 kg), 0.94 (95% CI, 0.87–1.01) for >4.0 kg (versus <4.0 kg), and 1.08 (95% CI, 0.95–1.23) for >4.5 kg (versus <4.5 kg).
- For hypertension, among 53 studies with 4 335 149 participants, the association was inverse, with pooled HRs of 0.77 (95% CI, 0.68–0.88) per 1-kg higher birth weight, 1.30 (95% CI, 1.16–1.46) for <2.5 kg, 0.88 (95% CI, 0.81–0.95) for >4.0 kg, and 1.05 (95% CI, 0.93–1.19) for >4.5 kg.
- For CVD, among 33 studies with 5 949 477 participants, the association was also J shaped, with pooled HRs of 0.84 (95% CI, 0.81–0.86) per 1-kg higher birth weight, 1.30 (95% CI, 1.01–1.67) for <2.5 kg, 0.99 (95% CI, 0.90–1.10) for >4.0 kg, and 1.28 (95% CI, 1.10–1.50) for >4.5 kg.
- In a pooled analysis from 22 389 men from the HPFS and 162 231 women from the Nurses' Health and Nurses Health II Studies, participant-reported LBW was associated with a greater risk of cardiovascular and respiratory disease mortality among women, and high birth weight was associated with a greater cancer mortality risk in both men and women.¹⁴⁵ Compared with women with a birth weight of 3.16 to 3.82 kg, the pooled HRs for all-cause mortality were 1.13 (95% CI, 1.08–1.17), 0.99 (95% CI, 0.96–1.02), 1.04 (95% CI, 1.00–1.08), and 1.03 (95% CI, 0.96–1.10) for women with a birth weight of <2.5, 2.5 to 3.15, 3.83 to 4.5, and >4.5 kg, respectively. Women with a birth weight <2.5 kg had an elevated risk of mortality

resulting from CVDs (HR, 1.251) and respiratory (1.18–1.541), whereas those who had a higher risk of cancer (95% CI, 1.00–1.311). Among unrelated to all-cause associated with CVD mortality associated with cancer mortality ($P_{\text{linear trend}}=0.012$ and 0.0039.

- of miscarriages in females recurrent pregnancy loss with nonrecurrent pregnancy
- Fetal single-gene disorders in recurrent pregnancy loss: found that 3.3% of stillbirths variants in LOTS genes of <0.05% in the general
- A study to identify novel recurrent pregnancy loss analyzed rare variants
 - In 2021, the stillbirth (≥ 28 weeks' gestation) rate in

Pregnancy Loss

Incidence, Prevalence, and Secular Trends

using whole-exome sequencing in 75 females with either recurrent pregnancy loss or lack of achieving clinical pregnancy and identified the presence of rare variants in 13% of the females with recurrent pregnancy loss.¹⁴⁶

the United States was 2.80 per 1000 live births and fetal deaths.¹⁴⁶

- Black birthing people had a substantial decrease in infant mortality rates from 2020 to 2021, declining 4% from 10.34 to 9.89 per 1000. However,

pregnancy loss.¹⁵¹

- In a GWAS of 69 054 females with sporadic pregnancy loss, the infant mortality rate for Black birthing people in 2021 was still nearly double the national rate of

pregnancy loss, 750 females with recurrent pregnancy loss, and 359 469 control subjects, only 1 genome-wide significant variant was found for sporadic pregnancy loss (OR, 1.4 [95% CI, 1.2–1.6]; $P=3.2\times10^{-8}$), and 3 were found for recurrent pregnancy loss (OR, 1.7–3.8), including variants in *FGF9*, *TLE1*, and *TLE4*.¹⁴⁸

5.74 per 1000.

nancy loss (OR, 1.7–3.8), including variants in *FGF9*, *TLE1*, and *TLE4*.¹⁴⁸

Risk Factors (Including Social Determinants)

- Antiphospholipid syndrome was associated *Prevention*

higher risk for pregnancy loss (RR, 2.42 [95% CI, 1.46–4.01] for loss at <10 weeks; RR, 1.33 [95% CI, 1.00–1.76] for loss at ≥10 weeks) in a meta-analysis of 212 184 females (including 770 with antiphospholipid syndrome) from 8 studies.¹⁴⁷

- In a systematic review of studies examining associations of air pollution in US populations, significant associations with stillbirth risk were found for 4 of 5 studies (examining a total of >5 million births) in which the median risk for stillbirth was 14.5% higher (range, 6.0%–23.0%) for whole-pregnancy PM2.5 exposure per IQR greater exposure, and risk was higher by 42% (95% CI, 6%–91%) with high third-trimester PM2.5 exposure.¹⁰⁵

- In a systematic review of 2 US studies (>200 000 births) examining heat, the risk for stillbirth was 6% higher per 1° C higher ambient temperature the week before delivery during the warm season.¹⁰⁵ Similarly, in a separate meta-analysis of 8 studies (including international populations), the odds of stillbirth were 1.05 times higher (95% CI, 1.01–1.08) for each 1° C rise in environmental temperature.¹⁰⁷

Genetics/Family History

- The heritability of any pregnancy loss has been reported at 29% (95% CI, 20%–38%) for any

- In a meta-analysis of 23 relatively homogeneous studies of 608 243 pregnant females, having been vaccinated with the COVID-19 mRNA vaccine was associated with a lower risk of stillbirth by 15% (pooled OR, 0.85 [95% CI, 0.73–0.99]).¹⁵² COVID-19 mRNA vaccination in pregnancy is shown to be safe; there was no evidence of a higher risk of adverse outcomes, including miscarriage, earlier gestation at birth, placental abruption, PE, postpartum hemorrhage, maternal death, ICU admission, lower birthweight z score, or neonatal ICU admission ($P>0.05$ for all outcomes).

Complications: Maternal CVD

- Among >95 000 ever-gravid females in the Nurses' Health Study II followed up for a mean of 23 years, a history of pregnancy loss was independently associated with a 21% greater risk for developing incident CVD (HR, 1.21 [95% CI, 1.10–1.33]), with similar associations for incident CHD (HR, 1.20 [95% CI, 1.07–1.35]) and stroke (HR, 1.23 [95% CI, 1.04–1.44]), compared with no pregnancy loss.¹⁵³ The risk was greater for females with ≥ 2 pregnancy losses (HR, 1.34 [95% CI, 1.21–1.62]) compared with those with 1 pregnancy loss (HR, 1.18 [95% CI, 1.04–1.44]). Mediation analysis suggested that transplacental exposure to fetal DNA in miscarriage.¹⁴⁸ Additional risk factors such as hypertension, hyperlipidemia, and diabetes were also seen in recurrent pregnancy loss, increasing with maternal age (in 1 study accounting for 78% of recurrent pregnancy loss).
- Fetal genetic factors also play a role in recurrent pregnancy loss. Fetal aneuploidy is common in first-trimester spontaneous miscarriages but is

idemia, and type 2 diabetes explained only <2% of the association between pregnancy loss and CVD. • Data from the Nurses' Health Study II identified higher rates of type 2 diabetes (HR, 1.20 [95% CI, 1.07–1.34]), hypertension (HR, 1.05 [95% CI,

1.00–1.11]), and hyperlipidemia (HR, 1.06 [95% CI, 1.02–1.10]) with early miscarriage (<12 weeks) with similar findings for late miscarriage (12–19 weeks). Rates of type 2 diabetes (HR, 1.45 [95% CI, 1.13–1.87]) and hypertension (HR, 1.15 [95% CI, 1.01–1.30]) were higher in females with a history of stillbirth delivery.¹⁵⁴

- In 79 121 postmenopausal females from the WHI, ≈35% experienced a history of CVD (HR, 1.11 [95% CI, 1.06–1.16]) over a mean follow-up of 16 years.¹⁵⁵

- A systematic review of 84 studies (28 993 438 patients) with a median follow-up of 7.5 years

- A GWAS in the PAGE study (507 placental abruption cases and 1090 controls) and a GWAS meta-analysis in 2512 participants (959 placental abruption cases and 1553 controls) that included PAGE and the previously reported PAPE study were undertaken.¹⁵⁹ Independent loci suggestively associated with placental abruption included

post-partum evaluated the associations between APOs and CVD.¹²⁴ The risk of CVD was higher among females with stillbirth (OR, 1.5 [95% CI, 1.1–2.1]). In this meta-analysis, miscarriage was not associ-

and rs35271178 near *KCNJ11*. Independent loci in the GWAS meta-analysis included rs76258369 *ADAM12*. Functional analyses of these genes system disorders, CVDs, and cellular function.¹⁵⁹ ated with CVD.

suggestively associated with placental abruption near *IRX1* and rs7094759 and rs12264492 in showed trophoblast-like cell interaction, endocrine Mendelian randomization causal inference studies of hypertensive indices suggest that SBP increases the odds of placental abruption (OR, 1.33 [95% CI,

Placental Abruption

Incidence, Prevalence, and Secular Trends

- The majority of studies have reported an incidence of 0.5% to 1% for placental abruption.¹⁵⁶ In the nuMoM2b study, placental abruption was identified in 62 of 9450 nulliparous females (0.66%): 35 (56%) were antepartum and 27 (44%) were intrapartum.¹⁵⁷

Risk Factors (Including Social Determinants)

- In the nuMoM2b study, risk factors for placental abruption were studied in 9450 females.¹⁵⁷ For females with abruption, the mean gestational age at delivery was 35.6±4.4 weeks; it was 38.8±2.2 weeks for females without abruption. Several risk factors for placental abruption were identified in a case-

crossover study (mothers with placental one pregnancy vs no placental abruption pregnancy) in Finland, Malta, and Preeclampsia (194 [6.5%] versus 115 1.69 [95% CI, 1.23–2.33]), idiopathic hemorrhage (556 [18.6%] versus 69 27.05 [95% CI, 16.61–44.03]), placenta previa (80 [2.7%] versus 21 [0.7%]; aOR, 1.74–5.36), maternal age of 35 with 20 to 25 years (365 [10.8%]; aOR, 1.32 [95% CI, marital status (aOR, 1.36 were independently associated with placental abruption.

abruption in another study in Aberdeen.¹⁵⁸ [3.8%]; aOR, antepartum [2.3%]; aOR, placenta previa 3.05 [95% CI, to 39 years compared [12.2%] versus 323 1.01–1.73]), and single [95% CI, 1.04–1.76]) associated with placental

Genetics/Family History

- A study from the medical birth register of Norway estimated the heritability of placental abruption between sisters to be 16% (95% CI, 8%–23%).¹⁵⁹

Maternal CVD

- A meta-analysis of 11 cohort studies of 6 325 152 pregnancies analyzed the association between placental abruption and CVD.¹⁶¹ Risks of CVD morbidity/mortality among the abruption and nonabruption groups were 16.7 and 9.3 per 1000 births, respectively (RR, 1.76 [95% CI, 1.24–2.50]; $I^2=94\%$).
- Among >1.5 million pregnancies from the HCUP in California, placental abruption occurred in 14 881 females (1%).¹⁶² Median follow-up time from delivery to event or censoring was 4.87 years (IQR, 3.54–5.96 years). Placental abruption was associated with HF (aHR, 1.44 [95% CI, 1.09–1.90]). HDP and PTB modified and mediated, respectively, the association between placental abruption and HF.

Health Care Use

- In 2021, there were 451 945 hospital discharges for HDP, 170 975 for preexisting diabetes and gestational diabetes, 105 480 for PTB, and 15 855 for SGA/LBW.
- In 2021, there were 137 213 visits to the ED for HDP, 28 568 for preexisting diabetes and gestational diabetes, 46 517 for PTB, and 391 for SGA/ LBW.
- According to a systematic review and meta-analysis that included 52 articles, late-preterm infants born at 34 to 36 weeks' gestation compared with term infants had a higher aOR of all-cause admissions in the neonatal period (OR, 2.34 [95% CI, 1.19–4.61]) and through adolescence (OR, 1.09 [95% CI, 1.05–1.13]).¹⁶³

Cost

- Pregnancy and postpartum care \$71.3 (\$64.9–\$77.7) billion in spending in 2016. and PTB were estimated to (\$4.8–\$6.3) billion and \$28.2 respectively.¹⁶⁴
- The cost of the 9 common conditions for all US births in from conception through the day.¹⁶⁵ Two-thirds of these the first year postpartum, and costs were due to child maternal outcomes: 74% costs included maternal (\$18.1 billion), hypertensive gestational diabetes (\$4.8 billion),

[95% CI, 2.32–4.58]) but not sia (4.2% versus 4.5%; associations were found HDP.

- Globally, 2.5 million (million) third-trimester weeks' gestation or late fetal annually with a PAF of 6.7% years, 8.2% for malaria, 14% nancy (>42 weeks' gestation), factors and obesity.¹⁶⁹
- Based on 204 countries and incidence of maternal highest for regions in sub-est for East Asia (Chart 11-7). dence of maternal females 15 to 49 years of age UI, 15.30–21.47) million new age rate of 923.48 (95% UI.

Global Burden

(See Tables 11-1 and 11-2 and Charts 11-7 and 11-8)

- In 2015, an estimated 20.5 million infants were born with LBW worldwide.¹⁶⁶
- Analysis of WHO and UNICEF data estimates that 23.4 million liveborn babies (17.4%) were born SGA in 2020 worldwide. There was marked regional variation in SGA, with more than a third (40.9%) of all newborns in southern Asia being SGA compared with 10.7% in sub-Saharan Africa and <10% in other regions.¹⁶⁷
- In an analysis of data from the WHO Global Survey for Maternal and Perinatal Health (conducted in African, Latin American, and Asian countries), higher risks for gestational hypertension (aOR among nulliparous females, 1.56 [95% CI, 0.94– 2.58]; aOR

among multiparous females, 1.73 [95% CI, 1.25–2.39]) were observed for females with severe anemia (hemoglobin <7 mg/dL) at delivery compared with females with hemoglobin ≥7 mg/dL at delivery. The risk for preeclampsia/ eclampsia was also higher with severe anemia (hemoglobin <7 mg/dL) at delivery compared with hemoglobin ≥7 mg/dL at delivery (aOR among nulliparous females, 3.74 [95% CI, 2.90–4.81]; aOR among multiparous females, 3.45 [95% CI, 2.79–4.25]).¹⁶⁸

- Sickle cell disease was associated with higher risk for gestational hypertension (7.2% versus 2.1%; aOR among nulliparous females, 2.41 [95% CI, 1.42–4.10]; aOR among multiparous females, 3.26

100 000 female population 15 to 49 years of age (Table 11-1).¹⁷⁰

- Based on 204 countries and territories in 2021, the highest rates of neonatal PTB among regions were found for South Asia, followed by the Caribbean and Oceania. Rates were lowest for East Asia (Chart 11-8). The incidence of neonatal PTB was 21.55 (95% UI, 21.38–21.73) million new cases with an average rate of 16 658.81 (95% UI, 16 523.66–16 795.10) per 100 000 births (Table 11-2).¹⁷⁰

Table 11-1. Global Incidence of Maternal Hypertensive Disorders Among Females 15 to 49 Years of Age, 2021

	Incidence, female (95% UI)
No. (millions), 15-49 y, 2021	18.00 (15.30 to 21.47)
Percent change (%) in number, 15–49 y, 1990–2021	15.29 (8.08 to 21.03)
Percent change (%) in number, 15–49 y, 2010–2021	3.17 (0.01 to 6.08)
Rate per 100 000, 15–49 y, 2021	923.48 (785.15 to 1101.80)
Percent change (%) in rate, 15–49 y, 1990–2021	–20.89 (–25.83 to –16.95)
Percent change (%) in rate, 15–49 y, 2010–2021	–4.08 (–7.02 to –1.37)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁷⁰

Table 11-2. Global Incidence of Neonatal PTB by Sex, 2021

	Incidence		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
No. (millions), 2021	21.55 (21.38 to 21.73)	12.33 (12.19 to 12.46)	9.22 (9.11 to 9.33)
Percent change (%) in number,	−6.29 (−7.37 to −5.20)	−8.34 (−9.49 to −6.91)	−3.41 (−5.11 to −1.75)
Percent change (%) in number,	−8.12 (−9.17 to −7.08)	−9.07 (−10.53 to −7.67)	−6.81 (−8.34 to −5.33)
Rate per 100 000, at birth, 2021	16,658.81 (16,523.66 to 16,795.10)	18,418.41 (18,214.58 to 18,620.88)	14,772.58 (14,595.11 to 14,941.39)
Percent change (%) in rate, at birth,	−4.55 (−5.65 to −3.44)	−6.48 (−7.65 to −5.02)	−1.79 (−3.52 to −0.10)
Percent change (%) in rate, at birth,	−2.16 (−3.28 to −1.06)	−3.09 (−4.64 to −1.60)	−0.87 (−2.50 to 0.70)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Diseases, Injuries, and Risk Factors; PTB, preterm birth; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁷⁰

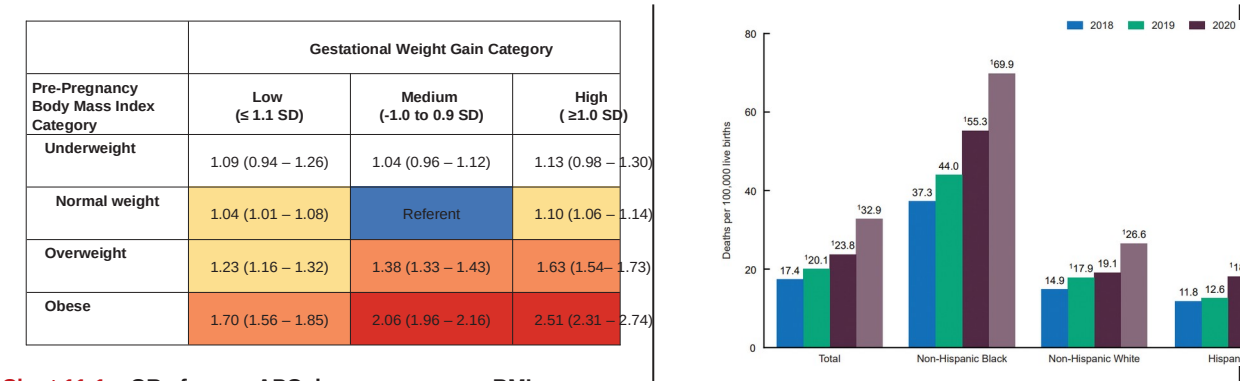


Chart 11-1. aORs for any APO, by prepregnancy BMI and gestational weight gain categories.

Chart 11-2. Maternal mortality rates, by race and Hispanic origin: United States, 2018 to 2021.

small (birth weight <10th percentile) or large (birth weight >90th

percentile) size for sex, and gestational age at birth.

Prepregnancy

BMI categories are as follows: underweight, <18.5 kg/m²;

normal

weight, 18.5 to 24.9 kg/m²; overweight, 25.0 to 29.9 kg/m²; and

obesity, ≥30 kg/m². Gestational weight gain values

corresponding

to the SD cutoffs were not provided by the source, but the

median

gestational weight gain was 14.0 kg (95% CI, 3.9–27.0).

aOR indicates adjusted odds ratio; APO, adverse pregnancy

outcome;

BMI, body mass index; HDP, hypertensive disorders of pregnancy;

and

PTB, preterm birth.

Source: Data derived from Santos et al.⁸

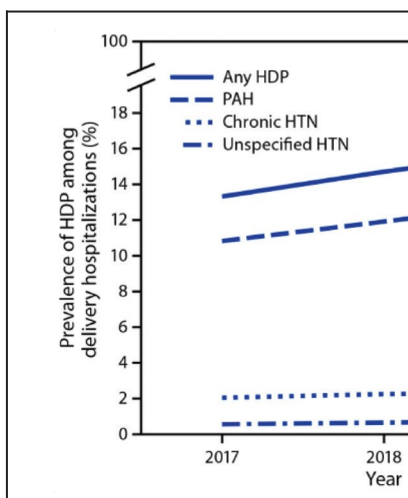


Chart 11-3. Prevalence of hypertensive disorders in pregnancy* among delivery hospitalizations, by year, NIS, United States, 2017 to 2019.

HDP indicates hypertensive disorder in pregnancy; HTN, hypertension; NIS, National Inpatient Sample; and PAH, pregnancy-associated hypertension. *HDPs are defined as chronic hypertension, PAH (ie, gestational hypertension, preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia), and unspecified maternal hypertension.

Source: Reprinted from Ford et al.¹⁷¹

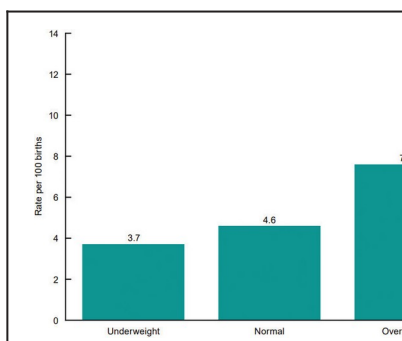


Chart 11-5. Rate of gestational diabetes. States, 2020.

Significant increasing trend ($P < 0.05$).

BMI indicates body mass index.

Source: Reprinted from Gregory and Ely.⁸⁰

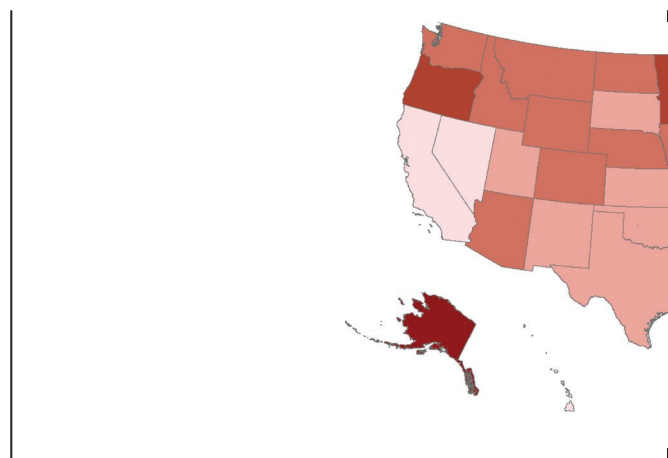


Chart 11-4. State-level rates of de novo hypertension in pregnancy per 1000 live births, United States, 2019.

Unadjusted rates are calculated for each state based on 3 736 144 females 15 to 44 years of age with a live birth.

Source: Unpublished map using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.¹⁷²

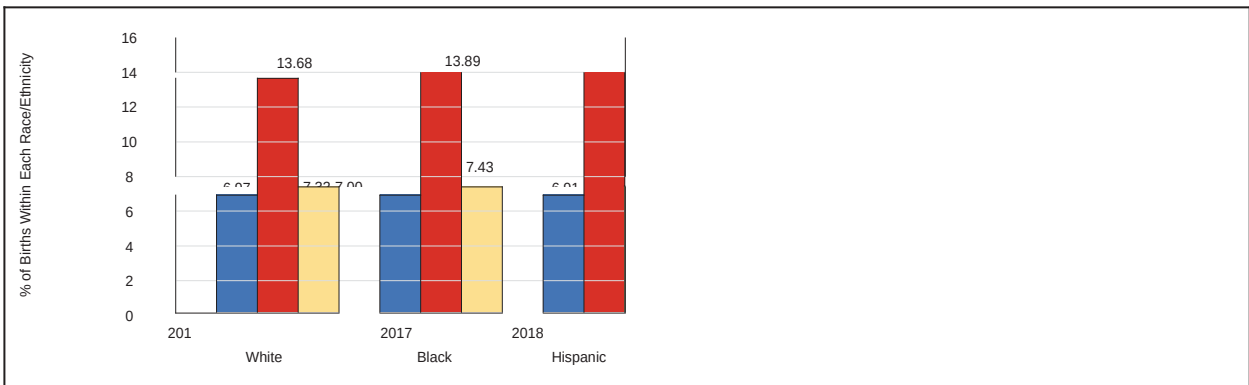


Chart 11-6. Trends in the rates of infants with LBW (<2500 g) in the United States, by race and ethnicity of females with a live birth, 2016 to 2018.

LBW indicates low birth weight.
Source: Data derived from Martin et al.¹⁷³

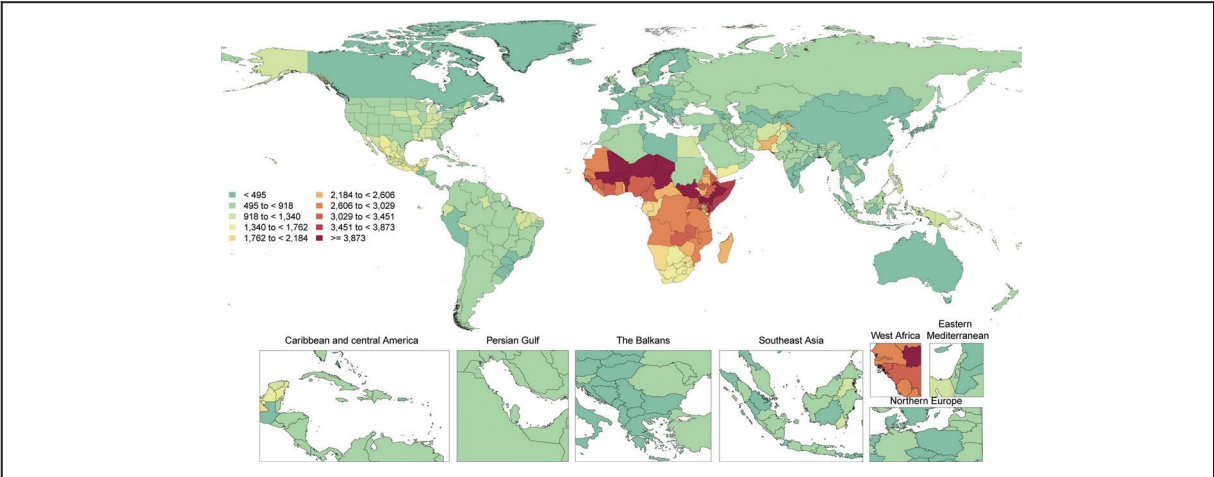


Chart 11-7. Global incidence rates of maternal hypertensive disorders per 100 000 females, 15 to 49 years of age, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁷⁰

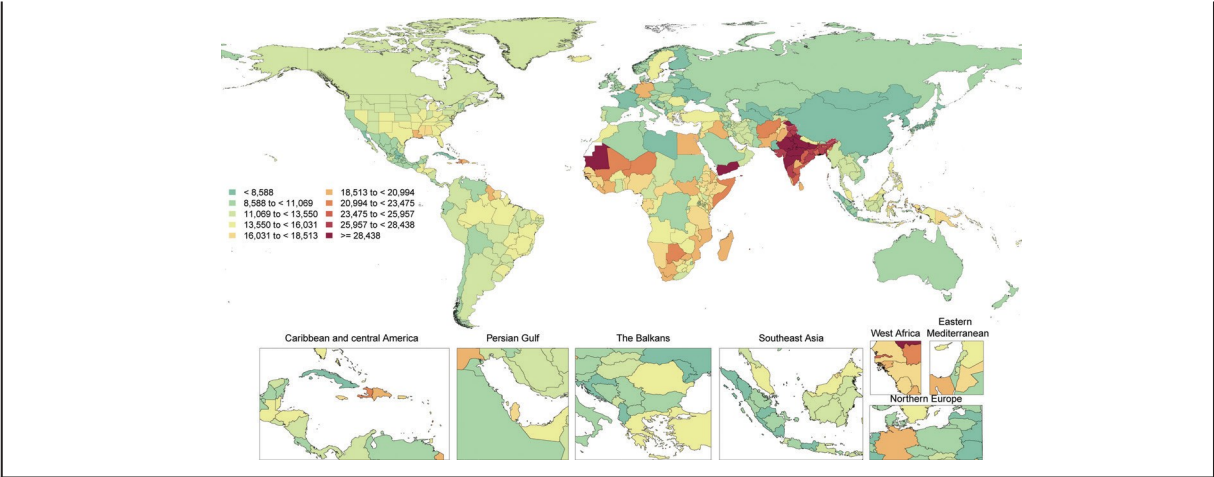


Chart 11-8. Global incidence rates of neonatal PTB per 100 000, both sexes, at birth, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and PTB, preterm birth.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁷⁰

REFERENCES

1. Parikh NI, Gonzalez JM, Anderson CAM, MA, Gunderson EP, Stuart JJ, Vaidya D; Heart Association Council on Epidemiology on Arteriosclerosis. Thrombosis and Cardiovascular and Stroke Nursing: and nancy outcomes and cardiovascular cardiovascular disease prevention in the American Heart Association. 10.1161/CIR.0000000000000961
2. Brown HL, Warner JJ, Giano E, Gulati M, Rosser ML, Wenger NK; on behalf of the the American College of Obstetricians and identification and reduction of collaboration with obstetricians and sorv from the American Heart Association Obstetricians and Gynecologists. 10.1161/CIR.0000000000000582
3. Khan SS, Brewer LC, Canobbio MM, Michos ED, Miller EC, Perak AM, Wei GS. Heart Association Council on Epidemiology on Clinical Cardiology: Council on Council on Arteriosclerosis. Thrombosis on Hypertension: Council on Lifestyle and Council on Peripheral Vascular Disease: pre-pregnancy cardiovascular health to and postpartum individuals and offspring: a the American Heart Association. 10.1161/CIR.0000000000000124
4. Bello NA, Zhou H, Cheatham TC, Miller E, Reynolds K. Prevalence of hypertension when using the 2017 American College of Heart Association blood pressure ternal and fetal outcomes. *JAMA Netw* 10.1001/jamanetworkopen.2021.3808
5. Zhu K, Wactawski-Wende J, Mendola P, Barnabei VM, Hageman Blair R, Manson Adverse pregnancy outcomes and risk of pausal women. *Am J Obstet Gynecol*. 10.1016/j.ajog.2023.07.030
6. ICD-10: *International Statistical Health Problems: Tenth Revision*. World Health
7. Lane-Cordova AD, Khan SS, Grobman term cardiovascular risks associated with JACC review topic of the week. *J Am Coll* doi: 10.1016/j.jacc.2018.12.092
8. Santos S, Voerman E, Amiano P, Barros H, Charles MA, Chatzi L, Chevrier C, body mass index and gestational weight tions: an individual participant data meta-American and Australian cohorts. *BJOG*. 10.1111/1471-0528.15661
9. Sendeku FW, Bevene FY, Tesfu AA, Bante and its associated factors in Ethiopia: a analysis. *Afr Health Sci*. 2021;21:1321–
10. Hounkpatin OI, Amidou SA, Houehanou YC, DS, Bezanaharv H. Systematic review of of cardiovascular risk factors on *Pregnancy Childbirth*. 2021;21:97. doi: 10.1097/AOG.00000000000005346
11. Wano S, Mitsunami M, Ortiz-Panoso E, Rich-Edwards JW, Chvarro JE. verse pregnancy outcomes. *Obstet* 10.1097/AOG.00000000000005346
12. Martínez-Vizcaíno V, Sanabria-Martínez G, Cavero-Redondo I, Pascual-Morena C. JA Exercise during pregnancy for and hypertensive disorders: an umbrella trials and an updated meta-analysis. *BMJ* Reexamining the Guidelines. National Academies cohort study. *Int J Environ Res Public* 10.3390/ijerph17124606
15. Fleszar LG, Brvant AS, Johnson CO, Dwver-Lindgren L, Kelly YO, Maass K. maternal mortality by racial and ethnic 2023;330:52–61. doi:
16. Division of Reproductive Health and Pregnancy Mortality Surveillance
17. Centers for Disease Control and Pregnancy Mortality Surveillance
18. Say L, Chou D, Gemmill A, Tunçalp O, AM, Temmerman M, Alkema L. Global WHO systematic analysis. *Lancet* 10.1016/S2214-109X(14)70227-X
19. Hinkle SN, Schisterman EF, Liu D, Grantz KL, Oiao Y, Perkins NJ, Mills long-term mortality in a diverse cohort. doi:
20. Crump C, Sundquist J, Sundquist K. risk of hypertension in women. *JAMA* 10.1001/jamacardio.2021.4127
21. Sondergaard MM, Hlatky MA, Stefanick M, Gemmill A, Van Horn L, Park K. of adverse pregnancy outcomes with disease in postmenopausal women. doi: 10.1001/jamacardio.2020.4097
22. Hansen AL, Sondergaard MM, Hlatky Stefanick ML, Manson JE, Farland LV, M. et al. Adverse pregnancy outcomes Women's Health Initiative. *JAMA Netw* 10.1001/
23. Egawa M, Kanda E, Ohtsu H. disorders of pregnancy are associated in middle- and older-aged Japanese 2023;30:1420–1426. doi:
24. Freaney PM, Harrington K, Molsberry Greenland P, Allen NB, Capewell S. adverse pregnancy outcomes in the United States. 2007 to 2019. *J Am* doi: 10.1161/JAHA.121.025050
25. Perak AM, Lancki N, Kuang A, Labarthe LP, Grobman WA, Scholtens DM. Adverse Pregnancy Outcome Study Associations of gestational the Hyperglycemia and Adverse *Gynecol*. 2021;224:210 e211–210
26. Pan H, Xian P, Yang D, Zhang C, Tang Lai M. Polycystic ovary syndrome is hypertensive disorders of pregnancy: analysis, and meta-regression. 10.1007/s12020-021-02886-9
27. Bartsch E, Medcalf KE, Park AL, Ray eclampsia determined in early of large cohort studies. *BMJ*.
28. American College of Obstetricians and Opinion No. 548: weight gain during 2013;121:210–212. doi:
29. Mustafa HJ, Seif K, Javani A, A. Crimmins S. Gestational weight guidelines per class of maternal analysis of obstetrical and neonatal 2022;4:100682. doi:
30. Rasmussen KM, Yaktine AL, eds.

10.1111/1471-0528.17304

13. Hoyert DL. Maternal mortality rates in the United States, 2021. *NCHS Health E-Stats*. 2023. Accessed March 15, 2021.

14. Jeong W, Jang SI, Park EC, Nam JY. The effect of socioeconomic status on all-cause maternal mortality: a nationwide population-based

31. Ren M, Li H, Cai W, Niu X, Ji W, Zhang Z, Niu J, Zhou X, Li Y. Excessive gestational weight gain in accordance with the IOM criteria and the risk of hypertensive disorders of pregnancy: a meta-analysis. *BMC Pregnancy Childbirth*. 2018;18:281. doi: 10.1186/s12884-018-1922-y

32. Dude AM, Kominiarek MA, Haas DM, Iams J, Mercer BM, Parry S, Reddy UM, Saade G, Silver RM, Simhan H, et al. Weight gain in early, mid, and late

- pregnancy and hypertensive disorders of pregnancy. *Pregnancy Hypertens.* 2020;20:50–55. doi: 10.1016/j.preghy.2020.03.001
33. Nagpal TS, Souza SCS, Moffat M, Hayes L, Nuyts T, Liu RH, Bogaerts A, Dervis S, Piccinini-Vallis H, Adamo KB, et al. Does prepregnancy weight change have an effect on subsequent pregnancy health outcomes? A systematic review and meta-analysis. *Obes Rev.* 2022;23:e13324. doi: 10.1111/obr.13324
34. Martínez-JA. Cavero-Redondo I. Álvarez-Bueno C. Sanabria-Martínez G, Poyatos-León R, Martínez-Vizcaíno V. Interpregnancy weight change and hypertension during pregnancy: a systematic review and meta-analysis. *Obstet Gynecol.* 2020;135:68–79. doi: 10.1097/AOG.0000000000003573
35. Nobles CJ, Mendola P, Mumford SL, Silver RM, Kim K, Andriessen VC, Connell M, Sjaarda L, Perkins NJ, Schisterman EF. Preconception blood pressure and its change into early pregnancy: early risk factors for pre-eclampsia and gestational hypertension. *Hypertension.* 2020;76:922–929. doi: 10.1161/hypertensionaha.120.14875
36. Tita AT, Szychowski JM, Boggess K, Dugoff L, Sibai B, Lawrence K, Hughes BL, Bell J, Aagaard K, Edwards RK, et al; Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med.* 2022;386:1781–1792. doi: 10.1056/NEJMoa2111111

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52. Raina J, El-Messidi A, Badeghiesh A, Tulandi T, Nguyen TV, Suarathana mood disorders: a population-based study of 9 million pregnancies. *J Ayorinde AA, Bhattacharya S. Inherited predisposition to preeclampsia: 2017;8:37–41. doi: 10.1016/j.preghy.2017.03.001 10.1056/NEJMoa2201295*
37. Gunderson EP, Greenberg M, Nguyen-Huynh MN, Tierney C, Roberts JM, Go AS, Tao W, Alexeeff SE. Early pregnancy blood pressure patterns identify risk of hypertensive disorders of pregnancy among racial and ethnic groups. *Hypertension*. 2022;79:599–613. doi: 10.1161/HYPERTENSIONAHA.121.18568
38. Minhas AS, Hong X, Wang G, Rhee DK, Liu T, Zhang M, Michos ED, Wang X, Mueller NT. Mediterranean-style diet and risk of preeclampsia by race in the Boston Birth Cohort. *J Am Heart Assoc*. 2022;11:e022589. doi: 10.1161/JAHA.121.022589
39. Arvizu M, Bjerregaard AA, Madsen MTB, Granström C, Halldorsson TI, Olsen SF, Gaskins AJ, Rich-Edwards JW, Rosner BA, Chavarro JE. Sodium intake during pregnancy, but not E. Pregnancy hypertension and its association with maternal anxiety and *Affect Disord*. 2021;281:533–538. doi: 10.1016/j.jad.2020.10.058 53. analysis of the Aberdeen intergenerational cohort. *Pregnancy Hypertens*.
54. Cnattingius S, Reilly M, Pawitan Y, Lichtenstein P. Maternal and fetal other diet recommendations aimed at preventing cardiovascular disease, is positively related to risk of hypertensive disorders of pregnancy. *J Nutr*. 2020;150:159–166. doi: 10.1093/jn/nxz197 40. Yee LM, Silver RM, Haas DM, Parry S, Mercer BM, Iams J, Wing D, Parker CB, Reddy UM, Wapner RJ, et al. Quality of periconceptional dietary intake and maternal and neonatal outcomes. *Am J Obstet Gynecol*. 2020;223:121.e1–121.e8. doi: 10.1016/j.ajog.2020.01.042
41. Zahid S, Tanveer ud Din M, Minhas AS, Rai D, Kaur G, Carfagnini C, Khan MZ, Ullah W, Van Spall HGC, Hays AG, et al. Racial and socioeconomic disparities in cardiovascular outcomes of preeclampsia hospitalizations in the United States 2004–2019. *JACC Adv*. 2022;1:100062. doi:

- genetic factors account for most of familial aggregation of preeclampsia: a population-based Swedish cohort study. *Am J Med Genet A*. 2004;130A:365–371. doi: 10.1002/ajmg.a.30257
55. Honigberg MC, Chaffin M, Aragam K, Bhatt DL, Wood MJ, Sarma AA, Scott NS, Peloso GM, Natarajan P. Genetic variation in cardio-metabolic traits and medication targets and the risk of hypertensive disorders of pregnancy. *Circulation*. 2020;142:711–713. doi: 10.1161/CIRCULATIONAHA.120.047936
56. Tyrmi JS, Kaartokallio T, Lokki AI, Jaaskelainen T, Kortelainen E, Ruotsalainen S, Karjalainen J, Ripatti S, Kivioja A, Laisk T, et al; FINNPEC Study Group, FinnGen Project, and the Estonian Biobank Research Team. Genetic risk factors associated with preeclampsia and hypertensive disorders of pregnancy. *JAMA Cardiol*. 2023;8:674–683. doi: 10.1001/jamacardio.2023.1312
57. Honigberg MC, Truong B, Khan RR, Xiao B, Bhatta L, Vy HMT, Guerrero RF, Schuermans A, Selvaraj MS, Patel AP, et al. Polygenic prediction of preeclampsia and gestational hypertension. *Nat Med*. 2023;29:1540–1549. doi: 10.1038/s41591-023-02374-9
58. Gray KJ, Kovacheva VP, Mirzakhani H, Bjornes AC, Almoguera B, Wilson ML, Ingles SA, Lockwood CJ, Hakonarson H, McElrath TF, et al. Risk of preeclampsia in patients with a maternal genetic predisposition to common medical conditions: a case-control study. *BJOG*. 2021;128:55–65. doi: 10.1016/j.jacadv.2022.100062
42. Francis B, Pearl M, Colen C, Shoben A, Sealy-Jefferson S. Racial and economic segregation over the life course and incident hypertensive disorders of pregnancy among Black women in California. *Am J Epidemiol*. 2024;193:277–284. doi: 10.1093/aje/kwad192
43. Boakye E, Sharma G, Ogunwole SM, Zakaria S, Vaught AJ, Kwapong YA, Hong X, Ji Y, Mehta L, Creanga AA, et al. Relationship of preeclampsia with maternal place of birth and duration of residence among non-Hispanic Black women in the United States. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007546. doi: 10.1111/1471-0528.16441

59. Gammill HS, Chettier R, Brewer A, Roberts JM, Shree R, Tsigas E, Ward K. Cardiomyopathy and preeclampsia. *Circulation*. 2018;138:2359–2366. doi: 10.1161/CIRCULATIONAHA.117.031527
60. Nieves-Colon MA, Badiño Rivera KM, Sandoval K, Villanueva Davalos V, Enriquez Lencinas LE, Mendoza-Revilla J, Adhikari K, Gonzalez-Buenfil R, Chen JW, Zhang ET, et al. Clotting factor genes are associated with preeclampsia in high-altitude pregnant women in the Peruvian Andes. *Am J Hum Genet*. 2022;109:1117–1139. doi: 10.1161/CIRCOUTCOMES.120.007546
44. Facco FL, Redline S, Hunter SM, Zee PC, Grobman WA, Silver RM, Louis JM, Pien GW, Mercer B, Chung JH, et al. Sleep-disordered breathing in pregnancy and after delivery: associations with cardiometabolic health. *Am J Respir Crit Care Med*. 2022;205:1202–1213. doi: 10.1164/rccm.202104-0971OC
45. Sun M, Yan W, Fang K, Chen D, Liu J, Chen Y, Duan J, Chen R, Sun Z, Wang X, et al. The correlation between PM(2.5) exposure and hypertensive disorders in pregnancy: a meta-analysis. *Sci Total Environ*. 2020;703:134985. doi: 10.1016/j.scitotenv.2019.134985
46. Xue R-H, Wu D-D, Zhou C-L, Chen L, Li J, Li Z-Z, Fan J-X, Liu X-M, Lin 10.1016/j.ajhg.2022.04.014
61. Rayes B, Ardissino M, Slob EAW, Patel KHK, Girling J, Ng FS. Association of hypertensive disorders of pregnancy with future cardiovascular disease. *JAMA Netw Open*. 2023;6:e230034. doi: 10.1016/j.ajhg.2022.04.014
- X-H, Huang H-F. Association of high maternal triglyceride levels early and late in pregnancy with adverse outcomes: a retrospective cohort study. *J Clin Lipidol*. 2021;15:162–172. doi: 10.1016/j.jacl.2020.10.001
47. Papageorgiou AT, Deruelle P, Gunier RB, Rauch S, García-May PK, Mhatre M, Usman MA, Abd-El salam S, Etuk S, Simmons LE, et al. Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study. *Am J Obstet Gynecol*. 2021;225:289.e1–289.e17. doi: 10.1016/j.ajog.2021.05.014
48. Zahid S, Agrawal A, Rai D, Khan MZ, Michos ED. Cardiovascular

62. Magnus MC, Wallace MK, Demirci JR, Catov JM, Schmella MJ, Fraser A. Breastfeeding and later-life cardiometabolic health in women with and without hypertensive disorders of pregnancy. *J Am Heart Assoc*. 2023;12:e026696. doi: 10.1161/JAHA.122.026696
63. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54:1451–1462. doi: 10.1136/bjsports-2020-102955
64. Mottola MF, Davenport MH, Ruchat SM, Davies GA, Poitras VJ, Gray CE, Jaramillo Garcia A, Barrowman N, Adamo KB, Duggan M, et al. 2019 Canadian guideline for physical activity throughout pregnancy. *Br J Sports Med*. 2018;52:1339–1346. doi: 10.1136/bjsports-2018-100056
65. US Department of Health and Human Services. Physical Activity Guidelines for Americans. 2nd ed. 2018. Accessed April 7, 2024.

complications associated with COVID-19 during delivery Guidelines_2nd_edition.pdf

66. Davenport MH, Ruchat SM, Poitras VJ, Barrowman N, Skow R.J, Meah VL, Riske L. Exercise for the prevention of gestational disorders of pregnancy: a systematic review. *Med. 2018;52:1367–1375*. doi: 10.1136/bisports-2017-96:921–931. doi: 10.1111/aoms.13151
67. Mauro-Malosso ER, Saccone G. Di Exercise during pregnancy and risk of disorders: a systematic review and meta-analysis. *Diabetes Res Clin Pract. 2017;96:921–931*. doi: 10.1111/aoms.13151
68. Schenkelaars N, Rousian M, Hoek J, Steegers-Theunissen R. Preconceptional gestational disorders in pregnancy: a systematic review. *Clin Nutr. 2021;75:1684–1697*. doi: 10.1016/j.clnu.2021.05.013
69. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin use to prevent preeclampsia and related morbidity and mortality: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA. 2021;326:1192–1206*. doi: 10.1001/jama.2021.1192
70. MacGrogan C, Freedman A, Keenan P, Simhan HN, Buss C, Borders A. and association with gestational diabetes. *Diabetes Res Clin Pract. 2020;2:100222*. doi: 10.1016/j.diabres.2020.100222
71. Medici Dualib P, Onassavara J, Mattar S, de Almeida Pitiito B. Gut microbiota and association with gestational diabetes: a systematic review. *Diabetes Res Clin Pract. 2021;109078*. doi: 10.1016/j.diabres.2021.109078
72. Shah NS, Wang MC, Kandula NR, WA, Khan SS. Gestational diabetes pregnancy by maternal birthplace. *Am J Preventive Services Task Force. JAMA. 2021;326:1192–1206*. doi: 10.1001/jama.2021.1192

10.1016/j.amepre.2021.10.007

86. Jang HC, Min HK, Lee HK, Cho NH, Metzger BE. Short stature in
mellitus. *Diabetologia*. 1998;41:778–783. doi:

10.1001/jama.2021.8551

70. Van Doorn R, Mukhtarova N, Flyke IP, Lasarev M, Kim K, Hennekens
CH, Hoppe KK. Dose of aspirin to prevent preterm preeclampsia in
women with moderate or high-risk factors: a systematic review and
meta-analysis.

PLoS One. 2021;16:e0247782. doi: 10.1371/journal.pone.0247782

71. Miller EC, Zambrano Espinoza MD, Huang Y, Friedman AM, Boehme

Korean women: a contribution to the multifactorial predisposition to gestational diabetes

10.1007/s001250050987

AK, Bello NA, Cleary KL, Wright JD, D'Alton ME. Maternal
race/ethnicity, hy- pertension, and risk for stroke during
delivery admission. *J Am Heart Assoc*.

87. Powe CE, Kwak SH. Genetic studies of gestational diabetes and
10.1007/s11892-020-01355-3

88. Changalidis AI, Maksiutenko EM, Barbitoff YA, Tkachenko AA, Vashukova
genome-
2022;13:2255. doi:
2020;9:e014775. doi: 10.1161/JAHA.119.014775

72. Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D,
Casas JP, Chappell L. Preeclampsia and cardiovascular dis-ease in a
large UK pregnancy cohort of linked electronic health re-cords: a

glucose metabolism in pregnancy. *Curr Diab Rep.* 2020;20:69. doi:

ES, Pachuliia OV, Nasykhova YA, Glotov AS. Aggregation of
risk loci for pregnancy complications. *Genes (Basel)*.
10.3390/genes13122255

CALIBER study. *Circulation.* 2019;140:1050–1060.
doi:

89. Pervjakova N, Moen GH, Borges MC, Ferreira T, Cook JP, Allard C, Beaumont RN, Canouil M, Hatem G, Heiskala A, et al. Multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes. *Hum Mol Genet.* 2022;31:3377–3391. doi: 10.1161/CIRCULATIONAHA.118.038080

73. Honigberg MC, Riise HKR, Daltveit AK, Tell GS, Sulo G, Igland J, Klungsoyr K, Scott NS, Wood MJ, Natarajan P, et al. Heart failure in women with hypertensive disorders of pregnancy: insights from the Cardiovascular Disease in Norway project. *Hypertension.* 2020;76:1506–1513. doi: 10.1161/HYPERTENSIONAHA.120.15654

74. Stuart JJ, Tanz LJ, Rimm EB, Spiegelman D, Missmer SA, Mukamal KJ, Rexrode KM, Rich-Edwards JW. Cardiovascular risk factors mediate the long-term maternal risk associated with hypertensive dis-

90. Elliott A, Walters RK, Pirinen M, Kurki M, Junna N, Goldstein JI, Reeve MP, Siirtola H, Lemmelä SM, Turley P, et al; Estonian Biobank Research Team and FinnGen. Distinct and shared genetic architectures of gestational diabetes mellitus and type 2 diabetes. *Nat Genet.* 2024;56:377–382. doi: 10.1038/s41588-023-01607-4

91. Ding M, Chavarro J, Olsen S, Lin Y, Ley SH, Bao W, Rawal S, Grunnet LG, Thuesen ACB, Mills JL, et al. Genetic variants of gestational diabetes mellitus: a study of 112 SNPs among 8722 women in two independent populations. *Diabetologia.* 2018;61:1758–1768. doi: 10.1016/j.diabet.2018.07.016

75. Hoodbhoy Z, Mohammed N, Nathani KR, Sattar S, Chowdhury D, Maskatia S, Tierney S, Hasan B, Das JK. The impact of maternal preeclampsia and hyperglycemia on the cardiovascular health of the offspring: a systematic review and meta-analysis. *Am J Perinatol.* 2021;40:363–374. doi: 10.1055/s-0041-1728823

76. Wang H, Li N, Chivese T, Werfalli M, Sun H, Yuen L, Hoegfeldt CA, Elise Powe C, Immanuel J, Karuranga S, et al; IDF Diabetes Atlas Committee. Hyperglycaemia in Pregnancy Special Interest Group. IDF Diabetes Atlas: estimation of global and regional gestational diabetes mellitus prevalence. *Diabetologia.* 2021;64:1055–1068. doi: 10.1007/s00125-020-05000-0

92. Pagel KA, Chu H, Ramola R, Guerrero RF, Chung JH, Parry S, Reddy UM, Silver RM, Steller JG, Yee LM, et al. Association of genetic pre- disposition and physical activity with risk of gestational diabetes in nulliparous women. *JAMA Netw Open*. 2022;5:e2229158. doi: 10.1001/jamanetworkopen.2022.29158

93. Lamri A, Mao S, Desai D, Gupta M, Pare G, Anand SS. Fine-tuning of genome-wide polygenic risk scores and prediction of gesta- tional diabetes in South Asian women. *Sci Rep*. 2020;10:8941. doi: 10.1038/s41598-020-65360-y

94. Davidson SJ, Barrett HL, Price SA, Callaway LK,

Study Group's criteria. *Diabetes Res Clin Pract*. 2022;183:109050. doi: 10.1016/j.diabres.2021.109050

77. Huang C, Wei K, Lee PMY, Qin G, Yu Y, Li J. Maternal hypertensive dis-order of pregnancy and mortality in offspring from birth to young adult- hood: national population based cohort study. *BMJ*. 2022;379:e072157. doi: 10.1136/bmj-2022-072157

Dekker Nitert M. Probiotics for preventing gestational diabetes. *Cochrane Database Syst Rev.* 2021;2021:CD009951. doi: 10.1002/14651858.CD009951.pub3

95. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL.

Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ.* 2020;369:m1361.

78. Paulo MS, Abdo NM, Bettencourt-Silva R, Al-Rifai RH. Gestational diabetes mellitus in Europe: a systematic review and meta-analysis of prevalence studies. *Front Endocrinol (Lausanne).* 2021;12:691033. doi: 10.3389/fendo.2021.691033

79. QuickStats: percentage of mothers with gestational diabetes, by maternal age—National Vital Statistics System, United States, 2016 and 2021. *MMWR Morb Mortal Wkly Rep.* 2023;72:16. doi: 10.15585/mmwr.mm7201a4

80. Gregory ECW, Ely DM. Trends and characteristics in gestational diabetes: United States, 2016–2020. Accessed April 7, 2024.

81. Shah NS, Wang MC, Freaney PM, Perak AM, Carnethon MR, Kandula

NR, Gunderson EP, Bullard KM, Grobman WA, O'Brien MJ, et al. Trends in gestational diabetes at first live birth by race and ethnicity in the US, 2011–2019. *JAMA.* 2021;326:660–669. doi: 10.1001/jama.2021.7217

82. Facco FL, Grobman WA, Reid KJ, Parker CB, Hunter SM, Silver RM, Basner RC, Saade GR, Pien GW, Manchanda S, et al. Objectively measured short sleep duration and later sleep midpoint in pregnancy are associated with

96. Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. *J Dev Orig Health Dis.* 2020;11:599–616. doi: 10.1017/S2040174419000850

97. Yu Y, Arah OA, Liew Z, Cnattingius S, Olsen J, Sorensen HT, Qin G, Li J. Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. *BMJ.* 2019;367:l6398. doi: 10.1136/bmj.l6398

98. Martin JA, Osterman MJK. Shifts in the distribution of births by gestational age: United States, 2014-2022. *Natl Vital Stat Rep.* 2024;73:1–11.

99. Lemon L, Edwards RP, Simhan HN. What is driving the decreased incidence of preterm birth during the COVID-19 pandemic? *Am J Obstet Gynecol MFM.* 2021;3:100330. doi: 10.1016/j.ajogmf.2021.100330

100. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy:

- living systematic review and meta-analysis. *BMJ*. 2020;370:m3320. doi: 10.1136/bmj.m3320
101. Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, Aveni K, Yazdy MM, Harvey E, Longcore ND, et al; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy—SET-
NET, 16 jurisdictions, March 29–October 14, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1635–1640. doi: 10.15585/mmwr.mm6944e2
102. Sutton EF, Hauspurg A, Caritis SN, Powers RW, Catov JM. Maternal outcomes associated with lower range stage 1 hypertension. *Obstet Gynecol*. 2018;132:843–849. doi: 10.1097/AOG.0000000000002870
103. Warland J, Dorrian J, Morrison JL, O'Brien LM. Maternal sleep duration with meta-analysis. *Sleep Med Rev*. 2018;41:197–219. doi: 10.1016/j.smrv.2018.03.004
104. Mitrogiannis I, Evangelou E, Efthymiou A, Kanavos T, Birbas E, Makrydimas
119. Chen J, Bacelis J, Sole-Navais P, Srivastava A, Juodakis J, Rouse A, Hallman M, Teramo K, Melbye M, Feenstra B, et al. Dissecting maternal and fetal genetic effects underlying the associations between maternal phenotypes, birth outcomes, and adult phenotypes: a mendelian-randomization and haplotype-based genetic score analysis in 10,734 mother-infant pairs. *PLoS Med*. 2020;17:e1003305. doi: 10.1371/journal.pmed.1003305
120. Grobman WA, Parker CB, Willinger M, Wing DA, Silver RM, Wapner RJ, Simhan HN, Parry S, Mercer BM, Haas DM, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-

121. Brown CC, Moore JE, Felix HC, Stewart MK, Bird TM, Lowery CL, Tilford JM. Association of state Medicaid expansion status with low birth weight and preterm birth. *JAMA*. 2019;321:1598–1609. doi: 10.1001/jama.2019.3678
- G, Papatheodorou S. Risk factors for preterm birth: an umbrella review of meta-analyses of observational studies. *BMC Med*. 2023;21:494. doi: 10.1186/s12916-023-03171-4 10.1001/jamanetworkopen.2020.8243
105. Bekkar B, Pacheco S, Basu R, DeNicola N. Association of air pollution and heat exposure with preterm birth, low birth weight, and stillbirth in the US: a systematic review. *JAMA Netw Open*. 2020;3:e208243. doi: 10.1001/jamanetworkopen.2020.8243
106. Basu R, Chen H, Li DK, Avalos LA. The impact of maternal factors on the association between temperature and preterm delivery. *Environ Res*. 2017;154:109–114. doi: 10.1016/j.envres.2016.12.017
107. Chersich MF, Pham MD, Areal A, Haghighi MM, Manyuchi A, Swift CP,

122. Johnson JD, Green CA, Vladutiu CJ, Manuck TA. Racial disparities in pre-maturity persist among women of high socioeconomic status. *Am J Obstet Gynecol*. 2020;2:100104. doi: 10.1016/j.ajogmf.2020.100104
 123. Tanz LJ, Stuart JJ, Williams PL, Missmer SA, Rimm EB, James-Todd TM, Rich-Edwards JW. Preterm delivery and maternal cardiovascular disease risk factors: the Nurses' Health Study II. *J Womens Health (Larchmt)*. 2019;28:677–685. doi: 10.1089/jwh.2018.7150
 124. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Ray JG, Nerenberg K, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. *Circulation*. 2019;139:1069–1079. doi: 10.1136/bmj.m3811
- between high temperatures in pregnancy and risk of preterm birth, low birth weight, and stillbirths: systematic review and meta-analysis. *BMJ*. 2020;371:m3811. doi: 10.1136/bmj.m3811

125. Crump C, Sundquist J, Sundquist K. Preterm delivery and long term mortality in women: national cohort and co-sibling study. *BMJ*. 2020;370:m2533.
108. Lee KJ, Moon H, Yun HR, Park EL, Park AR, Choi H, Hong K, Lee J. doi: 10.1136/bmj.m2533
- Greenness, civil environment, and pregnancy outcomes: perspectives with a systematic review and meta-analysis. *Environ Health*. 2020;19:91. doi: 10.1186/s12940-020-00649-z
109. van Daalen KR, Kaiser J, Kebede S, Cipriano G, Maimouni H, Olumese E, Chui A, Kuhn I, Oliver-Williams C. Racial discrimination and adverse pregnancy outcomes: a systematic review and meta-analysis. *BMJ Glob Health*. 2022;7:e009227. doi: 10.1136/bmjgh-2022-009227
110. Himmelstein G, Desmond M. Association of eviction with adverse birth outcomes among women in Georgia, 2000 to 2016. *JAMA Pediatr*. 2021;175:494–500. doi: 10.1001/jamapediatrics.2020.6550
111. Hendryx M, Chojenta C, Byles JE. Latent class analysis of low birth weight and preterm delivery among Australian women. *J Pediatr*. 2020;218:42–48.e1. doi: 10.1016/j.jpeds.2019.11.007
112. Pantell MS, Baer RJ, Torres JM, Felder JN, Gomez AM, Chambers BD, Dunn J, Parikh NI, Pacheco-Werner T, Rogers EE, et al. Associations between unstable housing, obstetric outcomes, and perinatal health care utilization. *Am J Obstet Gynecol MFM*. 2019;1:100053. doi: 10.1016/j.ajogmf.2019.100053
113. Salazar EG, Montoya-Williams D, Passarella M, McGann C, Paul K, Murosko D, Pena MM, Ortiz R, Burris HH, Lorch SA, et al. County-level maternal vulnerability and preterm birth in the US. *JAMA Netw Open*. 2023;6:e2315306. doi: 10.1001/jamanetworkopen.2023.15306
114. Urquia ML, Wall-Wieler E, Ruth CA, Liu X, Roos LL. Revisiting the association between maternal and offspring preterm birth using a sibling design. *BMC Pregnancy Childbirth*. 2019;19:157. doi: 10.1186/s12884-019-2304-9
115. Wadon M, Modi N, Wong HS, Thapar A, O'Donovan MC. Recent advances in the genetics of preterm birth. *Ann Hum Genet*. 2020;84:205–213. doi:

126. Liao L, Deng Y, Zhao D. Association of low birth weight and premature birth with the risk of metabolic syndrome: a meta-analysis. *Front Pediatr.* 2020;8:100104. doi: 10.3389/fped.2020.00405
127. Crump C, Sundquist J, Sundquist K. Preterm birth and risk of type 1 and type 2 diabetes: a national cohort study. *Diabetologia.* 2020;63:508–518. doi: 10.1007/s00125-019-05044-z
128. Crump C, Sundquist J, Sundquist K. Risk of hypertension into adulthood in persons born prematurely: a national cohort study. *Eur Heart J.* 2020;41:1542–1550. doi: 10.1093/eurheartj/ehz904
129. Crump C, Sundquist J, Sundquist K. Association of preterm birth with lipid disorders in early adulthood: a Swedish cohort study. *PLoS Med.* 2019;16:e1002947. doi: 10.1371/journal.pmed.1002947
130. Brewer PL, D'Agata AL, Roberts MB, Wild RA, Shadyab AH, Saquib N, Manson J, Eaton CB, Sullivan MC. Association of preterm birth with prevalent and incident hypertension, early-onset hypertension, and cardiovascular disease in the Women's Health Initiative. *Am J Cardiol.* 2023;192:132–138. doi: 10.1016/j.amjcard.2023.01.033
131. Telles F, McNamara N, Nanayakkara S, Doyle MP, Williams M, Yaeger L, Marwick TH, Leeson P, Levy PT, Lewandowski AJ. Changes in the pre-term heart from birth to young adulthood: a meta-analysis. *Pediatrics.* 2020;146:1–13. doi: 10.1542/peds.2020-0146
132. Crump C, Groves A, Sundquist J, Sundquist K. Association of preterm birth with long-term risk of heart failure into adulthood. *JAMA Pediatr.* 2021;175:689–697. doi: 10.1001/jamapediatrics.2021.0131
133. Crump C, Howell EA, Stroustrup A, McLaughlin MA, Sundquist J, Sundquist K. Association of preterm birth with risk of ischemic heart disease in adulthood. *JAMA Pediatr.* 2019;173:736–743. doi: 10.1111/ahg.12373
116. Pasanen A, Karjalainen MK, Zhang G, Tiensuu H, Haapalainen AM, Ojaniemi M, Feenstra B, Jacobsson B, Palotie A, Laivuori H, et al; FinnGen. Meta-analysis of genome-wide association studies of gestational duration and spontaneous preterm birth identifies new maternal risk loci. *PLoS Genet.* 2023;19:e1010982. doi: 10.1371/journal.pgen.1010982
117. Zhang G, Feenstra B, Bacelis J, Liu X, Muglia LM, Juodakis J, Miller DE, Litterman N, Jiang PP, Russell L, et al. Genetic associations with gestational duration and spontaneous preterm birth. *N Engl J Med.* 2017;377:1156–1167. doi: 10.1056/NEJMoa1612665
118. Sole-Navais P, Flatley C, Steinthorsdottir V, Vaudel M, Juodakis J, Chen J, Laik T, LaBella AL, Westergaard D, Bacelis J, et al; Early Growth Genetics Consortium. Genetic effects on the timing of parturition and links to fetal birth weight. *Nat Genet.* 2023;55:559–567. doi: 10.1001/jamapediatrics.2019.1327

134. Crump C, Sundquist J, Winkleby MA, Sundquist K. Gestational age at birth and mortality from infancy into mid-adulthood: a national cohort study. *Lancet Child Adolesc Health*. 2019;3:408–417. doi: 10.1016/S2352-4642(19)30108-7
135. Osterman MJK, Hamilton BE, Martin JA, Driscoll AK, Valenzuela CP. Births: final data for 2021. *Natl Vital Stat Rep*. 2023;72:1–53.
136. Kharbanda EO, Vazquez-Benitez G, Kunin-Batson A, Nordin JD, Olsen A, Romitti PA. Birth and early developmental screening outcomes associated with cannabis exposure during pregnancy. *J Perinatol*. 2020;40:473–480. doi: 10.1038/s41372-019-0576-6
137. Retnakaran R, Shah BR. Patterns of cardiovascular risk factors in the years before pregnancy in nulliparous women with and without preterm birth and small-for-gestational-age delivery. *J Am Heart Assoc*. 2021;10:e021321. doi: 10.1038/s41588-023-01343-9

141. Svensson AC, Pawitan Y, Cnattingius S, Reilly M, Lichtenstein P. Familial aggregation of small-for-gestational-age births: the importance of fetal genetic effects. *Am J Obstet Gynecol*. 2006;194:475–479. doi: 10.1016/j.ajog.2005.08.019
142. Beaumont RN, Kotecha SJ, Wood AR, Knight BA, Sebert S, McCarthy MI, Hattersley AT, Jarvelin MR, Timpson NJ, Freathy RM, et al. Common maternal and fetal genetic variants show expected polygenic effects on risk of small- or large-for-gestational-age (SGA or LGA), except in the smallest 3% of babies. *PLoS Genet*. 2020;16:e1009191. doi: 10.1371/journal.pgen.1009191
143. Timpka S, Fraser A, Schyman T, Stuart JJ, Asvold BO, Mogren I, Franks PW, Rich-Edwards JW. The value of pregnancy complication history for 10-year cardiovascular disease risk prediction
138. Sheikh J, Allotey J, Kew T, Fernandez-Felix Thangaratinam S; IPPIC Collaborative. Interv on perinatal outcomes in high-income tries: an individual participant data meta-*Lancet*. 2022;400:2049–2062. doi: 10.1016/S0140-6736(22)00340-0
139. Nasiri K, Moodie EEM, Abenhaim HA. To between race/ethnicity and fetal growth of prenatal care? A mediation analysis of a *Am J Epidemiol*. 2020;189:1360–1368. doi: 10.1093/aje/kwz340
140. Lahti-Pulkkinen M, Bhattacharva S, JE, Reynolds RM. Intergenerational across 3 generations. *Am J Epidemiol*. 2020;189:1360–1368. doi: 10.1093/aje/kwz340
156. Downes KL, Grantz KL, Shenassa ED. tal outcomes associated with placental *J Perinatol*. 2017;34:935–957. doi: 10.1055/s-00042672
157. Lueth A, Blue N, Silver RM, Allshouse HN, Reddy U, Haas DM. Prospective nulliparous women. *J Matern Fetal* doi: 10.1080/14767058.2021.1989405
158. Anderson E, Raia EA, Shetty A, S. Bhattacharva S. Changing risk tion: a case crossover study using Finland, Malta and Aberdeen. *PLoS* 10.1371/journal.pone.0233641
159. Rasmussen S, Irgens LM. Occurrence in middle-aged women. *Eur J Epidemiol*. 2018;33:1003–1010. doi: 10.1007/s10654-018-0429-1
144. Knop MR, Geng TT, Gorny AW, Ding R, Li C, Ley SH, Huang T. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7 646 267 participants from 135 studies. *J Am Heart Assoc*. 2018;7:e008870. doi: 10.1161/JAHA.118.008870
145. Wang YX, Ding M, Li Y, Wang L, Rich-Edwards JW, Florio AA, Manson JE, Chavarro JE. Birth weight and long-term risk of mortality among US

- BJOG. 2009;116:693–699. doi: 10.1111/j.1471-0528.2008.02064.x 160. Ardissino M, Reddy RK, Slob EAW, Griffiths J, Girling J, Ng FS. Maternal hypertensive traits and adverse outcome in pregnancy: a mendelian randomization study. *J Hypertens*. 2023;41:1438–1445. doi: 10.1097/HJH.0000000000003486
161. Ananth CV, Patrick HS, Ananth S, Zhang Y, Kostis WJ, Schuster M. Maternal cardiovascular and cerebrovascular health after placental abruption: a systematic review and meta-analysis (CHAP-SR). *Am J Epidemiol*. 2021;190:2718–2729. doi: 10.1093/aje/kwab206
162. DesJardin JT, Healy MJ, Nah G, Vittinghoff E, Agarwal A, Marcus GM, Velez JMG, Tseng ZH, Parikh NI. Placental abruption as a risk factor for heart failure. *Am J Cardiol*. 2020;131:17–22. doi: 10.1016/j.amjcard.2020.06.034
163. Isayama T, Lewis-Mikhael AM, O'Reilly D, Beyene J, McDonald SD. Health services use by late preterm and term infants from infancy to adulthood: a meta-analysis. *Pediatrics*. 2017;140:e20170266. doi: 10.1016/j.peds.2017-0266
164. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyas T, Scott KW, et al. US health care spending by payer and health condition, 1996–2016. *JAMA*. 2020;323:863–884. doi: 10.1001/jama.2020.0734
- men and women: results from three prospective cohort studies. *Lancet Reg Health Am*. 2022;15:100344. doi: 10.1016/j.lana.2022.100344
146. Gregory ECW, Valenzuela CP, Hoyert DL. Fetal mortality: United States, 2021. *Natl Vital Stat Rep*. 2023;72:1–21.
147. Liu L, Sun D. Pregnancy outcomes in patients with primary antiphospholipid syndrome: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2019;98:e15733. doi: 10.1097/md.00000000000015733
148. Laisk T, Soares ALG, Ferreira T, Painter JN, Censin JC, Laber S, Bacelis J, Chen CY, Lepamets M, Lin K, et al. The genetic architecture of sporadic and multiple consecutive miscarriage. *Nat Commun*. 2020;11:5980. doi: 10.1038/s41467-020-19742-5
149. Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. *Fertil Steril*. 2010;94:1473–1477. doi: 10.1016/j.fertnstert.2009.06.041
150. Crotti L, Tester DJ, White WM, Bartos DC, Insolia R, Besana A, Kunic JD, Will ML, Velasco EJ, Bair JJ, et al. Long QT syndrome-associated mutations in intrauterine fetal death. *JAMA*. 2013;309:1473–1482. doi: 10.1001/jama.2013.3219
151. Maddirevula S, Awartani K, Coskun S, AlNaim LF, Ibrahim N, Abdulwahab F, Hashem M, Alhassan S, Alkuraya FS. A genomics approach to females with infertility and recurrent pregnancy loss. *Hum Genet*. 2020;139:605–613. doi: 10.1007/s00439-020-02143-5
152. Prasad S, Kalafat E, Blakeway H, Townsend R, O'Brien P, Morris E, Draycott T, Thangaratinam S, Le Doare K, Ladhani S, et al. Systematic re-view and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. *Nat Commun*. 2022;13:2414. doi: 10.1038/s41467-022-30052-w
153. Wang YX, Minguez-Alarcon L, Gaskins AJ, Wang L, Ding M, Missmer

165. O'Neil S, Platt I, Vohra D, Pendl-Robinson E, Dehus E, Zephyrin L, Zivin K. The high costs of maternal morbidity show why we need greater investment in maternal health. The Commonwealth Fund. 2021. Accessed April 7, 2024.
166. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, Borghi E, Hayashi C, Estevez D, Cegolon L, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health*. 2019;7:e849–e860. doi: 10.1016/S2214-109X(18)30565-5
167. Lawn JE, Ohuma EO, Bradley E, Idueta LS, Hazel E, Okwaraji YB, Erchick DJ, Yargawa J, Katz J, Lee ACC, et al; Lancet Small Vulnerable Newborn Steering Committee. Small babies, big risks: global estimates of prevalence and mortality for vulnerable newborns to accelerate change and improve counting. *Lancet*. 2023;401:1707–1719. doi: 10.1016/S0140-6736(23)00522-6
168. Chen C, Grewal J, Betran AP, Vogel JP, Souza JP, Zhang J. Severe anaemia, sickle cell disease, and thalassemia as risk factors for hypertensive disorders in pregnancy in developing countries. *Pregnancy Hypertens*. 2018;13:141–147. doi: 10.1016/j.preghy.2018.06.001
169. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, Flenady V, Froen JF, Qureshi ZU, Calderwood C, et al; Lancet Ending Preventable Stillbirths Series Study Group. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet*. 2016;387:587–603. doi: 10.1016/S0140-6736(15)00837-5
170. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed July 1, 2024.
- SA, Rich-Edwards JW, Manson JE, Chavarro JE. Pregnancy loss and risk of cardiovascular disease: the Nurses' Health Study II. *Eur Heart J*. 2019;126:33–42. doi: 10.1111/1471-0528.15452
- 2022;43:190–199. doi: 10.1093/eurheartj/ehab737
154. Horn J, Tanz LJ, Stuart JJ, Markovitz AR, Skurnik G, Rimm EB, Howard BV, Sarto GE, Gass ML, Sealy-Jefferson SM, Salmoirago-Blotcher E, et al. Relation of pregnancy loss to risk of cardiovascular disease in parous post-menopausal women (from the Women's Health Initiative). *Am J Cardiol*. 2019;123:1620–1625. doi: 10.1016/j.amjcard.2019.02.012

171. Ford ND, Cox S, Ko JY, Ouyang L, Romero L, Colarusso T, Ferre CD, Kroelinger CD, Hayes DK, Barfield WD. Hypertensive disorders in pregnancy and mortality at delivery hospitalization—United States, 2017–2019. *MMWR Morb Mortal Wkly Rep.* 2022;71:585–591. doi: 10.15585/mmwr.mm7117a1

172. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.

173. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: final data for 2018. *Natl Vital Stat Rep.* 2019;68. Accessed April 15, 2024.

12. KIDNEY DISEASE

ICD-10 N18.0. See Table 12-1 and Charts 12-1 through 12-13

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Definition
(See Chart 12-1)

CKD, defined as reduced eGFR (<60 mL·min⁻¹·1.73 m⁻²), excess urinary albumin excretion (ACR ≥30 mg/g), or both, is a serious health condition and a worldwide public health problem that is associated with poor outcomes and a high cost to the US health care system.¹

- eGFR is usually determined from serum creatinine level with equations that account for age, sex, and race. Given that race is a social construct and its inclusion in eGFR equations may perpetuate bias by wrongly ascribing biological differences to race, a task force from the American Society of Nephrology and the National Kidney Foundation recommended using the eGFR equation without the race variable and to facilitate increased and timely use of cystatin C, which is a filtration marker not affected by race.^{2–5} Newer versions of the eGFR equations that do not incorporate race have been developed and validated. The eGFR equation with creatinine from 2021 was used for calculating CKD estimates in the 2023 USRDS report.⁶ The 2024 Kidney Disease: Improving Global Outcomes CKD guidelines recommend using the combination of creatinine- and cystatin C–based eGFR equation for CKD staging when cystatin C is available.⁷ The spot (random) urine ACR is recommended as a measure of urine albumin excretion.

- CKD is characterized by eGFR category (G1–G5) and albuminuria category (A1–A3).

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

Prevalence
(See Charts 12-1 through 12-3)

- Using data from NHANES 2017 to 2020, USRDS has estimated the prevalence of CKD by eGFR and albuminuria categories as shown in Chart 12-1. The overall prevalence of CKD (eGFR <60 in yellow, orange, and red in Chart 12-1) in 2017 to 2020 was 14.0%.⁹
- The overall prevalence of CKD increases substantially with age, with 9% of adults <65 years of age and 33.2% of adults ≥65 years of age having CKD in 2017 to 2020.⁹
- According to NHANES 2017 to 2020, the prevalence of ACR ≥30 mg/g was 13.5% for NH Black adults, 10.9% for Hispanic adults, and 9.2% for NH White adults. In contrast, the prevalence of eGFR <60 mL·min⁻¹·1.73 m⁻², calculated with the newer eGFR equations without the race coefficient, was lowest among Hispanic adults (2.2%) followed by NH White adults (6.3%) and highest for NH Black adults (9.1%).⁹
- The overall prevalence of CKD (incorporating eGFR <60 mL·min⁻¹·1.73 m⁻² or ACR ≥30 mg/g) was highest among NH Black adults (18.8%) followed by NH White adults (12.1%) and Hispanic adults (12.0%). The prevalence of CKD decreased compared with the previous NHANES cycle (2013–2016) for NH White adults and Hispanic adults but increased in NH Black adults.¹
- In the Framingham Offspring Study, the prevalence of mildly reduced eGFR (60–89 mL·min⁻¹·1.73 m⁻²) was reported in 62% of participants, higher than reported in the NHANES data, possibly related to the higher age of the cohort.¹⁰
- In 2021, the age-, race-, and sex-adjusted prevalence of ESKD in the United States was 2219 per million people, a decrease of 3.5% from its peak in 2019.¹ The overall prevalence count increased slightly, from 807 920 in 2020 to 808 536 in 2021.

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

adults. ESKD prevalence also was higher among Hispanic people than among NH people.

- Among those with prevalent ESKD, in 2021 compared with 2020, the use of in-center hemodialysis remained the most common modality but continued to decrease from 59.8% to 58.3% (Chart 12-3). All other modalities increased: transplantation from 30.6% to 31.8%, peritoneal dialysis from 8.1% to 8.3%, and home hemodialysis from 1.5% to 1.6%.¹

Incidence

(See Chart 12-4)

- According to 2022 data from the Health System, the CKD rates 3–5) increased with age. per 1000 patient-years were age). 12.6 (30–39 years of age). 51.4 (50–59 years of years of age). and 110.1 (≥ 70
- The incidence of ESKD in 2021, adjusted for age, sex, and race and ethnicity, was 363 per million people, a small increase from the low of 360 per million people in 2020. The incidence count increased from 130 522 in 2020 to 135 972 in 2021.⁹ The incidence of ESKD was higher in males than females (Chart 12-4).
- By modality, the initiation of in-center hemodialysis decreased from 83.9% to 83.8%, whereas peritoneal dialysis remained the same at 12.7%, and home hemodialysis also remained at 0.3%.¹

million population in 2006 to ulation in 2021). However, incidence rate, the absolute been steadily increasing over when it dropped from 134 837 in 2020. In the year 2020, the adjusted incidence rate was by a 1.9% decline in the and the accompanying in prevalence count. This

(See Charts 12-5 and 12-6)

- Among Medicare beneficiaries, the prevalence of CKD (based on coded diagnosis) increased from 9.2% in 2011 to 14.2% in 2021 (Chart 12-5).
- According to NHANES data, the overall prevalence of reduced eGFR and excess ACR across categories was generally similar from 2005 to 2020 (Chart 12-6).
- Between 2013 to 2016 and 2017 to 2020, the prevalence of CKD stage 3 decreased among indi-

Secular Trends

mostly by the effects of COVID-19 in the ESKD population. In 2021, the incident count increased sharply to 135 972, a number that is below the pre–COVID-19 trajectory for 2021 but above the expected number if pre-2020 growth rates had been applied to the 2020 count.

- The adjusted ESKD incidence by age declined slightly in most age groups except those ≥ 75 years of age.¹ This group had demonstrated a large decrease in the incidence rate from 2019 (1586 per million population) to 2020 (1452 per million population), which increased again to 1581 per million population in 2021, making the largest contribution to the increase in incidence count.
- The adjusted ESKD incidence decreased in all race and ethnicity groups from 2001 until 2018 or 2019.¹ After 2019, ESKD incidence increased among Black individuals but not among members of other race and ethnicity groups. In 2021, the incidence of ESKD among Black individuals was 3.8 times the incidence of NH White individuals; the incidence among Native American individuals was 2.3 times as high, and it was twice as high among Hispanic individuals.

viduals <65 years of age, from 1.6% to 1.3%, but was unchanged among those ≥ 65

Risk Factors

- By race and ethnicity, the prevalence of stage 3 and 4 CKD increased from 7.9% to 8.8% in NH Black individuals, was unchanged at 6.3%

among NH White individuals, and decreased slightly from

- In a pooled analysis of >5.5 million adults, higher BMI, WC, and waist-to-height ratio were independently associated with eGFR decline and death in individuals who had normal or reduced levels of eGFR.¹²
2.6% to 2.0 % in Hispanic individuals.⁹ However, the prevalence of stage 5 CKD remained unchanged at 0.1% in NH White individuals, decreased from 0.5% to 0.3% among NH Black individuals, but increased slightly from 0.1% to 0.2% in Hispanic

- In the ARIC study, incident hospitalization with any major CVD event (HF, AF, CHD, or stroke) was associated with an increased risk of ESKD (HR, 6.63 [95% CI, 4.88–9.00]). In analyses by CVD event type, the association with ESKD risk was more pronounced in individuals with HF and CHD, and less pronounced in individuals with AF and stroke. In analyses by CVD event type, the association with ESKD risk was more pronounced in individuals with HF and CHD, and less pronounced in individuals with AF and stroke.
- From 2001 to 2019, the prevalence count of ESKD had been increasing (409 226 in 2001 to 806 939 in 2019), attributable primarily to a combination of an aging and growing population and improved survival with ESKD.¹ This prevalence count has since slowed down or flattened in 2020 (805 629) and 2021 (808 536). The incidence rate itself has been declining since 2006 (sex- and age-adjusted incidence rate 425 per 100 000 per year).

nounced for HF (HR, 9.92 [95% CI, 7.14–13.79]) than CHD (HR, 1.80 [95% CI, 1.22–2.66]), AF (HR, 1.10 [95% CI, 0.76–1.60]), and stroke (HR, 1.09 [95% CI, 0.65–1.85]).¹³

- In the Framingham Offspring Study, maintaining Life's Simple 7 factors in the intermediate or ideal levels for 5 years was associated with lower risk of incident CKD during a median follow-up of 16 years (HR, 0.75 [95% CI, 0.63–0.89]).¹⁴

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- In the ARIC study, higher scores for HEI (HR per 1 SD, 0.94 [95% CI, 0.90–0.98]), AHEI (HR per 1 SD, 0.93 [95% CI, 0.89–0.96]), and alternative Mediterranean diet (HR per 1 SD, 0.93 [95% CI, 0.89–0.97]) were associated with a lower risk of incident CKD during a median follow-up of 24 years.¹⁵
 - In the CRIC study, with the use of unsupervised consensus clustering, a higher rate of progression of kidney function less favorable levels of bone mineral density, poor cardiac and kidney function markers, and inflammation (HR, 1.63 [95% CI, 1.27–2.09]) followed by (hospitalizations, OR, 1.48 [95% CI, 1.33–1.64]) during follow-up.²²
 - In an analysis of adults with obesity but without baseline CKD or diabetes enrolled in MESA, linear mixed-effects and multistate models adjusted for demographics, time-varying covariates including BP, and comorbidities were used to examine associations of weight change patients with a higher prevalence of diabetes and obesity and who used more medications (HR, 1.3 [95% CI, 1.05–1.67]) compared with the referent

atinine–cystatin equation $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$).²³ Among the 1208 included MESA participants, 15% developed CKD during follow-up. Slow walking pace was associated with eGFR decline ($-0.27 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ [95% CI, -0.42 to -0.12]) and CKD (aHR, 1.48 [95% CI, 1.08–2.01]). Weight gain cluster.¹⁶

- In a meta-analysis of 23 studies, preeclampsia was associated with increased risk of ESKD (RR, 4.90 [95% CI, 3.56–6.74]) and CKD (RR, 2.11 [95% CI, 1.72–2.59]).¹⁷
- In a meta-analysis of 31 studies, living kidney donation was associated with a greater decline in GFR in older donors (>60 years of age), female donors, and donors with obesity with a BMI $>30 \text{ kg/m}^2$.^{18,19}
- In a meta-analysis of 20 studies, lithium treatment was associated with a prevalence rate of 25.5% for impaired kidney function ($\text{eGFR} < 60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$). In a comparison of 14 187 patients on lithium and 722 529 on nonlithium treatment, lithium treatment was associated with higher risk of subsequent CKD ($\text{eGFR} < 60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) with a pooled OR of 2.09 (95% CI, 1.24–3.51).²⁰
- An analysis using NHANES data examined the relationship between LBW compared with nor-

- mal birth weight and subsequent development of reduced kidney function (defined as $\text{eGFR} < 90 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ using the pediatric Schwartz equation).²¹ The analysis included 6336 children (12–15 years of age) and reported the prevalence of reduced kidney function at 30.1% (95% CI, 25.2%–35.6%) for children born with LBW compared with 22.4% (95% CI, 20.5%–24.3%) in children with normal birth weight.
- A prospective study enrolled 3409 adults with autosomal dominant polycystic kidney disease and reported an association of each additional l/m of height-adjusted total kidney volume on MRI with lower eGFR (regression coefficient, 17.02 [95% CI, 15.94–18.11]) and worse patient-reported health-related quality of life (autosomal dominant polycystic kidney disease Impact Scale physical score regression coefficient, 1.02 [95% CI, 0.65–1.39]), decreased work productivity (work days missed, regression coefficient, 0.55 [95% CI, 0.18–0.92]), and increased health care resource use

Social Determinants of CKDs/Health Equity

- According to NHANES 2015 to 2018, the prevalence of CKD was 19.5% for adults with less than a high school education, 17.2% for those with a high school degree or equivalent, and 13.1% for those with some college or more.⁹
- In the CKiD study, Black children with CKD were more likely than White children to have public insurance, lower household income, and greater food insecurity (41% versus 14%; $P<0.001$).²⁴
- The REGARDS study included 4198 Black participants and 7799 White participants at least 45 years of age recruited from 2003 through 2007 across the continental United States with baseline eGFR $>60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ with a repeat kidney function assessment at 9 years of follow-up. Stroke Belt residence was independently associated with eGFR change (-0.10 ; $P<0.001$) and incident CKD (RR, 1.14 [95% CI, 1.01–1.30]).²⁵ Albuminuria was more strongly associated with eGFR change (β , -0.26 versus -0.17 ; $P_{\text{interaction}}=0.01$) in Black participants compared with White participants with similar results for incident CKD.

Genetics/Family History

- It is estimated that $\approx 30\%$ of early-onset CKD is caused by single-gene variants, and several hundred loci have been implicated in monogenic CKD.^{26,27}
- GWASs in >1 million individuals revealed >260 candidate loci for CKD phenotypes, including eGFR and serum urate.^{28–31}
- GWAS meta-analysis in individuals of European ancestry identified 424 genetic loci (201 novel loci) associated with eGFR (estimated with creatinine). Among these, 348 loci were validated in association with eGFR estimation

with the use of cystatin C. A multi-ancestry meta-analysis including >15,000,000 individuals for eGFR led to the identification of 10 loci. Heritability analysis showed that genetic variations mediated about half of the risk of kidney disease. Multiple lines of evidence established the causal role of genetic variation in the development of kidney disease.

- Whole-genome sequencing—provided a more granular understanding of the genetic architecture. In >23,000 multi-ancestry populations, 3 novel loci associated with eGFR that are more commonly observed in individuals from non-European ancestry.³⁴ Rare and low-frequency genetic variants are likely to be population-specific, and greater inclusion of individuals of non-European ancestry in future genomic discovery efforts may aid in understanding the comprehensive genetic

genome-wide CKD PRS and a higher risk of CKD across

- Using data from 293,151 individuals of European ancestry, a GWAS for urinary albumin levels identified 2 loci (*KRT40* and *WDR72*) in the same population. GWAS in the same population identified 2 loci (*WDR72* and *UMOD*) associated with annual decrease in eGFR.
- A GWAS meta-analysis in individuals with CKD identified 182 loci associated with the architecture of renal function and CKD.
- Refinement in discovery and validation efforts combining multiomics data has identified 182 likely causal genes for kidney function.³⁵ These data may be leveraged for drug repurposing, therapeutic pathway prioritization, and identification of potential

The 11 loci associated with eGFR decline were also associated with cross-sectional eGFR.⁴⁴ Apart from identifying the *UMOD-PDILT* locus, gene prioritization analysis identified *SPATA7*, *GALNTL5*, *TPPP*, and *FGF5* as candidate genes for eGFR decline.⁴⁴ An analysis combining genetic, gene expression, splicing, and methylation data from up to 430 human kidneys to examine the renal mechanisms in BP regulation revealed connections of 1038 renal genes with 479 variants associated with BP.⁴⁵ Colocalization and mendelian randomization analyses established the causal role of 179 renal genes in the regulation of BP.⁴⁵

- Post-GWAS analysis integrating Bayesian colocalizations, transcriptome-wide association studies, and mendelian randomization studies has prioritized drug interactions.
 - A transcriptome-wide association study combined with functional validation has identified *DACH1* as a CKD risk gene that contributes to tubular damage and kidney fibrosis.³⁶ Racial differences in CKD prevalence might be attributable partially to differences in ancestry and genetic risk. The *APOL1* gene has been well studied as a kidney disease locus in individuals of African ancestry.³⁷ Specific SNPs in *APOL1* are present in individuals of African ancestry but absent in other racial groups. This might have been subjected to positive selection, conferring protection against trypanosome infection but leading to increased risk of renal disease, potentially through disruption of mitochondrial function.³⁸
 - Although certain variants of *APOL1* increase risk, this explains only a portion of the racial disparity in ESKD risk.³⁷ For example, eGFR decline was faster even for Black adults with low-risk *APOL1* status (0 or 1 allele) than for White adults in CARDIA; this difference was attenuated by adjustment for SES and traditional risk factors.³⁹
 - In a large, 2-stage individual-participant data meta-analysis, *APOL1* kidney-risk variants were not associated with incident CVD or death independently of kidney measures.⁴⁰
 - Use of PRSs based on 35 blood and urine biomarkers

CASP9 as a risk locus for kidney disease.⁴⁶ Murine models showed that inhibition of CASP9, through either gene knockout or pharmacological inhibition, was associated with lower apoptosis, improved mitophagy, reduced inflammation, and protection from renal fibrosis.⁴⁶

Awareness, Treatment, and Control

- In a cohort study of 192 108 US patients with hypertension or diabetes, it was assessed that approximately two-thirds of patients with albuminuria were undetected because of lack of testing.⁴⁷
- A clinical trial found that home-based screening of the general population for increased ACR with a urine collection device had a high participation rate (59.4% [95% CI, 58.3%–60.5%]) with high sensitivity (96.6% [95% CI, 91.5–99.1]) and specificity (97.3% [95% CI, 94.7–98.8]) to detect high ACR.⁴⁸• CKD awareness has increased over time but remains low. In a study of NHANES 1999 to 2018, CKD awareness increased from 11.2% in 1999 to 2002 to 19.8% in 2015 to 2018.⁴⁹ Awareness increased with higher CKD stage and was generally higher among Black individuals, younger age groups, and individuals with diabetes, hypertension, and higher BMI.⁴⁹
- In a study of >363000 UK Biobank participants, including renal biomarkers, was found to improve genetic risk stratification for CKD.⁴¹ Individuals belonging to the highest 2% of the multi-ancestry

- Treatment and control of BP among those with CKD and hypertension improved from 31.1% in 2003 to 2006 to 37.5% in 2015 to 2018.⁹

- Among adults with CKD treated in the Veterans Health Administration, the proportion of adults with controlled BP 2011 to 2015 with a slight increase to 72.9% by 2019.⁵⁰ Among adults with CKD with BP above goal, the age-adjusted proportion who did not receive antihypertensive treatment throughout the decade increased from 10.8% to 21.6%.⁵⁰
- Among patients with CKD with hypertension, an intensive SBP treatment goal of <130 mm Hg compared with a standard goal of <140 mm Hg decreased the risk of all-cause mortality (HR, 0.79 [95% CI, 0.63–1.00]) in a pooled analysis of 4 randomized clinical trials.⁵¹
- In 2015 to 2018, 69% of those with CKD and diabetes had HbA1c <8%, and 11% of them had fasting LDL-C levels <70 mg/dL.⁹ In a study of patients with CKD with diabetes in a large health care system, HbA1c <6% and ≥9% was associated with high risk for all-cause death.⁵²
- Children <7 years of age with CKD are more likely to have both undiagnosed and unrecognized hypertension. Children <7 years of age had hypertensive BP readings, 46% had unrecognized and untreated hypertensive BP compared with 21% of visits for children ≥13 years of age. The youngest age group was associated with higher odds of
- Total hospitalization expenditure in Medicare fee-for-service beneficiaries with ESKD was \$12.1 billion in 2020.⁹

Global Burden of Kidney Disease (See Table 12-1 and Charts 12-7 and 12-8)

- Based on 204 countries and UI, 629.10–722.36) million cases, a 27.33% (95% UI, 26.32%–28.31%) increase since 2010. There were 1.53 (95% UI, 1.39–1.64) million total deaths attributable to CKD (Table 12-1). The age-standardized prevalence of CKD was highest for Central, Southeast, and South Asia. Prevalence was lowest for Western Europe (Chart 12-7).
- Central sub-Saharan Africa, central Latin America, and eastern sub-Saharan Africa had unrecognized hypertensive BP (aOR, 2.11 [95% CI, 1.37–3.24]) and lower odds of antihypertensive medication use among those with unrecognized hypertensive BP (aOR, 0.51 [95% CI,

Kidney Disease and CVD

CKD and CVD Outcomes

- There is a strong and consistent association of reduced eGFR and higher albuminuria with CVD risk.⁵⁶ In an analysis of 114 cohorts, lower eGFR based on creatinine alone, lower eGFR based on creatinine and cystatin C, and more severe urine ACR (compared with normal eGFR and urine ACR) were each associated with increased rates of

Complications

- DALYs for CKD were 457.25 per 100000 in 2002 versus 536.85 per 100000 in 2019.⁵⁴

adverse outcomes, including adverse kidney out-comes, CVDs, and hospitalizations. For example, eGFR based on creatinine and cystatin of 45 to 59 mL·min⁻¹·1.73 m⁻² and urine ACR of 10 to 29

mg/g was
associated higher

Cost

- In 2020, Medicare spent >\$85.4 billion caring for people with CKD and \$50.8 billion caring for people

mortality (HR, 2.7 [95% CI, 2.4–3.0]), and kidney failure with replacement therapy (HR, 12.5 [95% CI, 5.4–29.1]).

- ESKD care accounts for >7% of total Medicare expenditures for just 1% of the Medicare population.⁵⁵
- In inflation-adjusted dollars, Medicare spending per person per year for beneficiaries with ESKD decreased from \$96 451 in 2010 to \$79 439 in 2020: \$116 383 to \$95 932 for beneficiaries receiving hemodialysis, \$89 962 to \$81 525 for beneficiaries receiving peritoneal dialysis, and

found that compared with the reference group (quartile 1, ACR <4.171 mg/g), low-grade albumin-uria was associated with all-cause mortality (quar-tile 3, ACR ≥6.211–<10.010 mg/g: HR, 1.25 [95% CI, 1.11–1.41]; quartile 4, ACR ≥10.010 mg/g: HR, 1.57 [95% CI, 1.41–1.76]) in a multivariable model.⁴⁷

\$42 917 to \$39 264 for beneficiaries with a kidney transplantation.⁹ After adjustment for inflation, total spending among Medicare fee-for-service beneficiaries with CKD decreased for the first time in 2020 with expenditures \$2 billion lower than in

- The association of reduced eGFR with CVD risk is generally similar across age, race, and sex sub-groups,⁵⁷ although albuminuria tends to be a stronger risk factor for females than for males and for older (>65 years of age) than for younger people.⁵⁸

- In Framingham Offspring out CVD, participants with function (eGFR, 60–69 ended higher incidence of 1.02–1.93¹).¹⁰
 - The addition of eGFR and CVD prediction beyond The AHA's PREVENT CVD eGFR and albuminuria.⁶¹
 - In an analysis of >4 million adults inclusion of eGFR and albuminuria significantly improved prediction for CVD mortality beyond SCORE and ASCVD beyond PCE in validation
- the CKD population. CVD was patients with stage 1 to 2 stage 3 CKD, and 75.3% in CKD.¹
- Of the types of CVD, HF (24%) the most prevalent according beneficiaries in 2020.¹ munity based cohorts have the attributable risk of CKD to HF and CHD. After data-sets (ΔC statistic, 0.027 [95% CI, 0.018–0.036] and 0.010 [95% CI, 0.007–0.013]) and categori-

cohort, hypertension, diabetes, hyperlipidemia, and tobacco use, risk differences comparing participants with and those without CKD (per 1000 PY) were 2.3 (95% CI, 1.2–3.3) for HF, 2.3 (95% CI, 1.2–3.4) for CHD, and 0.8 (95% CI, 0.09–1.5) for

cal NRI (0.080 [95% CI, 0.032–0.127] and 0.056 [95% CI, 0.044–0.067], respectively).⁶⁰

- In a mendelian randomization analysis of 4 population data sources (Emerging Risk Factors Collaboration, European Prospective Investigation Into Cancer and Nutrition–Cardiovascular Disease Study, Million Veteran Program, and UK Biobank), in those with eGFR 60 mL·min⁻¹·1.73 m⁻², each 5-mL·min⁻¹·1.73 m⁻² lower eGFR was associated with a 14% (95% CI, 3%–27%) higher risk of CHD.⁶² • A meta-analysis of 21 cohort studies of 27 465 individuals with CKD found that nontraditional risk factors such as serum albumin, phosphate, urate, and hemoglobin are associated with CVD risk in this

stroke.⁶⁷

population.⁶³ In the CRIC study of 2399 participants without a history of CVD at baseline, a composite inflammation score (interleukin-6, tumor necrosis factor- α , fibrinogen, and serum albumin) was associated with increased CVD risk (ie, MI, PAD, stroke, or death; standardized HR, 1.47 [95% CI, 1.32–1.65]).⁶⁴

- In a randomized clinical trial of adults with PAD, CKD was associated with increased risk of MACEs (HR,

- The prevalence of CVD in patients with ESKD differs by treatment modality. Approximately 77.3% of patients with ESKD on hemodialysis have any CVD, whereas 66.4% of patients on peritoneal dialysis and 54.8% of patients receiving transplantation have any CVD (Chart 12-10).
- Among 2257 community-dwelling adults with CKD (ARIC study) monitored with an ECG for 2 weeks, nonsustained VT was the most frequent major arrhythmia, occurring at a rate of 4.2 episodes per person per month.⁶⁸ Albuminuria was associated with higher prevalence of AF and percent time in AF and nonsustained VT.
- Among patients with CKD, the presence of diabetes had less of an effect on hospitalization rate than did presence of CVD. For example, compared with beneficiaries with stage 3 CKD who had neither diabetes nor CVD, the adjusted hospitalization rate was ≈30% higher among beneficiaries with diabetes (but not CVD) but was ≈160% higher among beneficiaries with CVD (but not diabetes). The rate was 280% higher among individuals with both diabetes and CVD.¹
 - 1.45 [95% CI, 1.30–1.63] but not major amputation (HR, 0.92 [95% CI, 0.66–1.28]).⁶⁵
 - for those in the standard BP treatment arm (HR, 2.71 [95% CI, 1.61–4.55]) but not the intensive BP treatment arm (HR, 0.93 [95% CI, 0.48–1.78]).⁶⁶
- In a post hoc analysis of patients with hypertension in SPRINT, albuminuria was associated with increased stroke risk overall (HR, 2.24 [95% CI, 1.55–3.23]), with this association being present

- Rates of hospitalizations for cardiovascular causes were stable from 2013 to 2019 and then decreased substantially in 2020 (Chart 12-11).
- During 2018 to 2020, the 2-year adjusted survival probability after a first hospitalization for various cardiovascular conditions was lower among beneficiaries with CKD than for those without CKD and worse among those with more advanced CKD

(Chart 12-12).

Prevalence of CVD Among People With CKD

(See Charts 12-9 through 12-12)

- People with CKD, as well as those with ESKD, have an extremely high prevalence of comorbid CVDs, ranging from IHD and

HF to arrhythmias and VTE
(Charts 12-9 and 12-10).

- In 2020, CVD was present in 35.6% of patients

Incidence of CVD Events Among People With CKD • In 3 community-based cohort studies (JHS, CHS, and MESA), absolute incidence rates for HF, CHD, and stroke for participants with versus without CKD were 22 versus 6.2 (per 1000 PY) for HF, 24.5 versus 8.4 for CHD, and 13.4 versus 4.8 for stroke.⁶⁷ without CKD, but a higher prevalence was noted in

• Both eGFR and albuminuria appear to predict HF events (improvement in C statistic of 0.0258) more strongly than CHD or stroke events.⁵⁸

• In a meta-analysis of patients with CKD, the prevalence of PH was 23% and was associated with increased risk of CVD (RR, 1.67 [95% CI, 1.07–2.60]) and mortality (RR, 1.44 [95% CI, 1.17–1.76]).⁶⁹

• Among Medicare beneficiaries with CKD, mortality after 1 year (HR, 2.87 [95% CI, 2.79–2.95]), 2 to 3 years (HR, 1.56 [95% CI, 1.51–1.61]), and 4 to 5 years (HR, 1.47 [95% CI, 1.40–1.53]) of follow-up

7.5%, 17.4%, and 29.7% across eGFR categories of 60 to 74, 45 to 59, 30 to 44, 15 to 29, and <15 mL·min⁻¹·1.73 m⁻², respectively.⁷⁴

Although iron studies were checked infrequently in patients with anemia, low iron test results were highly prevalent in those tested: 60.4% and 81.3% of male and female, respectively.

Erythropoietin- and a higher risk of all-cause, cardiovascular, and noncardiovascular hospitalization during the same

bin <9 g/dL was associated with higher rates of CVD (HR, 2.09 [95% CI, 1.00–2.17] in men and HR, 1.93 [95% CI, 1.87–2.00] in women).

- In CRIC study participants with CKD, increases in NT-proBNP (the top quartile of NT-proBNP period. change) were significantly associated with greater death (HR, 0.96 [95% CI, 0.80–1.14]) after adjustment for demographic factors, baseline kidney function, and cardiovascular risk factors.⁷⁰ However, the risk of HF associated with CKD might be greater for Black people (HR, 1.59 [95% CI, 1.29–1.95]) than for White people.⁶⁷
- Despite having higher overall event rates than NH White people, NH Black people with CKD have similar (or possibly lower) rates of ASCVD events (HR, 1.08 [95% CI, 0.87–1.34]), HF events (HR, 1.05 [95% CI, 0.83–1.32]), or composite of HF or

risk of incident HF (HR, 1.79 [95% CI, 1.06–3.04]) and AF (HR, 2.32 [95% CI, 1.37–3.93]), and increases in soluble ST2 (the top quartile of soluble ST2 change) were associated with HF (HR, 1.89 [95% CI, 1.13–3.16]).⁷⁵

- A study found significant associations of fibroblast growth factor-23 with both HFpEF (HR, 1.41 [95% CI, 1.21–1.64] per 1-SD increase in the natural log of fibroblast growth factor-23) and HFrEF (HR, 1.27 [95% CI, 1.05–1.53] per 1-SD increase in the natural log of fibroblast growth factor-23) in patients with CKD.⁷⁶
- Clinically significant bradyarrhythmias (event rate, 3.90 [95% CI, 1.04–14.63] per patient-month) appear to be more common than ventricular arrhythmias (event rate, 0.00 [95% CI, 0.00–0.02] per patient-month) among patients on hemodialysis and are highest in the immediate hours before dialysis

- A study showed a significant association between severity of CKD and coronary flow reserve (adjusted $\beta=0.016$; $P=0.045$) Both CKD (HR, 2.6 [95% CI, 1.5–4.5]) and depressed coronary flow reserve (HR, 3.2 [95% CI, 2.0–5.2]) showed an independent association with higher risk of cardiac death or CVD.⁷¹
- In a prospective study of 7916 patients on hemodialysis and peritoneal dialysis, risk for ischemic stroke/ systemic embolism (subdistribution HR, 0.87 [95% CI, 0.79–0.96]) and major bleeding (subdistribution HR, 0.79 [95% CI, 0.64–0.97]) was lower in those undergoing peritoneal dialysis compared with those undergoing hemodialysis.⁷²

CKD-Specific Risk Factors for CVD

- In a study of 906 participants with CKD and hypertension, patients with ambulatory BP above goal, the risk of cardiovascular events was greater in the absence (HR, 2.79 [95% CI, 1.64–4.75]) and presence (HR, 2.05 [95% CI, 1.10–3.84]) of nocturnal dipping.⁷³ Patients at the ambulatory BP goal but who did not experience nocturnal dipping had an increased risk of the cardiovascular end point (HR, 2.06 [95% CI, 1.15–3.68]).

hospitalization for HF.⁷⁷

- In the German diabetes dialysis study (4D), patients in the highest oxalate quartile had an increased risk of cardiovascular events (HR, 1.40 [95% CI, 1.08–1.81]) and SCD (HR, 1.62 [95% CI, 1.03–2.56]).⁷⁸• In a secondary analysis of the STABILITY trial, elevated interleukin-6 level (≥ 2.0 ng/L versus < 2.0 ng/L) was associated with increased risk of major atherosclerotic cardiovascular events across kidney function strata: normal kidney function (HR, 1.35 [95% CI, 1.02–1.78]), mild CKD (HR, 1.57 [95% CI, 1.35–1.83]), and moderate to severe CKD (HR, 1.60 [95% CI, 1.28–1.99]).⁷⁹
- A proteomic risk model, which consisted of 32 proteins, was superior to both the 2013 ACC/AHA PCE and a modified PCE that included eGFR (C statistics were 0.84 and 0.89 for the protein models compared with 0.70 and 0.73 for the clinical models).⁸⁰
- In a study of 57 health care centers, lower eGFR was very strongly associated with increased prevalence of anemia. The prevalence of severe anemia (hemoglobin < 10 g/dL) in men was 1.3%, 3.1%,

- Lipoprotein(a) was not associated with the risk for recurrent ASCVD events [HR, 1.04 (95% CI, 0.95–1.15) per 1-SD increase in lipoprotein(a)] in adults

with CKD, although it was kidney failure [HR. 1.16 (95% 1-SD increase in

CVD as a Risk Factor for CKD and

- In an analysis of >25 million and incident CVDs were kidney failure with of 3.1 (95% CI, 2.9–3.3), 2.0 (95% CI, 4.2–4.9), and 2.8 incident CHD, stroke, HF, and
- A study of participants from the also demonstrated a 2- to 3-ESKD after HF hospitalizations.⁸⁸

Prevention and Treatment of CVD CKD

Medication Use

- According to NHANES data, the percentage of adults with CKD taking statins increased from 17.6% in 1999 to 2002 to 35.7% in 2011 to 2014. However, there was no difference in statin use for those with versus without CKD (RR, 1.01 [95% CI, 0.96–1.08]).⁸⁴
- Among veterans with diabetes and CKD, the proportion receiving an ACE inhibitor/ARB was 66% (95% CI, 62%–69%) in 2013 to 2014.^{85,86}
- In NHANES 1999 to 2014, 34.9% of adults with CKD used an ACE inhibitor/ARB. The use of ACE inhibitors/ARBs increased in the early 2000s among adults with CKD but plateaued subsequently.⁸⁵
- Among Medicare beneficiaries with CKD, in 2019, 54.4% of patients with CKD were on β -blockers and 64.3% were on lipid-lowering agents.⁹
- Among 22 739 Medicare beneficiaries with stage 3 to 5 CKD, apixaban compared with warfarin was associated with decreased risk of stroke (HR, 0.70 [95% CI, 0.51–0.96]) and major bleeding (HR, 0.47 [95% CI, 0.37–0.59]), but these risks did not differ with the use of rivaroxaban

increased significantly from sus 6.39 ± 7.3 ; $P=0.003$).⁹⁰

- In a target trial emulation of veterans >65 years of age 4 and no prior ASCVD, statin significantly associated with a mortality (HR, 0.91 [95% CI, MACEs (HR, 0.96 [95% CI,
- In 115000 adults with newly CKD severity was associated of rate control agents, procedures. For example, 15 to 29 mL·min⁻¹·1.73 m⁻² use of rate control agents 0.56–0.67]), warfarin (aHR, 0.94]), DOACs (aHR, 0.23 and dabigatran.⁸⁷
- A secondary analysis of the ASPREE clinical trial comparing 100 mg enteric-coated aspirin daily with matching placebo did not demonstrate cardiovascular benefit but showed increased risk of bleeding in those with CKD.⁸⁸
- In a post hoc analysis of the TIPS-3 trial, which randomized people without previous CVD to aspirin (75 mg daily) or placebo, aspirin reduced risk of cardiovascular events in patients with moderate to advanced CKD (HR, 0.57 [95% CI, 0.34–0.94]).⁸⁹
- A trial of 90 patients with CKD did not support the use of sodium bicarbonate for vascular dysfunction in participants with CKD and normal serum bicarbonate levels. After 1 month of treatment with sodium bicarbonate, flow-mediated dilation

and AF-related procedures (aHR, 0.73 [95% CI, 0.61–0.88]) compared with patients with eGFR >60 mL·min⁻¹·1.73 m⁻².⁹²

- Low eGFR is an indication for reduced dosing of non-vitamin K antagonist oral anticoagulant drugs. Among nearly 15000 US Air Force patients prescribed non-vitamin K antagonist oral anticoagulants in an administrative database, 1473 had a renal indication for reduced dosing, and 43% of these were potentially overdosed. Potential overdosing was associated with increased risk of major bleeding (HR, 2.9 [95% CI, 1.07–4.46]).⁹³
- In the Valkyrie study, among patients on hemodialysis with AF (n=132), a reduced dose of rivaroxaban significantly decreased the composite outcome of fatal and nonfatal cardiovascular events (HR, 0.41[95% CI, 0.25–0.68]).⁹⁴ In the RENAL-AF trial of 154 patients undergoing hemodialysis, there was inadequate power to draw any conclusion about rates of major or clinically relevant nonmajor bleeding comparing apixaban and warfarin in patients with AF and ESKD on hemodialysis.⁹⁵ Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism among this population on anticoagulation, highlighting the need for future randomized studies evaluating the risks versus benefits of anticoagulation among patients with AF and ESKD on hemodialysis.
- In a randomized trial of 97 patients comparing apixaban and vitamin K antagonist in patients with AF on hemodialysis (median follow-up time, 462 days [253–702 days]), no differences were observed in safety or efficacy outcomes. Composite primary safety outcome events occurred in 22 patients (45.8%) on apixaban and in 25 patients (51.0%) on vitamin K antagonist (HR, 0.93 [95% CI, 0.53–1.65]; $P_{\text{noninferiority}}=0.157$). Composite primary efficacy outcome events occurred in 10 patients (20.8%) on apixaban and in 15 patients (30.6%) on vitamin K antagonist ($P=0.51$, log rank). There

were no significant differences in individual outcomes (all-cause mortality, 18.8% versus 24.5%; major bleeding, 10.4% versus 12.2%; and MI, 4.2% versus 6.1%, respectively).⁹⁶

- SGLT-2 inhibitor (dapagliflozin) use reduced the risk of a composite of a sustained decline in eGFR of at least 50%, ESKD, or death attributable to renal and cardiovascular causes among those with 0.61 [95% CI, 0.48–0.78] in the primary prevention group versus 0.61 [95% CI, 0.47–0.79] in the secondary prevention group).
- A prespecified analysis showed that baseline kidney function did not modify the benefit of dapagliflozin in patients with HF and a mildly reduced or preserved EF. The effect of dapagliflozin on the primary outcome was not affected by baseline eGFR category (eGFR ≥ 60 mL $\cdot$ min $^{-1}\cdot 1.73$ m $^{-2}$: HR, 0.84 [95% CI, 0.70–1.00]; eGFR 45– <60 mL $\cdot$ min $^{-1}\cdot 1.73$ m $^{-2}$: HR, 0.68 [95% CI, 0.54–0.87]; eGFR <45 mL $\cdot$ min $^{-1}\cdot 1.73$ m $^{-2}$: HR, 0.93 [95% CI, 0.76–1.14]; $P_{\text{interaction}}=0.16$). Over a median follow-up of 2.3 years (IQR, 1.7–2.8 years), the overall incidence rate of the

- In a systematic review of clinical trials of interventions to attenuate vascular calcification in people with CKD, magnesium and sodium thiosulfate consistently showed attenuation of vascular calcification. Studies examining intestinal phosphate binders, alterations in dialysate calcium concentration, vitamin K therapy, calcimimetics, and kidney composite outcome was low (1.1 events per 100 patient-years) and was not influenced by treatment with dapagliflozin (HR, 1.08 [95% CI, 0.79–1.49]). However, dapagliflozin attenuated the decline in eGFR from baseline (difference, 0.5 mL $\cdot$ min $^{-1}\cdot 1.73$ m $^{-2}$ per year [95% CI, 0.1–0.9]; $P=0.01$) and from month 1 to month 36 (difference, 1.4 mL $\cdot$ min $^{-1}\cdot 1.73$ m $^{-2}$ per year [95% CI, 1.0–1.8]; $P<0.001$).⁹⁸
- Similarly, another trial examining another SGLT-2 inhibitor (empagliflozin) enrolled both individuals with CKD with diabetes and those with CKD without diabetes (n=6609) and reported a 28% reduction (HR, 0.72 [95% CI, 0.64–0.82]) in the progression of kidney disease or death resulting from cardiovascular causes compared with placebo.⁹⁹
- In an individual patient-level meta-analysis of 6 trials including 49 875 participants that studied 4 dif-

Cardiovascular Procedures and Devices in CKD

- In a study of 17 910 patients undergoing angiography for stable IHD in Alberta, Canada, those with ESKD (OR, 0.52 [95% CI, 0.35–0.79]) or mild to moderate CKD (OR, 0.80 [95% CI, 0.71–0.89]) were less likely to be revascularized for angiographically significant (>70%) coronary stenoses compared with those without CKD.¹⁰⁴
- Among patients who underwent TAVR in the PARTNER trial, CKD stage either improved or was unchanged after the procedure.¹⁰⁵
- In intermediate-risk patients with aortic stenosis and CKD, SAPIEN 3 TAVR and SAVR were associated with a similar risk of reaching the composite primary outcome of death, stroke, rehospitalization, and new hemodialysis after a 5-year follow-up.¹⁰⁶
- Among patients who underwent lower-extremity bypass surgery in the USRDS 2006 to 2011, females with ESKD were less likely than males with ESKD to receive an autogenous vein graft (55% versus 61%; $P<0.001$). Among those who received a prosthetic graft, acute graft failure was higher for females (HR, 1.23 [95% CI, 1.03–1.46]).¹⁰⁷
- In a pooled analysis of patients with stable IHD, diabetes, and CKD from 3 clinical trials, CABG plus optimal medical therapy was associated with lower risk of subsequent revascularization (HR, 0.25 [95% CI, 0.15–0.41]) and MACEs (HR, 0.77 [95% CI, 0.55–1.06]) compared with PCI plus optimal medical therapy.¹⁰⁸
- In a randomized clinical trial comparing an initial invasive strategy (coronary angiography and revascularization) with an initial conservative strategy (medical therapy), there was no difference in incidence of composite outcome of death resulting from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for HF (HR, 0.87 [95% CI,

cularization added to medical therapy) with an initial conservative strategy (medical therapy alone and angiography if medical therapy fails) among those with advanced kidney disease (eGFR $<30 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ or receiving dialysis) and moderate or severe myocardial ischemia reported similar rates of death or nonfatal MI (estimated 3-year event rate, 36.4% versus 36.7%; aHR, 1.01 [95% CI, 0.79–1.29]).¹⁰⁹

- In a secondary analysis of the FIDELIO-DKD trial enrolling patients with CKD and type 2 diabe-

tes, finerenone use was associated with lower incidence of new-onset AF (HR, 0.71 [95% CI, 0.53–0.94]).¹⁰²

- A study of the NIS from 2009 to 2018 found that a consistent downward trend in the percent-age of ICD implantation across all 3 subgroups by

CKD status was also 2009 versus 1.2% in 2018), versus 1.0% in 2018), and versus 0.6% in 2018). From was a significant increase in in-hospital mortality in overall ICD implantation (0.83% in $P=0.02$). However, no adjusted in-hospital mortality of no CKD ($P=0.35$). CKD ($P=0.16$) over the course of the study period.¹¹⁰

Lifestyle Interventions

- In a pooled analysis of data from the ARIC, MESA, and CHS studies, healthy lifestyle behaviors (no smoking, moderate to vigorous PA, no alcohol intake, adherence to healthy diet using diet score, and BMI <30 kg/m²) were associated with lower all-cause mortality, major coronary events, ischemic stroke, and HF.¹¹¹
- A randomized clinical trial enrolling 160 patients with stage 3 or 4 CKD noted that both V_{O2peak} and METs increased significantly in the lifestyle intervention group by 9.7% and 30%, respectively, without change in the usual care group during a 3-year lifestyle intervention program.¹¹²

- those with eGFR of 15 to 30 those with ACR >300 mg/a.
- Data from CARES and the & Medicaid Services dialysis cate that dialysis staff initiated events and applied in 52.3%. Staff-initiated CPR with a 3-fold increase in the charge and better discharge.¹¹⁴

- A study of CKD participants found that greater ultraprocessed food intake was associated with higher risk of CKD progression (tertile 3 versus tertile 1: HR, 1.22 [95% CI, 1.04–1.42]; $P_{trend}=0.01$).¹¹³

Cardiovascular Hospitalization and Mortality Attributable to CVD Among People With CKD

(See Chart 12-13)

- CVD is a leading cause of death for people with CKD. Mortality risk depends not only on eGFR but also on the category of albuminuria. The aRR of all-cause mortality and cardiovascular mortality is highest in

- Data from the prospective CRIC study demonstrated that the crude rate of HF admissions was 5.8 per 100 PY among those with CKD. The rates of both HF hospitalizations and rehospitalization were even higher across categories of lower eGFR and higher urine ACR (Chart 12-13).⁸³
- Elevated levels of the alternative glomerular filtration marker cystatin C have been associated with increased risk for CVD and all-cause mortality in studies from a broad range of cohorts.
 - Cystatin C levels predicted ASCVD (HR, 1.21 [95% CI, 1.08–1.36]), HF (HR, 1.43 [95% CI, 1.22–1.67]), all-cause mortality (HR, 1.23 [95% CI, 1.13–1.34]), and cardiovascular death (HR, 1.55 [95% CI, 1.29–1.87]) in the FHS after accounting for clinical cardiovascular risk factors.¹¹⁵
 - The stronger associations observed with outcomes (relative to creatinine or creatinine-based eGFR) might be explained in part by non-glomerular filtration rate determinants of cystatin C such as chronic inflammation.¹¹⁶

Footnote

A portion of the data reported here have been supplied by the USRDS.⁹ The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

Table 12-1. Global Mortality and Prevalence of CKD, by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	1.53 (1.39 to 1.64)	673.72 (629.10 to	0.79 (0.72 to 0.86)	314.95 (293.39 to	0.73 (0.65 to 0.80)	358.78 (335.68 to
Percent change (%) in total number, 1990–	176.41 (144.32 to 197.02)	91.96 (89.58 to 94.71)	172.41 (126.11 to 205.89)	93.48 (90.97 to 96.23)	180.88 (147.91 to 209.62)	90.65 (88.23 to 93.53)
Percent change (%) in	44.29 (35.20 to 51.41)	27.33 (26.32 to	43.20 (30.21 to 53.32)	27.12 (26.01 to	45.49 (35.48 to 54.61)	27.51 (26.54 to
Rate per 100 000,	18.50 (16.72 to 19.85)	8006.00 (7482.12 to	21.91 (19.66 to 23.60)	7808.96 (7288.71 to	15.90 (14.22 to 17.27)	8182.65 (7653.14 to
Percent change (%) in rate, age	24.53 (10.18 to 33.52)	−0.83 (−1.89 to 0.07)	20.88 (−0.37 to 34.22)	−0.05 (−1.03 to 0.86)	25.76 (11.86 to 38.20)	−1.33 (−2.47 to −0.37)
Percent change (%) in rate, age standardized,	5.39 (−1.15 to 10.43)	1.49 (0.98 to 2.02)	4.10 (−5.08 to 10.86)	1.43 (0.90 to 1.97)	6.07 (−0.96 to 12.62)	1.59 (1.07 to 2.20)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

CKD indicates chronic kidney disease; GBD, Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁵⁴

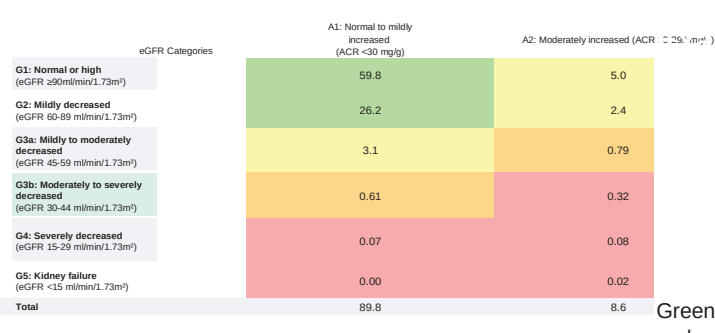


Chart 12-1. Percentage of NHANES participants within the KDIGO CKD risk categories defined by eGFR and ACR, United States, 2017 to 2020.

Green indicates low risk; yellow, moderately high risk; orange, high risk; and red, very high risk.

ACR indicates urinary albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney

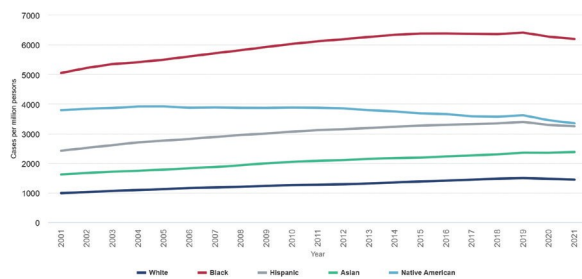


Chart 12-2. ESKD prevalence, by racial group, United States, 2000 to 2021.

Prevalence estimates are presented as cases per million people and are adjusted for age, sex, and ethnicity. ESKD indicates end-stage renal disease.

Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 2, Figure 1.8.¹

Disease: Improving Global Outcomes; and NHANES, National Health and Nutrition Examination Survey.

Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 1, Table 1.1,¹ using NHANES.¹¹⁷

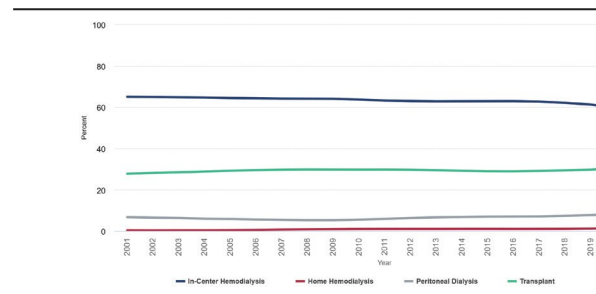


Chart 12-3. Prevalent ESKD, by modality, United States, 2000 to 2021.

ESKD indicates end-stage renal disease.

Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 2, Figure 1.6.¹

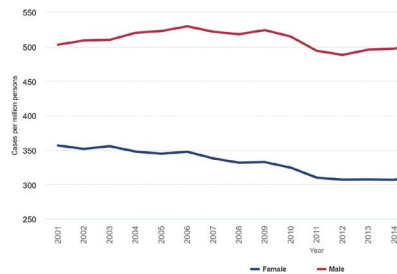


Chart 12-4. ESKD incidence, by sex, 2021.

Incidence estimates are presented as are adjusted for age, sex, race, and ESKD indicates end-stage renal disease. Source: Reprinted from 2023 United States Annual Data Report, volume 2, Figure 1.4.1

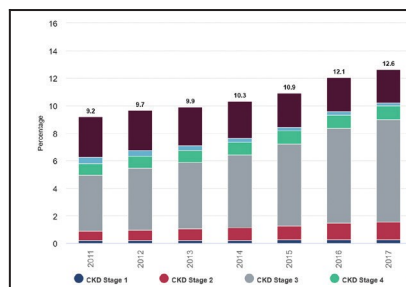


Chart 12-6. Prevalence of reduced eGFR States, 2005 to 2020.

A, Prevalence of eGFR by stage. **B**, eGFR stages 1 through 5. Adjusted for age, sample calibrated estimates of ACR; Chronic Kidney Disease Epidemiology ACR indicates albumin-to-creatinine ratio; disease; and eGFR, glomerular disease; and eGFR, glomerular disease. Source: Reprinted from 2023 United States Annual Data Report, volume 1, Figures Health and Nutrition Examination Survey.¹¹⁷

Chart 12-5. Prevalence of CKD, overall among Medicare beneficiaries ≥66 years States, 2011 to 2021.

CKD indicates chronic kidney disease. Source: Reprinted from 2023 United States Annual Data Report, volume 1, Figure 2.1.1

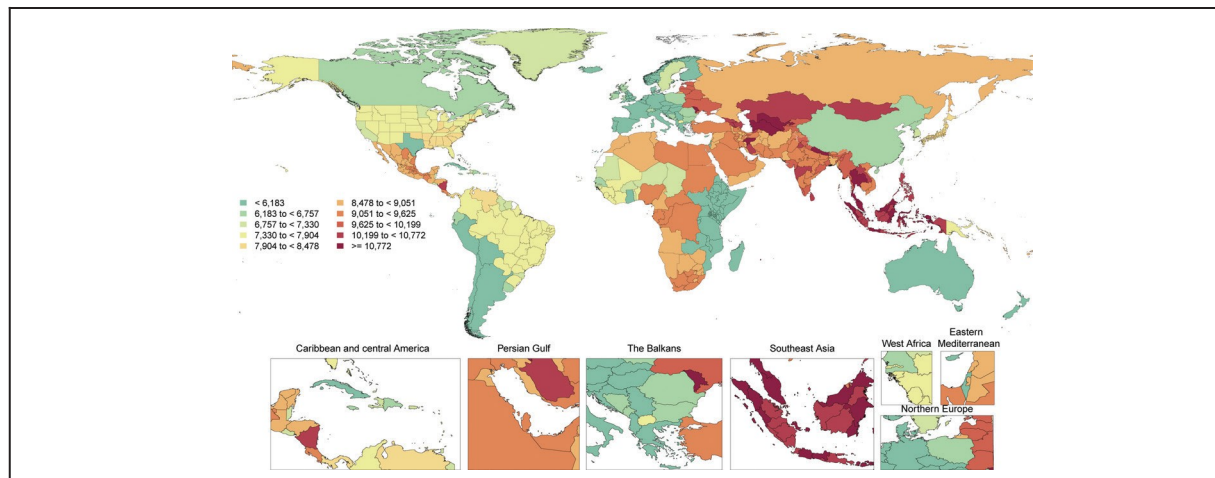


Chart 12-7. Age-standardized global prevalence rates for CKD per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

CKD indicates chronic kidney disease; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁵⁴

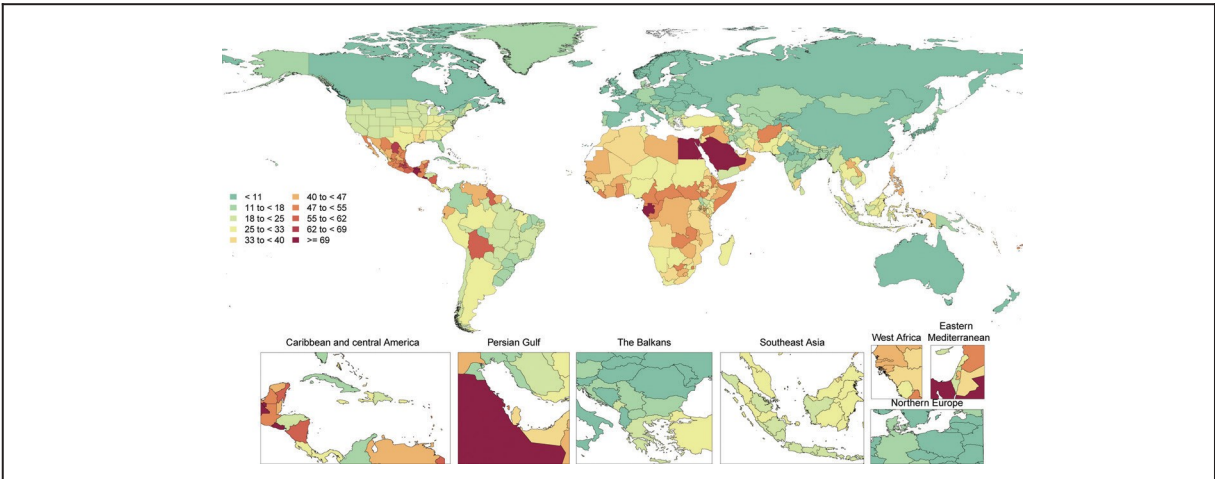


Chart 12-8. Age-standardized global mortality rates for CKD per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

CKD indicates chronic kidney disease; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁵⁴

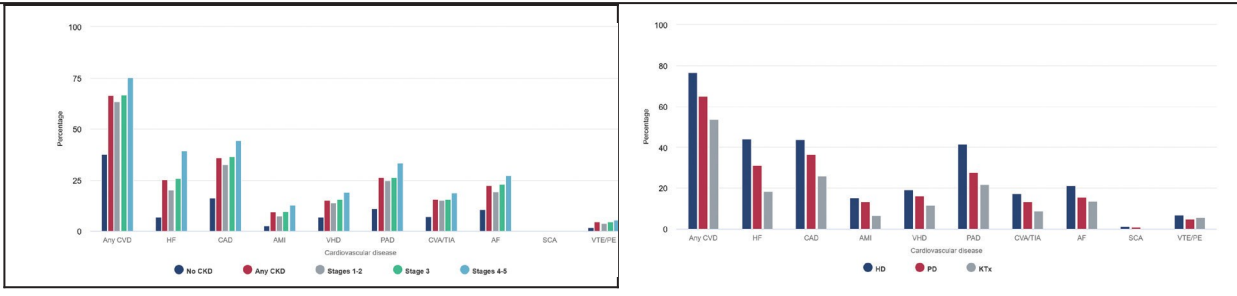


Chart 12-9. Adjusted prevalence of common CVDs in Medicare beneficiaries ≥66 years of age, by CKD status and stage, United States, 2018.

Special analyses, Medicare 5% sample.
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral artery disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 1, Figure 4.2.¹¹⁸

Chart 12-10. Unadjusted prevalence of common CVDs in adult patients with ESKD, by treatment modality, United States, 2018.

AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; ESKD, end-stage renal disease; HD, hemodialysis; HF, heart failure; KTx, kidney transplant recipients; PAD, peripheral artery disease; PD, peritoneal dialysis; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VHD, valvular heart disease; and VTE, venous thromboembolism.

Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 2, Figure 8.1.¹¹⁸

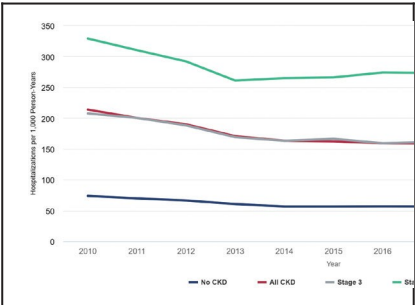


Chart 12-11. Rate of hospitalization for adults. 2010 to 2020.
CKD indicates chronic kidney disease: and disease.
Source: Reprinted from 2022 United States Annual Data Report, volume 1, Figure 3.9.⁹

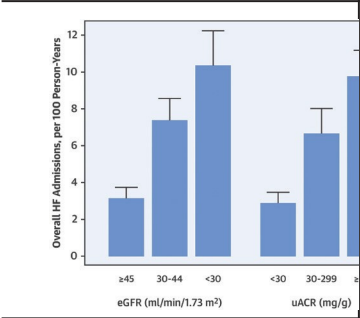


Chart 12-13. US HF hospitalization CKD based on eGFR and
Unadjusted rates of HF admissions among participants with CKD.
CKD indicates chronic kidney disease: filtration rate: HF, heart failure; and ratio.

Source: Reprinted from Bansal et al,⁸³ Copyright © 2019, with

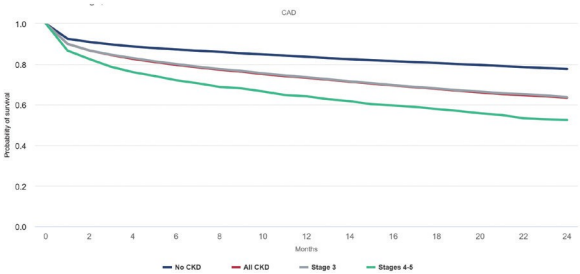


Chart 12-12. Survival probability in older US adults after

hospital admission for a CVD, by CKD status and stage, 2018 to 2020.

Older adults: ≥66 years of age.
CAD indicates coronary artery disease; CKD, chronic kidney disease;
and CVD, cardiovascular disease.
Source: Reprinted from 2022 United States Renal Data System
Annual Data Report, volume 1, Figure 3.10.⁹

REFERENCES

1. United States Renal Data System, National Institutes of Health and Institute of Diabetes and Digestive and Kidney Diseases. 2023 USRDS annual data report: epidemiology of kidney disease in the United States. 2023. Accessed April 9, 2024.

2. Grubbs V. Precision in GFR reporting: let's stop playing the race card. *Clin J Am Soc Nephrol*. 2020;15:1201–1202. doi: 10.2215/CJN.00690120

3. Mohottige D, Diamantidis CJ, Norris KC, Boulware LE. Time to repair the effects of racism on kidney health inequity. *Am J Kidney Dis*. 2021;77:951– 962. doi: 10.1053/j.ajkd.2021.01.010

4. Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney disease, race, and GFR estimation. *Clin J Am Soc Nephrol*. 2020;15:1203–1212. doi:

- management of chronic kidney disease. *Kidney Int.* 2024;105:S117–S314. doi: 10.1016/j.kint.2023.10.018
8. Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Hoorn EJ, Ingelfinger JR, Inker LA, Levin A, Mehrotra R, Palevsky PM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int.* 2020;97:1117–1129. doi: 10.1016/j.kint.2020.02.010
 9. United States Renal Data System, National Institutes of Health and Institute of Diabetes and Digestive and Kidney Diseases. 2022 USRDS annual data report: epidemiology of kidney disease in the United States. 2022. Accessed March 15, 2024. 10. Ataklte F, Song RJ, Upadhyay A, Musa Yola I, Vasan RS, Xanthakis V. Association of mildly reduced kidney function with cardiovascular disease: the Framingham Heart Study. *J Am Heart Assoc.* 2021;10:e020301. doi: 10.2215/CJN.12791019 10.1161/JAHA.120.020301
 5. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, 11. Centers for Disease Control and Prevention. Kidney Disease Surveillance System. Accessed November 6, 2021. Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. *J Am Soc Nephrol.* 2021;32:2994–3015. doi: 10.1681/asn.2021070988 6. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med.* 2021;385:1737–1749. doi: 10.1056/NEJMoa2102953
 7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and

12. Chang AR, Grams ME, Ballew SH, Bilo H, Correa A, Evans M, Gutierrez OM, Hosseinpanah F, Iseki K, Kenealy T, et al; CKD Prognosis Consortium (CKD-PC). Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ*. 2019;364:k5301. doi: 10.1136/bmj.k5301
13. Ishigami J, Cowan LT, Demmer RT, Grams ME, Lutsey PL, Carrero JJ, Coresh J, Matsushita K. Incident hospitalization with major cardiovascular diseases and subsequent risk of ESKD: implications for cardiorenal syndrome. *J Am Soc Nephrol*. 2020;31:405–414. doi: 10.1681/ASN.2019060574

14. Corlin L, Short MI, Vasan RS, Xanthakis V. Association of the duration of ideal cardiovascular health through adulthood with cardiometabolic out-comes and mortality in the Framingham Offspring Study. *JAMA Cardiol.* 2020;5:549–556. doi: 10.1001/jamacardio.2020.0109
15. Hu EA, Steffen LM, Grams ME, Crews DC, Coresh J, Appel LJ, Rebholz CM. Dietary patterns and risk of incident chronic kidney disease: the Atherosclerosis Risk in Communities study. *Am J Clin Nutr.* 2019;110:713–721. doi: 10.1093/ajcn/nqz146
16. Zheng Z, Waikar SS, Schmidt IM, Landis JR, Hsu CY, Shafi T, Feldman HI, Anderson AH, Wilson FP, Chen J, et al; CRIC Study Investigators. Subtyping CKD patients by consensus clustering: the Chronic Renal
17. Barrett PM, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, Kublickas M, Perry IJ, Stenvinkel P, Khashan AS. Adverse pregnancy outcomes and long-term maternal kidney disease: a systematic review and meta-analysis. *JAMA Netw Open.* 2020;3:e1920964. doi: 10.1001/jamanetworkopen.2019.20964
18. Bellini MI, Nozdrin M, Pengel L, Knight S, Papalois V. Risks for donors associated with living kidney donation: meta-analysis. *Br J Surg.* 2022;109:671–678. doi: 10.1093/bjs/znac114
19. Hirano K, Komatsu Y, Shimbo T, Nakata H, Kobayashi D. Longitudinal relationship between long sleep duration and future kidney function decline. *Clin Kidney J.* 2022;15:1763–1769. doi: 10.1093/ckj/sfac107
20. Schoretsanitis G, de Filippis R, Brady BM, Homan P, Suppes T, Kane JM. Prevalence of impaired kidney function in patients with long-term lithium treatment: a systematic review and meta-analysis. *Bipolar Disord.* 2022;24:264–274. doi: 10.1111/bdi.13154
21. Brathwaite KE, Levy RV, Sarathy H, Agalliu I, Johns TS, Reidy KJ, Fadrowski JJ, Schwartz GJ, Kaskel FJ, Melamed ML. Reduced kidney function and hypertension in adolescents with low birth weight, transcriptional pathways influencing human serum urate levels. *Nat Genet.* 2019;51:1459–1474. doi: 10.1038/s41588-019-0504-x
32. Stanzick KJ, Li Y, Schlosser P, Gorski M, Wuttke M, Thomas LF, Rasheed H, Rowan BX, Graham SE, Vanderweff BR, et al. Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals. *Nat Commun.* 2021;12:4350. doi: 10.1038/s41467-021-24491-0

34. Lin BM, Grinde KE, Brody JA, Breeze CE, Raffield LM, Mychaleckyj JC, Thornton TA, Perry JA, Baier LJ, de Las Fuentes L, et al; NHLBI Trans-Omics For Precision Medicine TOPMed Consortium, TOPMed Kidney Working Group. Whole genome sequence analyses of eGFR in 23,732 people representing multiple ancestries in the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. *EBioMedicine*. 2021;63:103157. doi: 10.1016/j.ebiom.2020.103157
35. Sheng X, Guan Y, Ma Z, Wu J, Liu H, Qiu C, Vitale S, Miao Z, Seasoek MJ, Palmer M, et al. Mapping the genetic architecture of human traits to cell types in the kidney identifies mechanisms of disease and potential treatments. *Nat Genet*. 2021;53:1322–1333. doi: 10.1038/s41588-021-00909-9
36. Doke T, Huang S, Qiu C, Liu H, Guan Y, Hu H, Ma Z, Wu J, Miao Z, Sheng X, et al. Transcriptome-wide association analysis identifies *DACH1* as a kidney disease risk gene that contributes to fibrosis. *J Clin Invest*. 2021;131:e141801. doi: 10.1172/JCI141801
37. Grams ME, Rebholz CM, Chen Y, Rawlings AM, Estrella MM, Selvin E, Appel LJ, Tin A, Coresh J. Race, *APOL1* risk, and eGFR decline in the general population. *J Am Soc Nephrol*. 2016;27:2842–2850. doi: 10.1007/s00467-023-05958-2
22. Perrone RD, Oberdhan D, Ouyang J, Bichet DG, Budde K, Chapman AB, Gitomer BY, Horie S, Ong ACM, Torres VE, et al. OVERTURE: a worldwide, prospective, observational study of disease characteristics in patients with ADPKD. *Kidney Int Rep*. 2023;8:989–1001. doi: 10.1016/j.ekir.2023.02.1073
23. Harhay MN, Kim Y, Moore K, Harhay MO, Katz R, Shlipak MG, Mattix-Kramer

38. Ma L, Chou JW, Snipes JA, Bharadwaj MS, Craddock AL, Cheng D, Weckerle A, Petrovic S, Hicks PJ, Hemal AK, et al. *APOL1* renal-risk variants induce mitochondrial dysfunction. *J Am Soc Nephrol.* 2017;28:1093–1105. doi: 10.1681/ASN.2016050567
39. Peralta CA, Bibbins-Domingo K, Vittinghoff E, Lin F, Fornage M, Kopp JB, Winkler CA. *APOL1* genotype and race differences in incident albumin-uria and renal function decline. *J Am Soc Nephrol.* 2016;27:887–893. doi: 10.1681/ASN.2015020124
- HJ. Modifiable kidney disease risk factors among nondiabetic adults with obesity from the Multi-Ethnic Study of Atherosclerosis. *Obesity (Silver Spring).* 2023;31:3056–3065. doi: 10.1002/oby.23883
24. Sgambati K, Roem J, Brady TM, Flynn JT, Mitsnefes M, Samuels JA, Warady BA, Furth SL, Moudgil A. Social determinants of cardiovascular health in African American children with CKD: an analysis of the Chronic Kidney Disease in Children (CKiD) Study. *Am J Kidney Dis.* 2021;78:66–74. doi: 10.1053/j.ajkd.2020.11.013
25. Cheung KL, Crews DC, Cushman M, Yuan Y, Wilkinson K, Long DL, Judd SE, Shlipak MG, Ix JH, Bullen AL, et al. Risk factors for incident CKD in Black and White Americans: the REGARDS study. *Am J Kidney Dis.* 2023;82:11–21.e1. doi: 10.1053/j.ajkd.2022.11.015
26. Connaughton DM, Kennedy C, Shril S, Mann N, Murray SL, Williams PA, Conlon E, Nakayama M, van der Ven AT, Iyell H, et al. Monogenic causes of chronic kidney disease in adults. *Kidney Int.* 2019;95:914–928. doi: 10.1016/j.kint.2018.10.031
27. Mann N, Braun DA, Amann K, Tan W, Shril S, Connaughton DM, Nakayama M, Schneider R, Kitzler TM, van der Ven AT, et al. Whole-exome sequencing enables a precision medicine approach for kidney transplant recipients. *J Am Soc Nephrol.* 2019;30:201–215. doi: 10.1681/ASN.2018060575
28. Schmitz B, Kleber ME, Lenders M, Delgado GE, Engelbertz C, Huang J, Pavenstadt H, Breithardt G, Brand SM, Marz W, et al. Genome-wide association study suggests impact of chromosome 10 rs139401390 on kidney function in patients with coronary artery disease. *Sci Rep.* 2019;9:2750. doi: 10.1038/s41598-019-39055-y
29. Graham SE, Nielsen JB, Zawistowski M, Zhou W, Fritsche LG, Gabrielsen ME, Skogholt AH, Surakka I, Hornsby WE, Fermin D, et al. Sex-specific and pleiotropic effects underlying kidney function identified from GWAS meta-analysis. *Nat Commun.* 2019;10:1847. doi: 10.1038/s41467-019-09861-z
30. Wuttke M, Li Y, Li M, Sieber KB, Feitosa MF, Gorski M, Tin A, Wang L, Chu AY, Hoppmann A, et al; Lifelines Cohort Study. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet.* 2019;51:957–972. doi: 10.1038/s41588-019-0407-x

40. Grams ME, Surapaneni A, Ballew SH, Appel LJ, Boerwinkle E, Boulware LE, Chen TK, Coresh J, Cushman M, Divers J, et al. *APOL1* kidney risk variants and cardiovascular disease: an individual participant data meta-analysis. *J Am Soc Nephrol.* 2019;30:2027–2036. doi: 10.1681/ASN.2019030240
41. Sinnott-Armstrong N, Tanigawa Y, Amar D, Mars N, Benner C, Aguirre M, Venkataraman GR, Wainberg M, Ollila HM, Kiiskinen T, et al; FinnGen. Genetics of 35 blood and urine biomarkers in the UK Biobank. *Nat Genet.* 2021;53:185–194. doi: 10.1038/s41588-020-00757-z
42. Khan A, Turchin MC, Patki A, Srinivasainagendra V, Shang N, Nadukuru R, Jones AC, Malolepsza E, Dikilitas O, Kullo IJ, et al. Genome-wide poly-genetic score to predict chronic kidney disease across ancestries. *Nat Med.* 2022;28:1412–1420. doi: 10.1038/s41591-022-01869-1
43. Joseph CB, Mariniello M, Yoshifuji A, Schiano G, Lake J, Marten J, Richmond A, Huffman JE, Campbell A, Harris SE, et al. Meta-GWAS reveals novel genetic variants associated with urinary excretion of uromodulin. *J Am Soc Nephrol.* 2022;33:511–529. doi: 10.1681/ASN.2021040491
44. Gorski M, Rasheed H, Teumer A, Thomas LF, Graham SE, Sveinbjornsson G, Winkler TW, Gunther F, Stark KJ, Chai JF, et al. Genetic loci and prioritization of genes for kidney function decline derived from a meta-analysis of 62 longitudinal genome-wide association studies. *Kidney Int.* 2022;102:624–639. doi: 10.1016/j.kint.2022.05.021
45. Eales JM, Jiang X, Xu XG, Saluja S, Akbarov A, Cano-Gamez E, McNulty MT, Finan C, Guo H, Wystrychowski W, et al. Uncovering genetic mechanisms of hypertension through multi-omic analysis of the kidney. *Nat Genet.* 2021;53:630–637. doi: 10.1038/s41588-021-00835-w
46. Doke T, Huang S, Qiu C, Sheng X, Seasock M, Liu H, Ma Z, Palmer M, Susztak K. Genome-wide association studies identify the role of caspase-9 in kidney disease. *Sci Adv.* 2021;7:eabi8051. doi: 10.1126/sciadv.abi8051
47. Chu CD, Xia F, Du Y, Singh R, Tuot DS, Lamprea-Montealegre JA, Gualtieri R, Liao N, Kong SX, Williamson T, et al. Estimated prevalence and testing for albuminuria in US adults at risk for chronic kidney disease. *JAMA Netw Open.* 2023;6:e2326230. doi: 10.1001/jamanetworkopen.2023.26230
48. van Mil D, Kienecker LM, Evers-Roeten B, Thelen MHM, de Vries H, Hemmelder MH, Dorgelo A, van Etten RW, Heerspink HJL, Gansevoort

- RT. Participation rate and yield of two detect increased albuminuria in the general (THOMAS): a prospective, randomised. *Lancet*. 2023;402:1052–1064. doi: 10.1016/S0140-6736(23)00105-2.
49. Hödlmoser S, Winkelmayer WC, Zee J, Robinson BM, Ristl R, Krenn S. Chronic kidney disease awareness among adults with chronic kidney disease. *One*. 2020;15:e0243431. doi: 10.1371/journal.pone.0243431.
50. Martinez JD, Thomas IC, Montez-Rath ME, An J, Odden MC, Kurella Tamura M, et al. Blood pressure targets in chronic kidney disease patients. *Hypertension*. 2019;73:1275–1282. doi: 10.1161/HYPERTENSIONAHA.119.12697.
51. Annamalai R, Petrie R, Rala W, Chiu N, Nally JV Jr. Diabetes control and the risks of ESRD and mortality in patients with CKD. *Am J Kidney Dis*. 2017;70:191–198. doi: 10.1053/j.ajkd.2016.11.018.
52. Navaneethan SD, Schold JD, Jolly SE, Arrigain S, Winkelmayer WC, Douglas CE, et al. Chronic Kidney Disease in Children Study Investigators. Effect of findings from the CRIC study. *Am J Kidney Dis*. 2018;90:1012–1022. doi: 10.1053/j.ajkd.2018.09.012.
53. Hoonley CW, Kavanagh S, Patel MR, Blomster JL, Fowkes FGR, Jones NE, et al. Intensive blood pressure control and risk for cardiovascular events in patients with albuminuria in the 3642 study. *Hypertension*. 2019;74:422–430. doi: 10.1161/HYPERTENSIONAHA.119.12697.
54. Leita L, Soares-Dos-Reis R, Neves MC, Causland FR. Intensive blood pressure control in patients with albuminuria in the 3642 study. *Hypertension*. 2019;74:422–430. doi: 10.1161/HYPERTENSIONAHA.119.12697.
55. Bansal N, Katz R, Robinson-Cohen C, Samak M, Siscovick DS, Zelnick ML, et al. Chronic Kidney Disease in Children Study Investigators. Effect of findings from the CRIC study. *Am J Kidney Dis*. 2018;90:1012–1022. doi: 10.1053/j.ajkd.2018.09.012.
56. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed July 1, 2024.

of heart failure, coronary heart disease, and stroke in chronic kidney disease: an analysis of 3 community-based cohort studies. *JAMA Cardiol.*

2017;2:314–318. doi: 10.1001/jamacardio.2016.4652

68. Kim ED, Soliman EZ, Coresh J, Matsushita K, Chen LY. Two-week burden of arrhythmias across CKD severity in a large community-based cohort: the ARIC study. *J Am Soc Nephrol.* 2021;32:629–638. doi: 10.1681/ASN.2020030301

69. Tang M, Batty JA, Lin C, Fan X, Chan KE, Kalim S. Pulmonary hypertension, mortality, and cardiovascular disease in CKD and ESRD patients: a systematic review and meta-analysis. *Am J Kidney Dis.* 2018;72:75–83.

doi: 10.1053/j.ajkd.2017.11.018

70. Lash JP, Ricardo AC, Roy J, Deo R, Fischer M, Flack J, He J, Keane M, Lora C, Ojo A, et al; CRIC Study Investigators. Race/ethnicity and cardiovascular outcomes in adults with CKD: findings from the CRIC

(Chronic

55. US Renal Data System. USRDS 2021 annual data report: atlas of end-stage renal disease in the United States. 2021. Accessed May 1, 2024.

56. Grams ME, Coresh J, Matsushita K, Ballew SH, Sang Y, Surapaneni A, Alencar de Pinho N, Anderson A, Appel LJ, Ärnlöv J, et al; Writing Group for the CKD Prognosis Consortium. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. *JAMA.* 2023;330:1266–1277. doi: 10.1001/jama.2023.17002

57. Gregg LP, Hedayati SS. Management of traditional cardiovascular risk factors in CKD: what are the data? *Am J Kidney Dis.* 2018;72:728–744. doi: 10.1053/j.ajkd.2017.12.007

58. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, et al; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol.* 2015;3:514–525. doi: 10.1016/S2213-8587(15)00040-6

59. Matsushita K, Kaptoge S, Hageman SHJ, Sang Y, Ballew SH, Grams ME, Surapaneni A, Sun L, Arnlöv J, Bozic M, et al. Including measures of chronic kidney disease to improve cardiovascular risk prediction by SCORE2 and SCORE2-OP. *Eur J Prev Cardiol.* 2023;30:8–16. doi:

- Renal Insufficiency Cohort) and Hispanic CRIC studies. *Am J Kidney Dis.* 2016;68:545–553. doi: 10.1053/j.ajkd.2016.03.429
71. Roy-Chaudhury P, Tumlin JA, Koplan BA, Costea AI, Kher V, Williamson D, Pokhariyal S, Charytan DM; MiD Investigators and Committees. Primary outcomes of the Monitoring in Dialysis study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int.* 2018;93:941–951. doi: 10.1016/j.kint.2017.11.019
 72. Chang CH, Fan PC, Lin YS, Chen SW, Wu M, Lin MS, Lu CH, Chang PC, Hsieh MJ, Wang CY, et al. Dialysis mode and associated outcomes in patients with end-stage renal disease and atrial fibrillation: a 14-year nationwide cohort study. *J Am Heart Assoc.* 2021;10:e019596. doi: 10.1161/JAHA.120.019596
 73. Borrelli S, Garofalo C, Gabbai FB, Chiodini P, Signoriello S, Paoletti E, Ravera M, Bussalino E, Bellizzi V, Liberti ME, et al. Dipping status, ambulatory blood pressure control, cardiovascular disease, and kidney disease progression: a multicenter cohort study of CKD. *Am J Kidney Dis.* 2023;81:15–24.e1. doi: 10.1053/j.ajkd.2022.04.010
 74. Farrington DK, Sang Y, Grams ME, Ballew SH, Dunning S, Stempniewicz N, Coresh J. Anemia prevalence, type, and associated risks in a cohort of 5.0 million insured patients in the United States by level of kidney function. *Am J Kidney Dis.* 2023;81:201–209.e1. doi: 10.1093/eurjpc/zwac176
 60. Matsushita K, Jassal SK, Sang Y, Ballew SH, Grams ME, Surapaneni A, Arnlov J, Bansal N, Bozic M, Brenner H, et al. Incorporating kidney disease measures into cardiovascular risk prediction: development and validation in 9 million adults from 72 datasets. *EClinicalMedicine.* 2020;27:100552. doi: 10.1016/j.eclinm.2020.100552
 61. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Ciemins E, et al; Chronic Kidney Disease Prognosis Consortium and the American Heart Association Cardiovascular-Kidney-Metabolic Science Advisory Group. Development and validation of the American Heart Association's PREVENT equations. *Circulation.* 2024;149:430–449. doi: 10.1161/CIRCULATIONAHA.123.067626
 62. Gaziano L, Sun L, Arnold M, Bell S, Cho K, Kaptoge SK, Song RJ, Burgess S, Posner DC, Mosconi K, et al; Emerging Risk Factors Collaboration/EPIC-CVD/Million Veteran Program. Mild-to-moderate kidney dysfunction and cardiovascular disease: observational and mendelian randomization analyses. *Circulation.* 2022;146:1507–1517. doi: 10.1161/CIRCULATIONAHA.122.060700
 63. Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, Brunskill NJ, Gray LJ. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS One.* 2018;13:e0192895. doi: 10.1371/journal.pone.0192895
 64. Amdur RL, Feldman HI, Dominic EA, Anderson AH, Beddhu S, Rahman M, Wolf M, Reilly M, Ojo A, Townsend RR, et al; CRIC Study Investigators. Use of measures of inflammation and kidney function for prediction of atherosclerotic vascular disease events and death in patients with CKD:

75. Bansal N, Zelnick LR, Soliman EZ, Anderson A, Christenson R, DeFilippi C, Deo R, Feldman HI, He J, Ky B, et al; CRIC Study Investigators. Change in cardiac biomarkers and risk of incident heart failure and atrial fibrillation in CKD: the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis.* 2021;77:907–919. doi: 10.1053/j.ajkd.2020.09.021
76. Leidner AS, Cai X, Zelnick LR, Lee J, Bansal N, Pasch A, Kansal M, Chen J, Anderson AH, Sondheimer JH, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Fibroblast growth factor 23 and risk of heart failure subtype: the CRIC (Chronic Renal Insufficiency Cohort) study. *Kidney Med.* 2023;5:100723. doi: 10.1016/j.xkme.2023.100723
77. Park S, Lee SH, Shin D, Hong D, Joh HS, Choi KH, Kim HK, Ha SJ, Park TK, Yang JH, et al. Prognostic impact of coronary flow reserve in patients with CKD. *Kidney Int Rep.* 2023;8:64–74. doi: 10.1016/j.ekir.2022.10.003
78. Pfau A, Ermer T, Coca SG, Tio MC, Genser B, Reichel M, Finkelstein FO, Marz W, Wanner C, Waikar SS, et al. High oxalate concentrations correlate with increased risk for sudden cardiac death in dialysis patients. *J Am Soc Nephrol.* 2021;32:2375–2385. doi: 10.1681/ASN.2020121793
79. Batra G, Ghukasyan Lakic T, Lindback J, Held C, White HD, Stewart RAH, Koenig W, Cannon CP, Budaj A, Hagstrom E, et al; STABILITY Investigators. Interleukin 6 and cardiovascular outcomes in patients with chronic kidney disease and chronic coronary syndrome. *JAMA Cardiol.* 2021;6:1440–1445. doi: 10.1001/jamacardio.2021.3079

80. Deo R, Dubin RF, Ren Y, Murthy AC, Wang J, Zheng H, Zheng Z, Feldman H, Shou H, Coresh J, et al. Proteomic cardiovascular risk assessment in chronic kidney disease. *Eur Heart J*. 2023;44:2095–2110. doi: 10.1093/eurheartj/ehad115
81. Poudel B, Rosenson RS, Kent ST, Bittner V, Gutierrez OM, Anderson AH, Woodward M, Jackson EA, Monda KL, Bajaj A, et al; CRIC Study Investigators. Lipoprotein(a) and the risk for recurrent atherosclerotic cardiovascular events among adults with CKD: The Chronic Renal Insufficiency Cohort (CRIC) study. *Kidney Med*. 2023;5:100648. doi: 10.1016/j.xkme.2023.100648
82. Mark PB, Carrero JJ, Matsushita K, Sang Y, Ballew SH, Grams ME, Coresh J, Surapaneni A, Brunskill NJ, Chalmers J, et al. Major cardiovascular events and subsequent risk of kidney failure with CKD Prognosis Consortium study. *Eur Heart J*. 2023;44:1157–1166. doi: 10.1093/eurheartj/ehac825
83. Bansal N, Zelnick L, Bhat Z, Dobre M, He J, Lash J, Jaar B, Mehta R, Raj D, Rincon-Choles H, et al; CRIC Study Investigators. Burden and outcomes of heart failure hospitalizations in adults with chronic kidney disease. *J Am Coll Cardiol*. 2019;73:2691–2700. doi: 10.1016/j.jacc.2019.02.071
84. Mefford MT, Rosenson RS, Deng L, Tanner RM, Bittner V, Safford MM, Coll B, Mues KE, Monda KL, Muntner P. Trends in statin use among US adults with chronic kidney disease, 1999–2014. *J Am Heart Assoc*. 2019;8:e010640. doi: 10.1161/JAHA.118.010640
85. Murphy DP, Drawz PE, Foley RN. Trends in angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use among those with impaired kidney function in the United States. *J Am Soc Nephrol*. 2019;30:1314–1321. doi: 10.1681/ASN.2018100971
86. Navaneethan SD, Akeroyd JM, Ramsey D, Ahmed ST, Mishra SR, Petersen LA, Muntner P, Ballantyne C, Winkelmayer WC, Reinecke H, Engelbertz C, Bauersachs R, Breithardt G, Echterhoff HH, Gerss J, Haeusler KG, Hewing B, Hoyer J, Juergensmeyer S, et al. A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 study. *Circulation*. 2023;147:296–309. doi: 10.1161/CIRCULATIONAHA.122.062779
97. McMurray JJV, Wheeler DC, Stefansson BV, Jongs N, Postmus D, Correa-Rotter R, Chertow GM, Greene T, Held C, Hou FF, et al; DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on clinical outcomes in patients with chronic kidney disease with and without diabetes and CKD. *Clin J Am Soc Nephrol*. 2018;13:1842–1850. doi: 10.2215/CJN.03830318
87. Wetmore JB, Roetker NS, Yan H, Reyes JL, Herzog CA. Direct-acting oral anticoagulants versus warfarin in Medicare patients with chronic kidney disease and atrial fibrillation. *Stroke*. 2020;51:2364–2373. doi: 10.1161/STROKEAHA.120.028934
88. Wolfe R, Wetmore JB, Woods RL, McNeil JJ, Gallagher H, Roderick P, Walker R, Nelson MR, Reid CM, Shah RC, et al. Subgroup analysis of the ASPirin in Reducing Events in the Elderly randomized clinical trial suggests aspirin did not improve outcomes in older adults with chronic kidney disease. *Kidney Int*. 2021;99:466–474. doi: 10.1016/j.kint.2020.08.011
89. Mann JFE, Joseph P, Gao P, Pais P, Tyrwhitt J, Xavier D, Dans T, Jaramillo PL, Gamra H, Yusuf S; TIPS-3 Investigators. Effects of aspirin on cardiovascular outcomes in patients with chronic kidney disease. *Kidney Int*. 2023;103:403–410. doi: 10.1016/j.kint.2022.09.023

- de Boer RA, Docherty K, Fang J, Hernandez AF, Inzucchi SE, et al. Dapagliflozin and kidney outcomes in patients with heart failure with mildly reduced or preserved ejection fraction: a prespecified analysis of the DELIVER randomized clinical trial. *JAMA Cardiol.* 2023;8:56–65. doi: 10.1001/jamacardio.2022.4210
99. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, Preiss D, Judge P, Mayne KJ, Ng SYA, et al; EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2023;388:117–127. doi: 10.1056/NEJMoa2204233
100. Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, Langkilde AM, Mahaffey KW, McGuire DK, Neal B, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. *Circulation.* 2022;145:1460–1470. doi: 10.1161/CIRCULATIONAHA.121.057736
101. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, Joseph A, Kolkhof P, Nowack C, Schloemer P, et al; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med.* 2021;385:2252–2263. doi: 10.1056/NEJMoa2110956
102. Filippatos G, Bakris GL, Pitt B, Agarwal R, Rossing P, Ruilope LM, Butler J, Lam CSP, Kolkhof P, Roberts L, et al; FIDELIO-DKD Investigators. Finerenone reduces new-onset atrial fibrillation in patients with chronic kidney disease and type 2 diabetes. *J Am Coll Cardiol.* 2021;78:142–152. doi: 10.1016/j.jacc.2021.04.079
103. Xu C, Smith ER, Tiong MK, Ruderman I, Toussaint ND. Interventions to attenuate vascular calcification progression in chronic kidney disease: a systematic review of clinical trials. *J Am Soc Nephrol.* 2022;33:1011–1032. doi: 10.1681/ASN.2021101327
104. Shavadia JS, Southern DA, James MT, Welsh RC, Bainey KR. Kidney function modifies the selection of treatment strategies and long-term survival in stable ischaemic heart disease: insights from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry. *Eur Heart J Qual Care Clin Outcomes.* 2018;4:274–282. doi: 10.1093/ehjqcco/qcx042
90. Kendrick J, You Z, Andrews E, Farmer-Bailey H, Moreau K, Chonchol M, Steele C, Wang W, Nowak KL, Patel N. Sodium bicarbonate treatment and vascular function in CKD: a randomized, double-blind, placebo-controlled trial. *J Am Soc Nephrol.* 2023;34:1433–1444. doi: 10.1681/ASN.000000000000161

105. Cubeddu RJ, Asher CR, Lowry AM, Blackstone EH, Kapadia SR, Alu MC, Thourani VH, Mack MJ, Kodali SK, Herrmann HC, et al; PARTNER Trial Investigators. Impact of transcatheter aortic valve replacement on severity of chronic kidney disease. *J Am Coll Cardiol*. 2020;76:1410–1421. doi: 10.1016/j.jacc.2020.07.048
91. Barayev O, Hawley CE, Wellman H, Gerlovin H, Hsu W, Paik JM, 10.1001/jamanetworkopen.2023.46373
- Mandel EI, Liu CK, Djousse L, Gaziano JM, et al. Statins, mortality, and major adverse cardiovascular events among US veterans with chronic kidney disease. *JAMA Netw Open*. 2023;6:e2346373. doi: 10.1001/jamanetworkopen.2023.46373
92. Bansal N, Zelnick LR, Reynolds K, Harrison TN, Lee MS, Singer DE, Sung SH, Fan D, Go AS. Management of adults with newly diagnosed atrial fibrillation with and without CKD. *J Am Soc Nephrol*. 2022;33:442–453. doi: 10.1681/ASN.2021060744
93. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol*. 2017;69:2779–2790. doi: 10.1016/j.jacc.2017.03.600
94. De Vriese AS, Caluwe R, Van Der Meersch H, De Boeck K, De Bacquer D. Safety and efficacy of Vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter random-ized controlled trial. *J Am Soc Nephrol*. 2021;32:1474–1483. doi: 10.1016/j.jacc.2017.03.600

106. Garcia S, Cubeddu RJ, Hahn RT, Ternacle J, Kapadia SR, Kodali SK, Thourani VH, Jaber WA, Asher CR, Elmariah S, et al. 5-Year outcomes comparing surgical versus transcatheter aortic valve replacement in patients with chronic kidney disease. *JACC Cardiovasc Interv.* 2021;14:1995–2005. doi: 10.1016/j.jcin.2021.07.004
107. Arhuidese I, Kernodle A, Nejim B, Locham S, Hicks C, Malas MB. Sex-based outcomes of lower extremity bypass surgery in hemodialysis patients. *J Vasc Surg.* 2018;68:153–160. doi: 10.1016/j.jvs.2017.10.063
108. Farkouh ME, Sidhu MS, Brooks MM, Vlachos H, Boden WE, Frye RL, Hartigan P, Siami FS, Bittner VA, Chaitman BR, et al. Impact of chronic kidney disease on outcomes of myocardial revascularization in patients with diabetes. *J Am Coll Cardiol.* 2019;73:400–411. doi: 10.1016/j.jacc.2018.11.044
109. Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, Kaul U, Reynolds HR, Mazurek T, Sidhu MS, et al; ISCHEMIA-CKD Research Group. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med.* 2020;382:1608–1618. doi: 10.1056/NEJMoa1915925
95. Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, Mussina K, Bansal N, Gadegbeku CA, Garcia DA, Garonzik S, et al; RENAL-AF Investigators. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. *Circulation.* 2022;146:1735–1745. doi: 10.1681/ASN.2020111566

110. Talha KM, Jain V, Yamani N, Fatima K, Rashid AM, Hernandez GA, Dani SS, Fudim M, Minhas AMK. Temporal trends and outcomes of implant-able cardioverter defibrillators in heart failure and chronic kidney dis-ease in the United States. *Curr Probl Cardiol.* 2023;48:101548. doi: 10.1016/j.cpcardiol.2022.101548
doi: 10.1161/CIRCULATIONAHA.121.054990

111. Schrauben SJ, Hsu JY, Amaral S, Anderson
Effect of kidney function on relationships
mortality or cardiovascular outcomes: a
Nephrol. 2021;32:663–675. doi:
Nephrol. 2021;32:663–675. doi:
112. Beetham KS, Krishnasamy R, Stanton T,
Coombs JS, Howden EJ. Effect of a 3-
tients with chronic kidney disease: a
Nephrol. 2022;33:431–441. doi:
113. Sullivan VK, Appel LJ, Anderson CAM, Kim
M, Sondheimer J, Dobie M, Pradhan N, et
Ultra-processed foods and kidney disease
disease risk in the CRIC study.
212. doi: 10.1053/j.ajkd.2023.01.452
114. Pun PH, Dupre ME, Starks MA, Tyson C, Vellano K, Svetkey LP,
Hansen S, Frizzelle BG, McNally B, Jollis JG, et al; the CARES
Surveillance Group. Outcomes for hemodialysis patients given
cardiopulmonary resuscitation for cardiac arrest at
outpatient dialysis clinics. *J Am Soc Nephrol*.
2019;30:461–470. doi: 10.1681/asn.2018090911
115. Ho JE, Lyass A, Courchesne P, Chen
JM, Larson MG, Lev D. Protein
and mortality in the community. *J Am*
10.1161/JAHA.117.008108
116. Schei J, Stefansson VT, Mathisen UD,
TG, Melsom T. Residual associations
eGFR after accounting for measured
cohort without CKD. *Clin J Am Soc*
10.2215/CJN.07360715
117. Centers for Disease Control and
Health Statistics. National Health and
(NHANES) public use data files.

118. United States Renal Data System and National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases. 2020 United States Renal Data System (USRDS) annual data report: epidemiol-ogy of kidney disease in the United States. 2020. Accessed March 15, 2024.

13. SLEEP

See Charts 13-1 through 13-

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In 2022, the AHA added sleep duration as an eighth metric of cardiometabolic health, elevating AHA's Simple 7 to Life's Essential 8.¹ Sleep duration is 1 component of sleep health, a construct that goes beyond the absence of a sleep disorder (eg, insomnia or OSA). Sleep health refers to regularity, satisfaction, alertness, timing, efficiency, and duration of sleep² that have been identified by the AASM to be essential to overall health.³ Sleep quality is frequently assessed with the Pittsburgh Sleep Quality Index, for which a score >5 is considered poor quality.⁴ The composite score of sleep health is assessed with a 7-day sleep diary and questionnaire and defined by 6 components: (1) regularity (midpoint of sleep deviating by ≤ 1 hour), (2) satisfaction (rating fair or very good to the question related to satisfaction with sleep), (3) alertness (score ≤ 7.5 on a sleepiness scale), (4) timing (average midpoint of sleep between 2 and 4 am), (5) efficiency (average $\geq 85\%$), and (6) duration (average total sleep duration within to promote optimal health.⁶ Sleeping >9 hours may be appropriate for some individuals (eg, younger individuals or ill adults), but for others, it is unclear whether this much sleep is associated with health benefits or health risks. The AASM also published guidelines for pediatric populations on a 24-hour scale: Infants 4 to 12 months of age should sleep 12 to 16 h/d; children 1 to 2 years of age should sleep 11 to 14 h/d; children 3 to 5 years of age should sleep 10 to 13 h/d; children 6 to 12 years of age should sleep 9 to 12 h/d; and adolescents 13 to 18 years of age should sleep 8 to 10 h/d.⁷ Unless otherwise noted, throughout this chapter, short sleep

SDB represents upper airway dysfunction and is characterized by snoring or increased resistance to airways. SDB encompasses loud snoring, OSA, and central apneas. OSA is the most common type of SDB and is categorized by the frequency of complete and incomplete neas, respectively) that results in reduced oxygen saturation and arousals calculated as the number of breathing interruptions per hour of sleep. OSA is characterized as mild (AHI 5–<15 events per hour), moderate (AHI 15–30 events per hour), and severe (AHI >30 events per hour) and diagnosed with overnight polysomnography or home sleep test.

Insomnia is characterized by 3 symptoms assessed by questionnaire: difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening. Adults with insomnia report dissatisfaction with their sleep, feeling unrefreshed on awakening, and experiencing sleep difficulties despite having adequate opportunity for sleep. Acute insomnia may occur over a short period of time and resolve on its own,

refers to <7 hours of sleep per night for adults and less than the minimum recommended daily hours of sleep for age for children; long sleep refers to >9 h/night for adults and more than the upper range of recommended duration for children.

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Prevalence

Adults

(See Charts 13-1 through 13-3)

- Data from NHANES 2017 to 2020, completed before the COVID-19 pandemic, showed that adults ≥ 20 years of age had shorter sleep duration on workdays (7.6 hours [95% CI, 7.5–7.6]) compared with free days (8.2 hours [95% CI, 8.2–8.3]).⁸ Overall, 23.1% (95% CI, 21.3%–24.9%) of adults had short sleep on workdays compared with 12.9% (95% CI, 11.6%–14.1%) on free days, and 19.7% (95% CI, 18.5%–21.0%) of adults had long sleep on workdays compared with 38.5% (95% CI, 36.7%–40.3%) on free days. Females reported 7.7 hours of sleep (95% CI, 7.7–7.8) on workdays and 8.4 hours (95% CI, 8.3–8.5) on free days compared with 7.4 hours (95% CI, 7.4–7.5) and 8.1 hours (95% CI, 8.0–8.2) of sleep for males on workdays and free days, respectively. Sleep debt, the difference between sleep duration on workdays and free days, was 0.73 hours (95% CI, 0.68–0.77). On average, 30.5% of adults had ≥ 1 -hour sleep debt (95% CI, 26.8%–33.3%) and 9.75% had ≥ 2 hours sleep debt (high sleep debt; 95% CI, 8.65%–10.8%). Prevalence of high sleep debt was greater in younger adults, NH Black adults, full-time workers, and regular shift workers.

- Analysis of BRFSS 2022 data (proportion of adults reporting hours) was lowest among of age) with 29.5% of females in this older age group per night (Chart 13-1).⁹
- The prevalence of short sleep status such as difficulty in or mobility or any difficulty in dent living. According to

of adults with at least 1 disability reported insufficient sleep compared with 31.6% of adults with no disability.¹⁰ Compared with having no disability, having an increasing number of disabilities was associated with a higher likelihood of reporting short sleep in the fully adjusted model: adjusted PR, 1.20 (95% CI, 1.17–1.23) for 1 type, 1.34 (95% CI, 1.30–1.38) for 2 types, 1.41 (95% CI, 1.35–1.47) for 3 types, and 1.55 (95% CI, 1.49–1.62) for ≥4 types.

- In adulthood, insomnia symptoms were least frequent in adults 26 to 40 years of age and most frequent in adults >65 years of age.¹¹ Females had higher odds of reporting difficulty initiating sleep (OR, 2.26 [95% CI, 2.16–2.36]), difficulty maintaining sleep (OR, 2.05 [95% CI, 1.91–2.19]), and early morning awakening (OR, 1.49 [95% CI, 1.37–1.62]) than males after adjustment for demographics. The prevalence of insomnia symptoms was 1.5 to 2.9 times more frequent in the United States across all adults >25 years of age compared with those in the Netherlands.
- The NHIS 2022 asked respondents, “During the past 30 days, how often did you wake up feeling well rested?” Results indicated that females reported never or some of the days more frequently than males for all age groups (unpublished tabulation using NHIS¹²; Chart 13-2).
- The NHIS 2022 asked respondents, “During the past 30 days, how often did you have trouble falling asleep?” and “During the past 30 days, how often did you have trouble staying asleep?” Females more often reported having any sleep problem on most or all days than males for all

recommended for their age.

sleep duration was 36.8%

in infants and children 4

35.2% (95% CI, 33.9%–

years of age, and 31.6%

for adolescents 12 to 17 years

- In the Penn State Child followed up from childhood to adulthood.¹⁴ Insomnia 23.9% of NH White children.

age groups (unpublished tabulation using NHIS¹²; Chart 13-3).

- Data from NHANES 2017 to 2020 showed that trouble sleeping was more prevalent in older adults, females, NH White adults, and unemployed individuals.⁸ Daytime sleepiness was more prevalent among younger adults, females, NH White adults, people who were unemployed, and people with lower income.

Children/Adolescents

- According to parental report in the 2020 to 2021 National Survey of Children's Health, 34.4% of children 4 months to 17 years of age slept less than

dren, and 24.3% of Hispanic children. Black children compared with NH White children had higher risk of childhood-onset persistent insomnia through young adulthood (OR, 2.58 [95% CI, 1.29–5.14]).

Adults: Young, Middle-Aged, and Old

- Older adults, but not middle-aged adults, are less likely to report short sleep than younger adults. The RR of reporting short sleep in adults ≥65 years of age relative to those 20 to 44 years of age in NHANES 2005 to 2016 was 0.81 (95% CI, 0.75–0.87).¹⁵ In middle-aged adults 45 to 64 years of age, the RR was 1.02 (95% CI, 0.97–1.08). Middle-aged adults had lower risk of reporting long sleep (RR, 0.80 [95% CI, 0.71–0.90]), whereas older adults had greater risk of reporting long sleep (RR, 1.41 [95% CI, 1.25–1.59]).

Risk Factors

- A meta-analysis evaluated the association of socio-economic indicators and sleep, measured with actigraphy, from studies performed in the United States, Europe, Asia, and Canada.¹⁶ Higher income and educational levels were associated with longer sleep duration ($r=0.18$ [95% CI, 0.13–0.24] and $r=0.12$ [95% CI, 0.04–0.21], respectively) and better sleep efficiency ($r=0.15$ [95% CI, 0.05–0.24] and $r=0.15$ [95% CI, 0.07–0.23], respectively).
- According to NHANES 2017 to 2020 data, the odds of reporting trouble sleeping were higher in adults 40 to 59 years of age (OR, 1.62 [95% CI, 1.37–1.92]) and 60 to 74 years of age (OR, 1.44 [95% CI, 1.21–1.71]) compared with adults 20 to 39 years of age.⁸ Males had lower odds than females (OR, 0.80 [95% CI, 0.68–0.93]). Hispanic adults and NH Black adults had lower odds than NH White adults (Hispanic adults: OR, 0.64 [95% CI, 0.50–0.81]; NH Black adults: OR, 0.64 [95% CI, 0.53–0.76]).
- Data from the MESA showed that greater AHI score was associated with obesity (+19 events/h per 11 kg/m²), male sex (+13 events/h versus female sex), older age (+7 events/h per 20 years of age), and Chinese ancestry (+5 events/h versus White ancestry, adjusted for obesity).¹⁷

• Data from the Ardakan cohort study on aging (N=5197) in Iran showed that 76.4% of community-dwelling adults ≥50 years of age had poor sleep quality measured with the Pittsburgh Sleep Quality Index.¹⁸ Male sex (aOR, 0.55 [95% CI, 0.46–0.66]), being married (OR, 0.41 [95% CI, 0.30–0.54]), having a college education (aOR, 0.73 [95% CI, 0.59–0.92]), working (aOR, 0.67 [95% CI, 0.57–0.80]), living with others [95% CI, 1.22–1.41]).

• In a community cohort of females, higher Mediterranean diet score was associated with better sleep quality ($\beta=-0.31$ [SE, 0.08]), better

Social Determinants/Health Equity

Race and Ethnicity and Sleep
(See Chart 13-4)

- According to parental report in the 2020 to 2021 National Survey of Children’s Health, among children 4 months to 17 years of age, 38.1% (95% CI, 36.2%–40.1%) of Hispanic children and 51.2% (95% CI, 49.1%–53.4%) of NH Black children slept less than recommended for their age compared with 28.4% (95% CI, 27.6%–29.1%) of NH White children.¹³
- In 2014, the prevalence of healthy sleep duration was lower among Native Hawaiian/Pacific Islander people (52.5%), NH Black people (50.4%), and NH multiracial people (49.6%) compared with White people (62.6%). There was no difference between White people and Hispanic people (61.1%) and Asian people (64.2%). All racial and ethnic groups other than Asian people were more likely to report short sleep than White people (RR for Native Hawaiian/Pacific Islander people, 1.61 [95% CI, 1.40–1.85]; Black people, 1.64 [95% CI, 1.48–1.82]; Hispanic people, 1.11 [95% CI, 1.00–1.23]; and NH multiracial people, 1.73 [95% CI, 1.18–2.55]). Long sleep was more likely in Black people than White people (RR reduction, 1.21 [95% CI, 1.02–1.43]) and less likely in Asian people than White people (RR reduction, 0.72 [95% CI, 0.55–0.94]).²²
- In BRFSS 2022, NH Black adults had the highest percentage of respondents reporting sleeping <7 h/night for males and females (47.6% and 45.4%, respectively), whereas NH Asian adults (33.3% and 36.0%) and NH White adults (34.4% and 32.4%) had the lowest percentage of respondents reporting sleeping <7 hours (Chart 13-4).
- In 890 patients newly diagnosed with OSA, Black males had the most severe OSA (AHI score 52.4±39.4 events/h) compared with White males (39.0±28.9 events/h), Black females (33.4±32.3 events/h), and White females (26.2±23.8 events/h).²³
- In a sample of Black adults from the JHS, participants who expressed increasing everyday discrimination between examinations 1 and 3 (spanning 2000–2004 and 2008–2013) had worsening sleep quality ($\beta=-0.13$ [SE, 0.06]) compared with those with stable low discrimination.²⁴ There was no association with self-reported sleep duration.

sleep efficiency ($\beta=-0.31$ [SE, 0.08]), and fewer sleep disturbances ($\beta=-0.31$ [SE, 0.08]) on the Pittsburgh Sleep Quality Index after 1 year.²¹

Other Social Determinants of Sleep

• In the combined BRFSS 2014 and 2016 surveys, bisexual males had higher rates of very short (≤ 4 h/night; 6.5% versus 4.0%) and long (≥ 9 h/night; 10.4% versus 6.5%) sleep durations compared with heterosexual males.²⁵ Lesbian and bisexual females had higher rates of very short (6.8% and

7.6%, respectively) and short and 37.1%, respectively) with heterosexual females short sleep, 30.5%). Among people (OR, 6.07 [95% CI, Latino people (OR, 4.61 [95% higher adjusted odds of very with gay White people. Asian gay people had lower odds of [95% CI, 0.02–0.93]) and long 0.03–0.74]) sleep but higher odds of short sleep (OR, 3.04 [95% CI, 1.25–7.41]) compared with gay

2.8% (variation in sleep of nocturnal sleep episodes).

- Several variants have been associated with self-reported sleep duration in >446 000 Biobank, including *PAX8*, *UBL5/PIN1*, with evidence for between insomnia and
- A GWAS of self-reported Biobank (N=452 633) and the

cohort (N=541 333) identified 61 replicated loci, including missense variants in established drug targets for sleep disorders (*HCRT1*, *HCRT2*).

White people.

Many

- In a cross-sectional survey of 3284 adults, sleep health was better with successively higher age groups. In all age groups, higher frequency of fast food consumption (young, $r=-0.135$; middle-aged, $r=-0.126$; older, $r=-0.135$), daily minutes of television watching (young, $r=-0.132$; middle-aged, $r=-0.171$; older, $r=-0.129$), social media use (young, $r=-0.131$; middle-aged, $r=-0.196$; older, $r=-0.163$), and internet use (young, $r=-0.152$;

middle-aged, $r=-0.233$; older, $r=-0.093$) and lower regularity of lifestyle behaviors (young, $r=-0.320$; middle-aged, $r=-0.340$; older, $r=-0.283$) were correlated with lower sleep health.²⁶ In young adults 18 to 34 years of age, number of pets ($r=-0.063$)

of the loci colocalized with loci for other sleep phenotypes and cardiometabolic outcomes. For example, mendelian randomization suggested a causal link between more frequent daytime napping and higher BP and WC.³⁰ • A GWAS of rapid eye movement sleep behavioral disorder, a more severe sleep subtype, identified 5 loci at or near <i>SNCA</i>, <i>GBA</i>, <i>TMEM175</i>, <i>INPP5F</i>, and <i>SCARB2</i> in 2 case-control GWASs (n cases=2843, n controls=139 636).³¹ Colocalization analyses to examine whether lead variants at these 5 loci also are associated with brain or whole-blood gene expression found strong evidence of colocalization in the <i>SNCA</i> locus with <i>SNCA</i> antisense-1 expression in the brain. and daily reading minutes ($r=-0.066$) were also inversely related to sleep health, whereas in middle-aged adults 35 to 54 years of age, higher daily minutes of reading ($r=-0.111$) and lower moderate to vigorous PA ($r=0.075$) were associated with poorer sleep health. In older adults ≥ 55 years of age, less time in moderate to vigorous PA ($r=0.090$) and higher percent of sedentary time ($r=-0.102$) were	ple, higher loci at n are in the <i>SNCA</i>

- Genetic factors may influence sleep either directly by controlling sleep disorders or indirectly through modulation of risk factors such as obesity. In a study of >120 000 individuals, gene-sleep interactions were identified for some lipid loci, including *LPL* and *PCSK9*, and 4.25% of the variance in triglycerides could be explained from gene–short sleep interactions.³²

- Data from 404 044 participants in the UK Biobank

Family History and Genetics

- Heritability estimates for sleep disorders, including OSA, are $\approx 40\%$.²⁷
- A UK Biobank study (N=85 670) using accelerometer-derived measures of sleep and rest-activity patterns identified 47 loci across 8 sleep traits encompassing sleep duration, quality, and timing.²⁸ Ten novel variants for sleep duration and 26 novel variants for sleep quality that were not detected in much larger studies of self-reported sleep traits were identi-

fied, including a missense variant (p.Tyr727Cys) in *PDE11A*. The cumulative variance explained by these loci ranged from 0.04% for sleep midpoint timing to 0.8% for number of nocturnal sleep episodes. These cumulative variance–explained estimates are considerably smaller than the expected proportion of phenotypic variance explained by commonly occurring SNPs, which ranged from

were used to derive a GRS for sleep duration. Mendelian randomization analyses showed increased odds of CVD with genetically predicted short sleep duration ≤ 6 hours: PE (OR, 1.30 [95% CI, 1.11–1.53]), arterial hypertension (OR, 1.15 [95% CI, 1.09–1.20]), AF (OR, 1.13 [95% CI, 1.03–1.24]), chronic IHD (OR, 1.15 [95% CI, 1.06–1.25]), CAD (OR, 1.24 [95% CI, 1.12–1.37]), and MI (OR, 1.21 [95% CI, 1.09–1.34]). There was no association with genetically predicted long sleep duration ≥ 9 hours.³³

- Data from the FinnGen study (217 955 individuals) estimated the heritability of OSA at 0.08 (95% CI, 0.06–0.11) and identified 5 loci associated with OSA located near *GAPVD1*, *RMST/NEDD1*, *CXCR4*, *CAMK1D*, and *FTO*. Genetic correlations were found between OSA and BMI ($r_g=0.72$ [95% CI, 0.62–0.83]), hypertension ($r_g=0.35$ [95% CI, 0.23–0.48]), type 2 diabetes ($r_g=0.52$ [95% CI,

0.37–0.66]), CHD ($r_g=0.38$ [95% CI, 0.17–0.58]), and stroke ($r_g=0.33$ [95% CI, 0.03–0.63]).³⁴

- The genetic architecture of sleep shares common- alities with several psychiatric disorders and plasma proteins. In the UK Biobank, significant genetic cor- relations were noted between a sleep health score composed of measures of sleep duration, snoring, insomnia, chronotype, and nia, and autism spectrum disorder) and 9 plasma proteins, including cytochrome c oxidase.³⁵ Elevated cytochrome c oxidase levels were associated with long-term sleep deprivation in rats.³⁶

Awareness, Treatment, and Control

- A retrospective chart review of 75 pediatric patients (7–17 years of age) referred to a sleep clinic for snoring compared 6-month change in BP between 3 groups (25 patients in each): snorers without OSA (AHI <1 event/h), with OSA but no treatment (AHI >1 event/h), and with OSA with CPAP treatment.³⁷ SBP was higher at baseline in the 2 OSA groups ($P<0.05$) but decreased in the CPAP-treated group over 6 months (median
- Data from the Southern Community Cohort Study revealed racial differences in associations between sleep duration and mortality in a predominantly low-income US population.⁴⁰ Sleeping <5 h/night versus 8 h/night was associated with increased all-cause mortality in NH White individuals (week-day: HR, 1.23 [95% CI, 1.04–1.46]; weekend: change, –5 mm Hg [25th–75th per-centile, –19 to 0 mm Hg]), whereas SBP increased in the untreated OSA group (median change, 4 mm Hg [25th–75th percentile, 0–10 mm Hg]). DBP did not differ between groups at baseline, nor did the 6-month change in DBP differ between groups.
- A meta-analysis of 8 RCTs examining patients with OSA (AHI ≥ 5 events/h) randomized to either CPAP therapy or control (sham CPAP, pills, or no CPAP) for follow-up of 6 to 84 months did not reveal any reduction in the risk of major cerebrovascular and cardiovascular events (RR, 0.87 [95% CI, 0.70–1.10]).³⁸ MI (RR, 1.04 [95% CI, 0.79–1.37]), stroke (RR, 0.94 [95% CI, 0.71–1.26]), hospital admission for heart failure (RR, 0.92 [95% CI, 0.68–1.23]), new-onset AF (RR, 0.94 [95% CI, 0.54–1.64]), and cardiovascular mortality (RR, 0.94 [95% CI, 0.62–1.43]) were not influenced by CPAP treatment.

were observed for long sleep. For NH White individuals but not Black individuals, sleeping ≥ 10 h/night versus 8 h/night was associated with higher risk of all-cause mortality (White individuals, week-day: HR, 1.23 [95% CI, 1.02–1.48]; weekend: HR, 1.25 [95% CI, 1.08–1.46]; Black individuals, week-day: HR, 1.14 [95% CI, 1.04–1.25]; weekend: HR, 1.08 [95% CI, 1.00–1.16]).

- A meta-analysis of 5 prospective studies of 116 969 employed adults from 5 countries (England, The Netherlands, Scotland, United States, and South Korea) found that short sleep duration (cutoff varied by study, ranging between <6 and <7 h/night) was associated with increased all-cause mortality risk (RR, 1.16 [95% CI, 1.11–1.22]).⁴¹ Long sleep duration (cutoff varied by study, ranging between ≥ 8 and >8 h/night) was also associated with increased risk of all-cause mortality (RR, 1.18 [95% CI, 1.12–1.23]) but with significant heterogeneity.
- The Japan Multi-Institutional Collaborative Cohort assessed sleep regularity using a single question, “Are your bedtimes and wake times regular?”⁴² In adults 35 to 69 years of age, having irregular sleep increased the risk of all-cause mortality compared with having regular sleep (HR, 1.30 [95% CI, 1.18–1.44]). Data were significant in adults <60 years of age (HR, 1.36 [95% CI, 1.14–1.55]) and ≥ 60 years of age (HR, 1.15 [95% CI, 1.00–1.31]) and in males (HR, 1.31 [95% CI, 1.16–1.48]) but not females (HR, 1.06 [95% CI, 0.89–1.27]).
- Data from the MESA Sleep Ancillary study (N=2032) showed that participants with more irregular (sleep duration SD >120 minutes) compared with more regular (sleep duration SD ≤ 60 minutes)

sleep duration were
more likely to have

Mortality

- A community-based prospective cohort study examined associations between sleep duration trajectories between 2006 and 2010 and mortality through 2017 in adults free of CVD and cancer.³⁹ Compared with those with normal stable

sleep (defined as sleep duration 7–8 h/night for 4 years), risk of all-cause mortality was increased in those with normal-decreasing (HR, 1.34 [95% CI, 1.15–1.57]) and those with low-stable (HR, 1.50 [95% CI, 1.07–2.10]) sleep patterns.

low ABI (<0.9; PR, 1.75 [95% CI, 1.03–2.95]) in fully adjusted models.⁴³

- In the Sleep Heart Health Study, middle-aged to older adults were followed up for 11.8 years (IQR, 10.4–15.9 years).⁴⁴ Insomnia was not associated with all-cause mortality (crude model: HR, 1.06 [95% CI, 0.75–1.50]; fully adjusted model: HR, 1.11 [95% CI, 0.77–1.62]). Presence of OSA, defined as AHI ≥15 events/h, was associated with increased risk of all-cause mortality in crude (HR,

1.47 [95% CI, 1.30–1.65]) but (HR, 1.01 [95% CI, 0.89–of co-occurring insomnia and with risk of all-cause mortality [95% CI, 1.29–2.42]) and fully [95% CI, 1.06–2.04]) models. co-occurring insomnia and the Wisconsin Sleep Cohort.⁴⁵

- A meta-analysis of 19 cohort increased risk of all-cause

ing difficulty initiating sleep (HR, 1.13 [95% CI, 1.03–1.23]) that was more pronounced in adults <65 years of age (HR, 1.33 [95% CI, 1.16–1.53]).

Difficulty initiating sleep also was associated with an increased risk of cardiovascular mortality (HR, 1.20 [95% CI, 1.01–1.43]). From 13 studies, there was no added risk of all-cause mortality (HR, 1.05 [95% CI, 0.96–1.14]) or cardiovascular mortality (HR, 1.03 [95% CI, 0.82–1.31]) in those reporting difficulty maintaining sleep. From 6 studies, there was no added risk of all-cause mortality (HR, 0.97 [95% CI, 0.91–1.04]) or cardiovascular mortality (HR, 0.93 [95% CI, 0.76–1.13]) in those reporting difficulty maintaining sleep.⁴⁶

- In the PURE study, which included participants 35 to 70 years of age from 21 countries, risk of mor-

burden with 3-dimensional 3804 adults between 40 and out a history of CVD or OSA.⁵⁰ els. sleeping <6 h/night was with a higher noncoronary with sleeping 7 to 8 h/night 1.06–1.52]). whereas sleeping 1.10 [95% CI, 0.94–1.30]) or [95% CI, 0.92–1.85]) did not to 8 h/night.

tality was increased in those sleeping ≤6 h/d (HR, 1.09 [95% CI, 0.99–1.20]), 8 to 9 h/d (HR, 1.05 [95% CI, 0.99–1.12]), 9 to 10 h/d (HR, 1.17 [95% CI, 1.09–1.25]), and ≥10 h/d (HR, 1.41 [95% CI, 1.30–1.53]) compared with those sleeping 6 to 8 h/d in fully adjusted models.⁴⁷

- Data from the 2020 Canadian Community Health Survey revealed that adults who met recommended sleep duration had 1.24 years (95% CI, 0.87–1.61) longer life expectancy at 20 years of age than those

- A cross-sectional study in Greece (N=1752) reported associations between self-reported sleep duration and carotid IMT from a carotid duplex ultrasonography examination.⁵¹ Compared with adequate sleep duration (7–8 hours), sleeping <6 hours (b=0.067 mm [95% CI, 0.003–0.132]) and sleeping >8 hours (b=0.054 mm [95% CI, 0.002–0.106]) were associated with larger mean carotid IMT. There was no difference between those reporting sleeping 7 to 8 hours and those reporting sleeping 6 to <7 hours (b=0.012 mm [95% CI, –0.043 to 0.068]). Maximum carotid IMT differed only for those reporting sleeping <6 hours (b=0.16 mm [95% CI, 0.033–0.287]) compared with those with adequate sleep duration, whereas those who reported sleeping 6 to <7 hours (b=0.057 mm [95% CI, –0.052 to 0.166]) or >8 hours (b=0.082 mm [95% CI, –0.019 to 0.184]) did not differ.
- Analysis of the UK Biobank study (N=468 941) found that participants who reported short sleep or long sleep had an increased risk of incident HF compared with adequate sleepers.⁵² In males, the aHR was 1.24 (95% CI, 1.08–1.42) for short sleep and 2.48 (95% CI, 1.91–3.23) for long sleep. In females, the aHR was 1.39 (95% CI, 1.17–1.65) for short sleep and 1.99 (95% CI, 1.34–2.95) for long sleep.
- A prospective, population-based cohort study in China enrolled 52 599 Chinese adults 18 to 98 years of age and examined self-reported sleep duration trajectories over 4 years.³⁹ They identified 4 sleep patterns: adequate

Complications

Sleep Duration

- A meta-analysis examined sleep duration and total CVD (26 articles), CHD (22 articles), and stroke (16 articles).⁴⁹ Relative to sleep of 7 to 8 h/night, every 1-hour reduction in sleep was associated with increased risk of total CVD (RR, 1.06 [95% CI, 1.03–1.08]), CHD (RR, 1.07 [95% CI, 1.03–1.12]), and stroke (RR, 1.05 [95% CI, 1.01–1.09]).
- Every 1-hour increase in sleep was associated with increased risk of total CVD (RR, 1.12 [95% CI, 1.08–1.16]), CHD (RR, 1.05 [95% CI, 1.00–1.10]), and stroke (RR, 1.18 [95% CI, 1.14–1.21]).
- A study in Spain estimated sleep duration with wrist actigraphy and measured atherosclerotic plaque

7.0 to 5.5 hours), short increasing (mean increase, 4.9 to 6.9 hours), and short stable (mean range, 4.2–4.9 hours).

Compared with the adequate stable group, increased risk of incident cardiovascular events was observed for the short-increasing group (HR, 1.22 [95% CI, 1.04–1.43]) and the short-stable group (HR, 1.47 [95% CI, 1.05–2.05]) but not the adequate-decreasing group (HR, 1.13 [95% CI, 0.97–1.32]). Risk of all-cause mortality was higher for the adequate-decreasing group (HR, 1.34 [95% CI, 1.15–1.57]) and the short-stable group (HR, 1.50 [95% CI, 1.07–2.10]) but not the short-increasing group (HR, 0.95 [95% CI, 0.80–1.13]).³⁹

• The association between daytime napping and CHD was evaluated in a meta-analysis of 5 prospective and 3 cross-sectional studies.⁵³ After adjustment for nighttime sleep duration and other confounders, the pooled RR of CHD was 1.30 (95% CI, 1.06–1.60). Each 15-minute increase in daytime napping was associated with 5% higher risk of CHD (RR, 1.05 [95% CI, 1.02–1.08]) with high heterogeneity. • In the Rush Memory was associated with higher risk of HF (per 1-SD increase in square root-transformed nap duration: HR, 1.38 [95% CI, 1.12–1.69]; frequency >1.7 times per day: HR, 2.20 [95% CI, 1.41–3.46]).⁵⁴ • In MESA, adding short sleep

sleepiness and risk of CVD events. Mean follow-up time was 5.4 years (range, 2–13.8 years). Excessive daytime sleepiness was associated with a higher risk of any cardiovascular event (RR, 1.28 [95% CI, 1.09–1.50]), CHD (RR, 1.28 [95% CI, 1.12–1.46]), stroke (RR, 1.52 [95% CI, 1.10–2.12]), and cardiovascular mortality (RR, 1.47 [95% CI, 1.09–

duration to Life's Simple 7 score improved the prediction of incident CVD. Those in the highest versus lowest tertile of Life's Simple 7 had 38% lower risk of developing

satisfaction, alertness, timing, efficiency, duration) with risk of HD (yes/no to question on diagnosis of HD). Sleep was assessed by questionnaire and actigraphy. Each 1-unit increase in the self-reported sleep health composite was associated with 54% higher risk of HD (b=0.43 [95% CI, 0.26–0.60]); the actigraphy sleep

health composite was associated with 141% higher risk (b=0.88 [95% CI, 0.44–1.32]).⁶⁰

CVD (HR, 0.62 [95% CI, 0.37–1.04]).⁵⁵ When adequate sleep duration was added to the score, those in the highest tertile had 43% lower risk of incident CVD (HR, 0.57 [95% CI, 0.33–0.97]).

- Data from NHANES 2005 to 2014 showed that having high CVH, assessed with the AHA's Life's Essential 8, which includes sleep duration, was associated with lower all-cause (HR, 0.60

[95% CI, 0.48–0.90]) and cardiovascular (HR, 0.46 [95% CI, 0.31–0.68]) mortality.⁵⁶ Meeting ideal sleep health metrics was associated with reduced all-cause (HR, 0.97 [95% CI, 0.95–0.99]) but not cardiovascular (HR, 0.97 [95% CI, 0.93–1.00]) mortality.

Restful Sleep and Sleepiness

Obstructive Sleep Apnea

• In the JHS Sleep Study, the associations between OSA and BP control or resistant hypertension were examined among 664 Black adults with hypertension (average, 65 years of age). In fully adjusted models, uncontrolled hypertension was not associated with either moderate to severe OSA or nocturnal hypoxemia. However, resistant hypertension was associated with moderate or severe OSA (OR, 2.04 [95% CI, 1.14–3.67]) and nocturnal hypoxemia (OR, 1.25 [95% CI, 1.01–1.55] per SD of percent sleep time <90% oxyhemoglobin saturation).⁶¹

• A prospective study examined 744 adults without hypertension

• Medical records from patients in Japan

(N=1 980 476) were examined to determine whether restful sleep was associated with incident CVD over an average of 1122 days (≈3 years).⁵⁷ Restful sleep was assessed with the question, “Do you have a good rest with sleep?” Restful sleep,

defined by answering “yes,” was associated with lower risk of MI (HR, 0.89 [95% CI, 0.82–0.96]), AP (HR, 0.85 [95% CI, 0.83–0.87]), stroke (HR, 0.86 [95% CI, 0.83–0.90]), HF (HR, 0.86 [95% CI, 0.83–0.88]), and AF (HR, 0.93 [95% CI, 0.88–0.98]) compared with nonrestful sleep (answering

that mild to moderate OSA was significantly associated with incident hypertension over an average of 9.2 years of follow-up (aHR, 2.94 [95% CI, 1.96–4.41]). This association also varied by age: Mild to moderate OSA was significantly associated with incident hypertension in those ≤60 years of age (HR, 3.62 [95% CI, 2.34–5.60]) but not in adults >60 years of age (HR, 1.36 [95% CI, 0.50–3.72]).⁶²• A meta-analysis of 32 observational studies indicated higher odds of having WMHs in those with mild (OR, 1.70 [95% CI, 0.9–3.6]), moderate to

- In the UK Biobank, a 1-point increase in healthy sleep score, including chronotype (morning), sleep duration (7–8 h/d), insomnia (never/rarely or

severe (OR, 3.9 [95% CI, 2.7–5.5]), and severe (OR, some-times), snoring (no), and excessive daytime sleepiness (never/rarely or sometimes), was associated with reduced incidence of HF (HR, 0.85 [95% CI,

4.3 [95% CI, 1.9–9.6]) OSA.⁶³

- In a meta-analysis of 3350 patients with ACS (7 associated with an increased risk of major cardiovascular events [95% CI, 1.45–3.26]). OSA was associated with 0.83–0.87]).⁵⁸
- A meta-analysis combined data from 17 prospective cohort studies with a total of 153

studies) or AMI (3 studies) and OSA, OSA was associated with an increased risk of major cardiovascular and cerebrovascular events (RR, 2.18

an increased risk of revascularization in 8 studies
909 participants to examine the association between excessive daytime

(3036 patients; RR, 1.93 [95% CI, 1.23–3.02]) and increased the risk of hospitalization for HF (RR, 2.06 [95% CI, 1.20–3.54]). Recurrent MI (RR, 1.44

[95% CI, 0.83–2.51]), all-
[95% CI, 0.58–2.54]), and
CI, 0.53–3.52]) were not
with and those without OSA.⁶⁴

Insomnia

- In 14 cohort studies with a mean
years, risk of hypertension
with insomnia (RR, 1.21 [95%
high heterogeneity].⁶⁵

- Trajectories of sleep quality were **Cost**

a median 19.15 years of follow-up in SWAN par-
ticipants (n=2964) 42 to 52 years of age at base-
line.⁶⁶ Females with trajectories characterized by
persistently high insomnia symptoms had higher
risk of CVD (HR, 1.71 [95% CI, 1.19–2.46]) com-
pared with females with persistently low
insomnia symptoms trajectories. Compared with
females with low insomnia symptoms and
moderate or moderate to long sleep duration,
females with high insomnia symptoms and

symptoms and CVD. Patients
difficulty initiating sleep, and
sleep had 16% (HR, 1.16
22% (HR, 1.22 [95% CI,
(HR, 1.14 [95% CI, 1.02–
respectively, compared with
any insomnia complaint was
higher risk (HR, 1.13 [95% CI,
1.00–1.40]).

short sleep duration (HR, 1.70 [95%
CI, 1.06–2.72]) or high insomnia
symptoms and moderate or
moderate to long sleep duration (OR,
1.75 [95% CI, 1.03–2.98]) had higher
risk of CVD. • A meta-analysis of 7
prospective studies with sam- ple
sizes of 2960 to 487 200 and a mean
follow-up of 10.6 years examined the
association of insomnia

- Analysis of data from the 2018 MEPS among a nationally representative US sample estimated that the direct health care costs of sleep disorders is approximately \$94.9 billion per year.⁶⁸ Individuals with sleep disorders have almost twice the number of office visits, 1.4 times the number of emergency visits, and 1.8 times the number of prescription fills as those without sleep disorders.

Global Burden

- An analysis of the global prevalence and burden of OSA estimated that 936 (95% CI, 903–970) million males and females 30 to 69 years of age have mild to severe OSA and 425 (95% CI, 399–450) million have moderate to severe OSA globally.⁶⁹

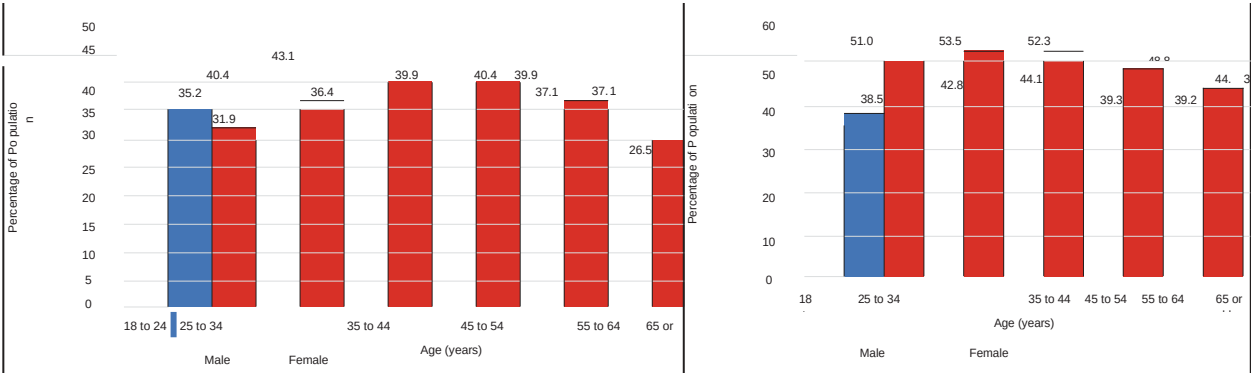


Chart 13-1. Prevalence of reporting sleep duration <7 h/night in US adults, by sex and age, 2022.

Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey question was “On average, how many hours of sleep do you get in a 24-hour period?”
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey.⁹

Chart 13-2. Prevalence of reporting being well rested never or some days, by sex and age, 2022.

Percentages are adjusted for complex sampling design, including primary sampling units, strata, and sampling weights. The survey question was “During the past 30 days, how often did you wake up feeling well rested?”
Source: Unpublished tabulation using National Health Interview Survey.¹²

21. Zuraikat FM, Makarem N, St-Onge MP, Xi H, B. A Mediterranean dietary pattern predicts US women from the American Heart Strategically Focused Research Network. *10.3390/nu12092830*
22. McElfish PA, Narcisse MR, Selin JP. Felix of race and poverty on sleep duration: Native Hawaiian and Pacific Islander and General National Health Interview *Disparities*. 2021;8:837–843. doi: 278. doi: 10.1513/AnnalsATS.202012-1483OC
23. Thornton JD, Dudley KA, Saeed GJ, Patel SR. Differences in symptoms and cardiovascular events in patients with atic review and meta-analysis. *Sleep* 10.1016/j.smrv.2020.101312
24. Johnson DA, Lewis TT, Guo N, Jackson CL, Sims M, Wilson JG, Diez Roux AV, Williams DR, Redline S. Associations between cardiovascular events in patients with atic review and meta-analysis. *Sleep* 10.1016/j.smrv.2020.101312
39. Wang YH, Wang J, Chen SH, Li JO, Lu Shi J, Lu L, et al. Association of tion with risk of cardiovascular events *Open*. 2020;3:e205246. doi: 10.1016/j.sleh.2019.04.008
40. Xiao O, Blot WJ, Matthews CE. and mortality among middle-to-older low-income southern US cohort. *Sleep* 10.1016/j.sleh.2019.04.008
41. Pienaar PR, Kolhe-Alexander TL, van Lambert EV, Rae DE. Associations everyday discrimination and sleep quality and duration among African-Americans over time in the Jackson Heart Study. *Sleep*. 2021;44:zsab162. doi: 10.1016/j.sleh.2019.04.008

- mortality in employed individuals: systematic review and meta-analysis. *Am J Health Promot.* 2021;35:853–865. doi: 10.1177/0890117121992288 42. Omichi C, Koyama T, Kadotani H, Ozaki E, Tomida S, Yoshida T, Otonari J, Ikezaki H, Hara M, Tanaka K, et al; J-MICC Study Group. Irregular sleep and all-cause mortality: a large prospective cohort study. *Sleep Health.* 10.1093/sleep/zsab162
25. Caceres BA, Hickey KT, Heitkemper EM, Hughes TL. An intersectional approach to examine sleep duration in sexual minority adults in the United States: findings from the Behavioral Risk Factor Surveillance System. *Sleep Health.* 2019;5:621–629. doi: 10.1016/j.sleh.2019.06.006
26. Dzierzewski JM, Sabet SM, Ghose SM, Perez E, Soto P, Ravyts SG, Dautovich ND. Lifestyle factors and sleep health across the lifespan. *Int J Environ Res Public Health.* 2021;18:6626. doi: 10.3390/ijerph18126626
27. Mukherjee S, Saxena R, Palmer LJ. The genetics of obstructive sleep apnoea. *Respirology.* 2018;23:18–27. doi: 10.1111/resp.13212
28. Jones SE, van Hees VT, Mazzotti DR, Marques-Vidal P, Sabia S, van der Spek A, Dashti HS, Engmann J, Kocavska D, Tyrrell J, et al. Genetic studies of accelerometer-based sleep measures yield new in-

43. Full KM, Huang T, Shah NA, Allison MA, Michos ED, Duprez DA, Redline S, Lutsey PL. Sleep irregularity and subclinical markers of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc.* 2023;12:e027361. doi: 10.1161/JAHA.122.027361
44. Lechat B, Appleton S, Melaku YA, Hansen K, McEvoy RD, Adams R, Catcheside P, Lack L, Eckert DJ, Sweetman A. Comorbid insomnia and sleep apnoea is associated with all-cause mortality. *Eur Respir J.* 2022;60:2101958. doi: 10.1183/13993003.01958-2021
45. Lechat B, Loffler KA, Wallace DM, Reynolds A, Appleton SL, Scott H, Vakulin A, Lovato N, Adams R, Eckert DJ, et al. All-cause mortality in people with co-occurring insomnia symptoms and sleep apnea: analysis of the Wisconsin Sleep Cohort. *Nat Sci Sleep.* 2022;14:1817–1828. doi: 10.2147/NSS.S379252
- 10.1038/s41467-019-09576-1
29. Dashti HS, Jones SE, Wood AR, Lane JM, van Hees VT, Wang H, Rhodes JA, Song Y, Patel K, Anderson SG, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat Commun.* 2019;10:1100. doi: 10.1038/s41467-019-08917-4
30. Dashti HS, Daghlasi I, Lane JM, Huang Y, Udler MS, Wang H, Ollila HM, Jones SE, Kim J, Wood AR, et al; 23andMe Research Team. Genetic determinants of daytime napping and effects on cardiometabolic health. *Nat Commun.* 2021;12:900. doi: 10.1038/s41467-020-20585-3
31. Krohn L, Heilbron K, Blauwendraat C, Reynolds RH, Yu E, Senkevich K, Rudakou U, Estià MA, Gustavsson EK, Brodin K, et al; 23andMe Research Team. Genome-wide association study of REM sleep behavior disorder identifies polygenic risk and brain expression effects. *Nat Commun.* 2022;13:7496. doi: 10.1038/s41467-022-34732-5
32. Noordam R, Bos MM, Wang H, Winkler TW, Bentley AR, Kilpeläinen TO, de Vries PS, Sung YJ, Schwander K, Cade BE, et al. Multi-ancestry sleep-by-SNP interaction analysis in 126,926 individuals reveals lipid loci stratified by sleep duration. *Nat Commun.* 2019;10:5121. doi: 10.1038/s41467-019-12958-0
33. Ai S, Zhang J, Zhao G, Wang N, Li G, So HC, Liu Y, Chau S-H, Chen J, Tan X, et al. Causal associations of short and long sleep durations with 12 cardiovascular diseases: linear and nonlinear mendelian randomization analyses in UK Biobank. *Eur Heart J.* 2021;42:3349–3357. doi: 10.1093/eurheartj/ehab170
34. Strausz S, Ruotsalainen S, Ollila HM, Karjalainen J, Kiiskinen T, Reeve M, Kurki M, Mars N, Havulinna AS, Luonsi E, et al; FinnGen. Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. *Eur Respir J.* 2021;57:2003091. doi: 10.1183/13993003.03091-2020
35. Yao Y, Jia Y, Wen Y, Cheng B, Cheng S, Liu L, Yang X, Meng P, Chen Y, Li C, et al. Genome-wide association study and genetic correlation scan provide insights into its genetic architecture of sleep health score in the UK Biobank cohort. *Nat Sci Sleep.* 2022;14:1–12. doi: 10.2147/nss.s326818
36. Cirelli C, Pfister-Genskow M, McCarthy D, Woodbury R, Tononi G. Proteomic profiling of the rat cerebral cortex in sleep and waking. *Arch Ital*

46. Ge L, Guyatt G, Tian J, Pan B, Chang Y, Chen Y, Li H, Zhang J, Li Y, Ling J, et al. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: systematic review and meta-analysis of prospective cohort studies. *Sleep Med Rev.* 2019;48:101215. doi: 10.1016/j.smrv.2019.101215
47. Wang C, Bangdiwala SI, Rangarajan S, Lear SA, AlHabib KF, Mohan V, Teo K, Poirier P, Tse LA, Liu Z, et al. Association of estimated sleep duration and naps with mortality and cardiovascular events: a study of 116 632 people from 21 countries. *Eur Heart J.* 2019;40:1620–1629. doi: 10.1093/eurheartj/ehy695
48. Chaput JP, Carrier J, Bastien C, Gariépy G, Janssen I. Years of life gained when meeting sleep duration recommendations in Canada. *Sleep Med.* 2022;100:85–88. doi: 10.1016/j.sleep.2022.08.006
49. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, Peng X, Peng Z, Yu K, Bao W, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc.* 2017;6:e005947. doi: 10.1161/JAHA.117.005947
50. Dominguez F, Fuster V, Fernandez-Alvira JM, Fernandez-Friera L, Lopez-Melgar B, Blanco-Rojo R, Fernandez-Ortiz A, Garcia-Pavia P, Sanz J, Mendiguren JM, et al. Association of sleep duration and quality with subclinical atherosclerosis. *J Am Coll Cardiol.* 2019;73:134–144. doi: 10.1016/j.jacc.2018.10.060
51. Oikonomou E, Theofilis P, Vogiatzi G, Lazaros G, Tsalamandris S, Mystakidi VC, Goliopoulou A, Anastasiou M, Fountoulakis P, Chasikidis C, et al. The impact of sleeping duration on atherosclerosis in the community: insights from the Corinthia study. *Sleep Breath.* 2021;25:1813–1819. doi: 10.1007/s11325-020-02267-y
52. Sillars A, Ho FK, Pell GP, Gill JMR, Sattar N, Gray S, Celis-Morales C. Sex differences in the association of risk factors for heart failure incidence and mortality. *Heart.* 2020;106:203–212. doi: 10.1136/heartjnl-2019-314878
53. Salari N, Moradi S, Bagheri R, Talebi S, Wong A, Babavaii B, Kermani MAH, Hemati N. Daytime napping and coronary heart disease risk in adults: a systematic review and dose-response meta-analysis. *Sleep Breath.* 2023;27:1255–1267. doi: 10.1007/s11325-022-02759-z
54. Li P, Gaba A, Wong PM, Cui L, Yu L, Bennett DA, Buchman AS, Gao L, Hu K. Objective assessment of daytime napping and incident heart failure in 1140 community-dwelling older adults: a prospective, observational study. *J Pediatr.* 2018;195:102–107.e1. doi: 10.1016/j.jpeds.2017.11.043
38. Labarca G, Dreyse J, Drake L, Jorquera J, Barbe F. Efficacy of continuous positive airway pressure (CPAP) in the prevention of

to include sleep:

Circulation.2025;151:e

- in the MESA Sleep Study. *J Am Heart Assoc.* 2022;11:e025252. doi: 10.1161/JAHA.122.025252
56. Yi J, Wang L, Guo X, Ren X. Association of Life's Essential 8 with all-cause and cardiovascular mortality among US adults: a prospective cohort study from the NHANES 2005-2014. *Nutr Metab Cardiovasc Dis.* 2023;33:1134–1143. doi: 10.1016/j.numecd.2023.01.021
57. Kaneko H, Itoh H, Kiriyaama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, et al. Restfulness from sleep and subsequent cardiovascular disease in the general population. *Sci Rep.* 2020;10:19674. doi: 10.1038/s41598-020-76669-z
58. Li X, Xue Q, Wang M, Zhou T, Ma H, Heianza Y, Qi L. Adherence to a healthy sleep pattern and incident heart failure: a prospective study of 408 802 UK Biobank participants. *Circulation.* 2021;143:97–99. doi: 10.1161/CIRCULATIONAHA.121.052033
60. Lee S, Mu CX, Wallace ML, Andel R, Almeida DM, Buxton OM, Patel SR. Sleep health composites are associated with the risk of heart disease across sex and race. *Sci Rep.* 2022;12:2023. doi: 10.1038/s41598-022-05203-0
- associated with incident hypertension: age effect. *Sleep.* 2019;42:zsy265. doi: 10.1093/sleep/zsy265
63. Lee G, Dharmakulaseelan L, Muir RT, Iskander C, Kendzerska T, Boulos MI. Obstructive sleep apnea is associated with markers of cerebral small vessel disease in a dose-response manner: a systematic review and meta-analysis. *Sleep Med Rev.* 2023;68:101763. doi: 10.1016/j.smrv.2023.101763
64. Yang SH, Xing YS, Wang ZX, Liu YB, Chen HW, Ren YF, Chen JL, Li SB, Wang ZF. Association of obstructive sleep apnea with the risk of repeat adverse cardiovascular events in patients with newly diagnosed acute coronary syndrome: a systematic review and meta-analysis. *Ear Nose Throat J.* 2022;101:022-05203-0
61. Johnson DA, Thomas SJ, Abdalla M, Guo N, Yano Y, Rueschman M, Tanner RM, Mittleman MA, Calhoun DA, Wilson JG, et al. Association between sleep apnea and blood pressure control among Blacks. *Circulation.* 2019;139:1275–1284. doi: 10.1161/CIRCULATIONAHA.118.036675
62. Vgontzas AN, Li Y, He F, Fernandez-Mendoza J, Gaines J, Liao D, Basta M, Bixler EO. Mild-to-moderate sleep apnea is

66. Thurston RC, Chang Y, Kline CE, Swanson LM, El Khoudary SR, Jackson EA, Derby CA. Trajectories of sleep over midlife and incident cardiovascular dis-ease events in the Study of Women's Health Across the Nation. *Circulation*. 2024;149:545–555. doi: 10.1161/CIRCULATIONAHA.123.066491
67. Hu S, Lan T, Wang Y, Ren L. Individual insomnia symptom and increased hazard risk of cardiocerebral vascular diseases: a meta-analysis. *Front Psychiatry*. 2021;12:654719. doi: 10.3389/fpsy.2021.654719
68. Huyett P, Bhattacharyya N. Incremental health care utilization and expenditures for sleep disorders in the United States. *J Clin Sleep Med*. 2021;17:1981–1986. doi: 10.5664/jcsm.9392
69. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pepin JL, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7:687–698. doi: 10.1016/S2213-2600(19)30198-5

14. TOTAL DISEASES

ICD-9 390 to 459; ICD-10 I00 to through 14-4 and Charts 14-1 through 14-16

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Prevalence

(See Table 14-1 and Chart 14-1)

- On the basis of NHANES 2017 to March 2020 data,¹ the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥ 20 years of age is 48.6% overall (127.9 million in 2020) and increases with age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.9% overall (28.6 million in 2020; Table 14-1). Chart 14-1 presents the prevalence breakdown of CVD by age and sex, with and without hypertension in the CVD definition.
- According to the NHIS₂ 2018:
 - The age-adjusted prevalence of all HD (CHD, angina, or heart attack, excluding hypertension) was 11.2%; the corresponding age-adjusted prevalences of HD among self-described racial and ethnic groups in which only 1 race was reported were 11.5% among NH White individuals, 10.0% among NH Black individuals, 8.2% among Hispanic individuals, 7.7% among Asian individuals, and 14.6% among American Indian or Alaska Native individuals.

30.5%; and stroke, prevalences of HD, CHD, among currently 4.0%, 21.8%, and 1.6%, adjusted prevalences of and stroke among worked were 10.2%, respectively.

- In a cross-sectional study years of age from northern China, 22.7% had high 10-year risk of CVD according to WHO/
 - The age-adjusted prevalences of HD, CHD, hypertension, and stroke in males were 12.6%, 7.4%, 26.1%, and 3.1%, respectively, and in females were 10.1%, 4.1%, 23.5%, and 2.6%, respectively.
 - The age-adjusted prevalences of HD, CHD, hypertension, and stroke among unemployed individuals who had previously worked were as follows: HD, 13.9%; CHD, 7.7%; hypertension,

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

International Society of Hypertension risk prediction charts.³ The age-adjusted prevalences of hypertension, dyslipidemia, obesity, and diabetes among all respondents were 54.3%, 36.5%, 24.8%, and 18.2%, respectively.

Incidence

- In a meta-analysis of 32 studies assessing CVD burden among Asian adults 18 to 92 years of age who were free of CVD at baseline and with >10 years of follow-up, the incidence of fatal CVD was 3.68 (95% CI, 2.84–4.53) events per 1000 PY.⁴ Risk factors for long-term fatal CVD were male sex (1.49, [95% CI, 1.36–1.64]), older age (7.55 [95% CI, 5.59–10.19]), and current smoking (1.68 [95% CI, 1.26–2.24]).

Lifetime Risk and Cumulative Incidence

- In a 20-year follow-up of the ATTICA study (2002–2022) with 1988 participants (50% male, 45±14 years of age), 718 experienced a fatal or nonfatal CVD event (crude incidence, 36.1%; males, 40.2%, females, 32.1%; $P<0.001$).⁵ Lifetime risk is the estimation of the cumulative risk of developing a certain disease during an individual's remaining life span. Lifetime CVD risk was similar for males and females ($P=0.245$), with a progressive decline from 68% and 63% at 40 years of age to 56% and 50% at age 50 years of age and 55% for both at 60 years of age, respectively. In an external validation study of the QRiskLifetime incident CVD risk prediction tool using Clinical Practice Research Datalink data ($n=1\,260\,329$ females and $n=1\,223\,265$ males), discrimination was excellent (Harrell C statistic, 0.844 in females, 0.808 in males) but moderate to poor when stratified by age group (Harrell C statistic in people 30 to 44 years of age, 0.714 for both; 75 to 84 years of age, 0.578 in females, 0.556 in males).⁶ QRiskLifetime underpredicted 10-year CVD risk in all age groups except females 45 to 64 years of age with worse underprediction in older age groups. Adults with the highest lifetime risk were

younger (mean, 50.5 years of age for females and 46.3 years of age for males) compared with those with the highest 10-year risk (mean, 71.3 years of age for females and 63.8 years of age for males). The Cardiovascular Lifetime Risk Pooling Project estimated the long-term risks of CVD among 30 447 participants with a mean of 55.0 years of age (SD, 13.9 years) from 7 US cohort studies.⁷ After 538 477 PY of follow-up, the 40-year risk of CVD for an adult <40 years of age with high CVH was 0.7% (95% CI, 0.0%–1.7%) for White males, 2.1% (95% CI, 0.0%–5.0%) for Black males, 1.7% (95% CI, 0.4%–3.0%) for White females, and 2.0% (95% CI, 0.0%–4.7%) for Black females. For an adult <40 years of age with low CVH, the 40-year risk of CVD was 14.4% (95% CI, 9.1%–19.6%) for White males, 17.6% (95% CI, 9.9%–25.3%) for Black males, 8.6% (95% CI, 2.1%–15.2%) for White females, and 8.4% (95% CI, 5.3%–11.5%) for Black females. White females ≥60 years of age with high CVH had a 35-year risk of CVD of 38.6% (95% CI, 22.6%–54.7%), but this risk was incalculable for older, high-CVH individuals in other race-sex groups because of insufficient follow-up. Among individuals ≥60 years of age with low CVH, the 35-year risk of CVD was highest in White males (65.5% [95% CI, 62.1%–68.9%]) followed by White females (57.1% [95% CI, 54.4%–59.7%]), Black females (51.9% [95% CI, 43.1%–60.8%]), and Black males (48.4% [95% CI, 41.9%–54.9%]). These estimated risks accounted for competing risks of death resulting from non-CVD causes.

- The remaining lifetime risk for ASCVD among pre-dominantly White participants from the FHS in 3 epochs (epoch 1, 1960–1979; epoch 2, 1980–1999; epoch 3, 2000–2018) was examined.⁸ Life expectancy increased by 10.1 years among males and 11.9 years among females across the 3 epochs. Furthermore, the remaining lifetime risk of ASCVD from 45 years of age reduced from 43.7% in epoch 1 to 28.1% in epoch 3 (2000–2018).⁸
- According to data from the COAST study (2000–2012), of 9012 people living with HIV in British Columbia, Canada, and free of CVD at baseline, the adjusted incidence rate of CVD per 1000 PY

Risk Factors

- During up to 30 years of follow-up in a prospective study of 210 240 participants in the Nurses' Health Study, those with a higher Portfolio Diet Score (plant protein, nuts, viscous fiber, phytosterols, and plant monounsaturated fats) had a lower risk of total CVD (pooled HR, quintile 5 versus 1, 0.86 [95% CI, 0.81–0.92]) after multivariable adjustment.¹⁰ A 25% higher Portfolio Diet Score was associated with a lower risk of total CVD (pooled HR, 0.92 [95% CI, 0.89–0.95]).
- In a cross-sectional study of 13 965 US adults without CVD from NHANES 2005–2018, 26.6% were current marijuana users.¹¹ After adjustment for sociodemographic and lifestyle factors using inverse probability of treatment weighting, there were no significant differences between current and never users in the burden of mean 10-year ASCVD risk scores (2.8% versus 3.0%; $P=0.49$), 30-year FRSs (22.7% versus 24.2%; $P=0.25$), and various cardio-metabolic biomarkers.
- A prospective study assessed the association between ultraprocessed food consumption and CVD risk in 26 369 participants from the Swedish Malmö Diet and Cancer Study.¹²
 - Over a median follow-up of 24.6 years, 6236 participants developed CVD. The aHR in the fourth versus first quartile of ultraprocessed food intake was 1.18 (95% CI, 1.08–1.29) for CVD, 1.20 (95% CI, 1.07–1.35) for CHD, and 1.17 (95% CI, 1.03–1.32) for ischemic stroke.
- In a prospective cohort study of 156 787 post-menopausal females ≥40 years of age from the UK Biobank followed up for a median of 12.5 years, the incidence of CVD remained relatively stable at 9.11 (95% CI, 5.87–14.13) in 2000 compared with 10.01 (95% CI, 7.55–13.27) in 2012.⁹ However, incidence rates of hypertension per 1000 PY increased significantly.

CVD and ischemic stroke over a mean follow-up of 7.1 years.¹⁴ Females in the highest quartile of total volume of PA (total average daily vector magnitude) and moderate to vigorous PA (>120 minutes) had a 43% (95% CI, 24%–58%) and 38% (95% CI, 18%–54%) lower hazard of total CVD, respectively, compared with those in the lowest quartile. Females who spent <7.4 hours sedentary per day had a 33%

(95% CI, 11%–49%) lower compared with those who tary. Replacing 10 minutes of with moderate to vigorous PA a 4% lower incidence of total CI, 0.93–0.99).

- In a meta-analysis of 13 cohort participants: 115 392 CVD, 30 stroke events), vegetarians

(RR, 0.79 [95% CI, 0.71–0.88]; $I^2=67\%$) compared with nonvegetarians. Vegans had a marginally lower risk of IHD (RR, 0.82 [95% CI, 0.68–1.00]; $I^2=0\%$) compared with nonvegetarians.

- Among 1252 participants from the Dallas Heart Study, CAC scores and hepatic steatosis

aerodynamic diameter <2.5

elevated blood glucose, poor incident CVD events, and all-accounts in part for the racial mortality and incident CVD.

HeartScore, a community-residing in western

ambient fine particulate

mean PM_{2.5} exposure among

16.1±0.75 $\mu\text{g}/\text{m}^3$ versus

prevalence were higher in those with type 2 diabetes.¹⁵ CAC was associated with ASCVD events regardless of type 2 diabetes status ($P_{\text{interaction}}=0.02$). Hepatic triglyceride content was inversely associated with ASCVD risk

individuals ($P=0.0001$). Black carbon exposure among Black individuals was $1.19 \pm 0.11 \mu\text{g}/\text{m}^3$, and mean black carbon exposure among White individuals was $1.16 \pm 0.13 \mu\text{g}/\text{m}^3$ ($P=0.0001$). Mediation analysis demonstrated that 24% of the association between race and the composite outcome of CVD deaths and nonfatal CVD events was mediated by exposure to PM_{2.5} and that the association between race and composite clinical outcome was no longer significant after adjustment for income and education.¹⁹

in participants with type 2 diabetes (HR, 0.91 [95% CI, 0.83–0.99] per 1% increase in hepatic triglyceride content; $P=0.02$, $P_{\text{interaction}}=0.02$).

- Among 42 711 adults from the NHANES, including 5015 adults with CVD, magnesium depletion scores were calculated from diuretic use, proton pump inhibitor use, eGFR, and heavy drinking.¹⁶ Individuals with magnesium depletion scores of ≥ 3 had higher odds of total CVD compared with those with magnesium depletion scores of 0 (aHR, 2.27 [95% CI, 1.38–3.72]).¹⁶
- Eating disorders are another risk factor for CVD. In a registry-based study of 416 709 females hospitalized in Quebec, Canada, from 2006 and 2018, 818 females who were hospitalized for bulimia nervosa were compared with 415 891 females without bulimia nervosa who were hospitalized for pregnancy-related events for a total follow-up period of 2 957 677 PY.¹⁷ Females hospitalized for bulimia nervosa had a higher incidence of CVD (10.34 [95% CI, 7.77–13.76] per 1000 PY) than females hospitalized for pregnancy-related events (1.02 [95% CI, 0.99–1.06] per 1000 PY). Furthermore, the risk of any CVD (4.25 [95% CI, 2.98–6.07]) or death (4.72 [95% CI, 2.05–10.84]) was higher among females hospitalized for bulimia nervosa compared with females hospitalized for pregnancy-related events (comparison group).
- Among participants of the WHS (N=27 858; 629 353 PY of follow-up), those with a self-reported history of migraine with aura had a higher incidence rate of major CVD (3.36 [95% CI, 2.72–3.99 per 1000 PY]) than females with migraine without aura or no migraine (2.11 [95% CI, 1.98–2.24]).¹⁸
- Air pollution, as defined by increased ambient exposure to particulate matter (particles with median

- Among 31 162 adults 35 to 74 years of age in the Henan Rural Cohort Study, each 1- $\mu\text{g}/\text{m}^3$ increase in particulate matter (PM1 [particles with aerodynamic diameter $<1\ \mu\text{m}$], PM2.5, PM10 [particles with aerodynamic diameter $<10\ \mu\text{m}$], and NO_2) was associated with a 4.4% (OR, 1.04 [95% CI, 1.03–1.06]) higher 10-year ASCVD risk for PM1, 9.1% (OR, 1.09 [95% CI, 1.08–1.10]) higher 10-year ASCVD risk for PM2.5, 4.6% (OR, 1.05 [95% CI, 1.04–1.05]) higher 10-year ASCVD risk for PM10, and 6.4% (OR, 1.06 [95% CI, 1.06–1.07]) higher 10-year ASCVD risk for NO_2 (all $P<0.001$).
However, PA attenuated the association between air pollution and 10-year ASCVD risk.²⁰
- In a meta-analysis of sex differences in the association between diabetes and CVD mortality (49 studies representing 5 162 654 participants), the pooled RR ratio demonstrated a 30% greater risk of all-cause mortality among females and males with diabetes (95% CI, 1.13–1.49). Females with diabetes also had a 58% greater risk of CHD.²¹
- In a meta-analysis of dietary sodium intake and CVD risk (36 studies representing 616 905 participants), those with high sodium intake had a higher adjusted risk of CVD (rate ratio, 1.19 [95% CI, 1.08–1.30]) than individuals with low sodium intake. CVD risk was up to 6% higher for every 1-g increase in dietary sodium intake.²² However, an increase in potassium intake may be beneficial in lowering BP levels, but excessive potassium supplementation should be avoided.²³
- A prospective analysis of dietary patterns among adults in the Nurses' Health Study (1984–2016), Nurses' Health Study II (1991–2017), and HPFS (1986–2012) with 5 257 190 PY of follow-up

found that greater adherence to healthy eating patterns was inversely and consistently associated with CVD risk (HEI-2015: HR, 0.83 [95% CI, 0.79–0.86]; AHEI: HR, 0.79 [95% CI, 0.75–0.82]; Alternate Mediterranean Diet Score: HR, 0.83 [95% CI, 0.79–0.86]; and Healthful Plant-Based Diet Index: HR, 0.86 [95% CI, 0.82–0.89]).²⁴

- In a systematic review of 19 observational studies aimed at assessing the association between diet and CVD, findings revealed that the highest intake of unhealthy foods was associated with a higher BMI (0.57 kg/m² [95% CI, 0.51–0.63]) and higher WC (0.57 cm [95% CI, 0.47–0.67]) compared with a low intake of unhealthy foods.²⁵ Children and adolescents with a Western dietary pattern (high intake of beef/lamb/other red meat, wheat, starch fibers, and light-colored vegetables) had a significantly higher odds of obesity (OR, 2.04 [95% CI, 1.38–3.02]) compared with youths who followed a healthier eating pattern (milk, yogurt, fruit, and vegetables with less sugar, beef/lamb/other red meat).
- In a prospective cohort study of 414 588 adults without CVD in the UK Biobank (2006–2010) with

for incident CVD was higher across the second (aHR, 1.30 [95% CI, 1.18–1.42]), third (aHR, 1.40 [95% CI, 1.26–1.55]), and fourth (aHR, 1.59 [95% CI, 1.41–1.77]) quartiles of HbA1c SD than the first quartile ($P_{\text{trend}} < 0.001$).

- Among 2 prospective cohorts of US males (HPFS, 1990–2018) and females (Nurses' Health Study), follow-up through 2018, perinatal exposure to maternal smoking was associated with higher risk of CVD (aHR, 1.10 [95% CI, 1.05–1.14]), MI (aHR, 1.10 [95% CI, 1.05–1.16]), and stroke (aHR, 1.10 [95% CI, 1.03–1.18]).²⁶ Furthermore, there were significant interactions between perinatal exposure to maternal smoking and adulthood smoking behaviors on MI and CVD (all $P < 0.05$).
- Among 116 806 individuals in the UK Biobank who had a mean follow-up of 4.9 years, there were 4245 cases of total CVD, 838 cases of fatal CVD, and 3629 deaths resulting from all causes.²⁷ Dietary patterns, assessed with a 24-hour online dietary assessment on at least 2 occasions, revealed a positive linear association between diets that were

mortality (aHR, 0.81 [95% CI, 0.75–0.87]) than those who had lower consumption of olive oil (never or less than once per month).

- In a meta-analysis of 10 studies including 9 cohorts (N=698 707) with 137 969 CVD events, higher adherence to a plant-based diet was associated with lower risk of CVD (aRR, 0.84 [95% CI, 0.79–0.89]) and CHD (aRR, 0.88 [95% CI, 0.81–0.94]) compared with low adherence.³¹
- Among 15 103 individuals with type 2 diabetes without CVD and with serum 25-hydroxyvitamin D measurements in the UK Biobank, there were 3534 incident CVD events over a median of 11.2 years of follow-up.³² Participants with higher serum 25-hydroxyvitamin D concentrations had lower CVD risk. The multivariable-adjusted HRs across categories of serum 25-hydroxyvitamin D of <25.0, 25.0 to 49.9, 50.0 to 74.9, and ≥75.0 nmol/L were 1.00 (reference), 0.87 (95% CI, 0.80–0.96), 0.80 (95% CI, 0.72–0.88), and 0.75 (95% CI, 0.64–0.88) for total CVD events ($P_{\text{trend}} < 0.001$).
- In a retrospective cohort study of medical records of females who had ≥1 singleton live births (N=2 359 386) from the National Health Service hospitals in England between 1997 and 2015, females who had prior gestational hypertension or prior preeclampsia had 1.45 (95% CI, 1.33–1.59) and 1.62 (95% CI, 1.48–1.78) higher adjusted hazards of total CVD, respectively, than those who were high in chocolate and confectionery, butter, and low-fiber bread and low in fresh fruit and vegetables and total CVD (aHR, 1.40 [95% CI, 1.31–1.50]) and all-cause mortality (aHR, 1.37 [95% CI, 1.27–1.47] in the highest quintile).
- In a prospective analysis of data of 3612 individuals 17 to 77 years of age from the Framingham Offspring Study who were examined between 1979 and 2014, 533 (15%) were diagnosed with normotensive.³³
- Among 29 260 adults with type 2 diabetes in the LEAD cohort study (2013 and 2018) with a mean follow-up of 4.2 years, there were 3746 incident CVD events. HbA1c variability, measured by SD, was associated with higher risk of CVD.²⁹ The aHR
- asthma, and 897 (25%) developed CVD.²⁸ Asthma was associated with higher risk of incident CVD (aHR, 1.28 [95% CI, 1.07–1.54]).

- Among 103 388 adults in the web-based NutriNet-Santé cohort (mean, 42.2±14.4 years of age; 79.8% female; 904 206 PY), consuming artificial sweeteners from all dietary sources, including beverages, tabletop sweeteners, and dairy products, among others, was associated with 1.09 (95% CI, 1.01–1.18) higher CVD risk.³⁴ Similarly, among 109 043 females in the WHS, during an average of 17.4 years of follow-up, 11 597 CVD events occurred.³⁵ Higher intake of added sugar (≥15.0% energy intake daily) was positively associated with total CVD (HR, 1.08 [95% CI, 1.01–1.15]). Consuming ≥1 servings of SSBs or ASBs daily was associated with 1.29 [95% CI, 1.17–1.42] and (1.14 [95% CI, 1.03–1.26]) higher risk of total CVD, respectively. A prospective analysis of participants

- in the International
ated whether 5 childhood
tors (BMI, SBP, TC level,
smoking) were associated
CVD events in adulthood after
of 35 years.³⁶ Each 1-unit
risk z score (unweighted
was associated with a 2.71
and 2.75 (95% CI, 2.48–3.06)
or nonfatal CVD event.
CVD in adulthood ranged from 1.30 (95% CI,
1.14–1.47) per 1-unit increase in the z score for
- CI, 1.63–1.95]) after
economic factors and CVD
centile point reduction in
was associated with 11% and
total mortality among males
tively, whereas a 30%
deprivation was associated
CVD and cancer-related
- In a retrospective cohort study
receiving care at a large
TC level to 1.61 (95% CI, 1.21–
2.13) for youth smoking (yes

patients in the highest quartile of weighted social determinants of health score (including foreign-born status, underrepresented race or ethnicity status, versus no).
edu-

social isolation, financial strain, health literacy, cation, stress, delayed care, census-based income)

Social Determinants of Health/Health Equity

- Data from 6 prospective cohort studies (1985–2015) with 40 998 participants were analyzed to assess the association between education and lifetime CVD risk.³⁷ Compared with college graduates, those with less than high school or high school completion had higher lifetime CVD risks. For middle-aged men, the HRs for a CVD event were 1.58 (95% CI, 1.38–1.80), 1.30 (95% CI, 1.10–1.46), and 1.16 (95% CI, 1.00–1.34) for those with less than high school, high school, and some college, respectively. For females, the HRs were 1.70 (95% CI, 1.49–1.95), 1.19 (95% CI, 1.05–1.35), and 0.98 (95% CI, 0.83–1.15).
- In a cross-sectional analysis of 6424 adults with diabetes from the 2019 and 2020 NHIS, 13.3% were identified as food insecure.³⁸ Adults with food insecurity were more likely to have ASCVD than food-secure adults (28.9% versus 23.7%; $P=0.008$). After adjustment for traditional CVD risk factors, all levels of food insecurity were associated with ASCVD compared with food security (marginal security: OR, 1.60 [95% CI, 1.18–2.18]; low security: OR, 2.09 [95% CI, 1.58–2.74]; very low security: OR, 1.69 [95% CI, 1.22–2.34]; $P=0.001$).
- According to data from a nationally representative sample of Canadian adults ($N=289\,800$), lower socioeconomic position was associated with 2.5 times increased odds of CVD morbidity and mortality (OR, 2.52 [95% CI, 2.28–2.76]).³⁹ Modifiable risk factors, including smoking, physical inactivity, obesity, diabetes, and hypertension, mediated 74% of associations between socioeconomic position and CVD morbidity and mortality.
- Among older adults in the NIH-AARP Diet and Health Study, the highest tertile of neighborhood socioeconomic deprivation in 1990 and 2000 compared with the lowest tertile was associated with a higher risk of CVD mortality (aHR for males, 1.47 [95% CI, 1.40–1.54]; aHR for females, 1.78 [95%

had higher CVD risk, measured with the FRS (OR, 1.84 [95% CI, 1.21–2.45]), than those in the lowest quartile.⁴¹

- Being divorced/separated or widowed or living alone was associated with a higher CVD risk (HR, 1.21 [95% CI, 1.08–1.35]) compared with being married or cohabitating in the Swedish Twin Registry (N=10 058; median follow-up, 9.8 years).⁴²
- Among Black adults and White adults in the ARIC study, residence in the lowest quartile of neighborhood socioeconomic status during young, middle, and older adulthood was associated with 18% (HR, 1.18 [95% CI, 1.02–1.36]), 21% (HR, 1.21 [95% CI, 1.04–1.39]), and 12% (HR, 1.12 [95% CI, 0.99–1.26]) higher risk of total CVD, respectively, compared with residence in the highest quartile.⁴³
- In a cross-sectional analysis of data on 387 044 adults in the 2016 to 2019 BRFSS, 9% had self-reported ASCVD (CHD or stroke).⁴⁴ Female sex, household income below \$75 000, unemployment, and challenges with health care access were significantly associated with a higher burden of comorbidities (hypertension, hyperlipidemia, diabetes, current cigarette smoking, and CKD) among those with ASCVD. An analysis using the CDC WONDER database to examine sex- and race-based differences in cardiovascular mortality from 1999 to 2019 determined that the age-adjusted mortality in Black females and White females declined over the observation years (from 602.1 and 447.0 per 100 000 population in 2009, respectively, to 351.8 and 267.5 per 100 000 population in 2019, respectively).⁴⁵ Cardiovascular mortality rates decreased for Black males from 824.1 in 1999 to 526.3 per 100 000 population in 2019 and in White males from 637.5 in 1999 to 396.0 per 100 000 population in 2019. The rate ratio for cardiovascular mortality in 2019 was 1.32 (95% CI, 1.30–1.33) for Black females and 1.33 (95% CI, 1.32–1.34) for Black males relative to their White counterparts.

Psychological Health

- In a study of 853 participants from the ATTICA study 1.75–3.23) higher risk of developing irrational beliefs and and total antioxidant association.
- A prospective of age from the WHI free of MI, stroke, or after adjustment for health behaviors, and loneliness were 1.03–1.12) and 1.05 risk of CVD, tion and high 1.13 (95% CI, 1.06–
- In a cross-sectional to 2018 NHANES of age (n=10 588) age (n=16 848), Patient Health associated with 10- by the PCE.⁴⁸ The among those with major depression no depression years of age to 79 years of age, higher among those and major with no depression risk was higher to 39 years of age depression ($P<0.001$).
- In a cross-sectional record data of 591 care in Minnesota and 2018, those with illness (bipolar affective disorder) had 9.44% [95% CI, out serious mental 7.97%–8.02%]).⁴⁹ significantly higher in illness (25% in the with those without $P<0.001$). In a dataset, patients with 10-year CVD risk 30-year CVD risk than those with controlled

current depression also had higher 10-year CVD risk ($b=0.55$ [95% CI, 0.37–0.73]) and 30-year CVD risk (OR, 1.56 [95% CI, 1.48–1.65]) than those without depression.

Risk Prediction

- Among 6434 participants from the MESA, a social disadvantage score was created that was based on household income, educational attainment, single-living status, and experience of lifetime discrimination.⁵¹ Over a median follow-up of 17.0 years, there were 775 incident ASCVD events and 1573 deaths. Increasing social disadvantage score was significantly associated with incident ASCVD (HR per 1-unit increase, 1.15 [95% CI, 1.07–1.24]) and all-cause mortality (HR per 1-unit increase, 1.13 [95% CI, 1.08–1.19]) after adjustment for traditional risk factors. However, adding the social disadvantage score to the PCE did not significantly improve discrimination ($P=0.208$) or reclassification ($P=0.112$) of 10-year ASCVD risk.
- In a cross-sectional study of 11 937 adults from NHANES 2003 to 2018, total TyG index, TyG-WC, TyG–waist-to-height ratio, and TyG-BMI were significantly and positively associated with CVD and CVD mortality.⁵² TyG–waist-to-height ratio was the strongest predictor of CVD mortality (HR, 1.66 [95% CI, 1.21–2.29]). TyG index correlated most strongly with CHD risk (OR, 2.52 [95% CI, 1.66–3.83]), whereas TyG-WC correlated most strongly with total CVD (OR, 2.37 [95% CI, 1.77–3.17]), congestive HF (OR, 2.14 [95% CI, 1.31–3.51]), and AP (OR, 2.38 [95% CI, 1.43–3.97]). TyG–waist-to-height ratio correlated most strongly with MI (OR, 2.24 [95% CI, 1.45–3.44]).
- The DIAL2 was updated using data from 467 856 people with type 2 diabetes without a history of CVD from the Swedish National Diabetes Register.⁵³ The updated DIAL2 model was recalibrated for Europe's low- and moderate-risk regions and externally validated in 218 267 individuals with type 2 diabetes from the Scottish Care Information–Diabetes and Clinical Practice Research Datalink. The DIAL2 model demonstrated good discrimination, with C indices of 0.732 (95% CI, 0.726–0.739) in Clinical Practice Research Datalink and 0.700 (95% CI, 0.691–0.709) in Scottish Care Information–Diabetes, providing a useful tool for predicting CVD-free life expectancy and lifetime CVD risk for people with type 2 diabetes without previous CVD in the European low- and moderate-risk regions.
- The PREVENT equations are risk prediction tools that estimate the 10- and 30-year risk of total CVD, which includes both ASCVD and HF, in adults 30 to 79 years of age.⁵⁴ The base equation

includes age, sex, non-HDL-SBP, antihypertensive status, diabetes, and eGFR competing risk of non-CVD add-on equations offer include urine ACR and indicated for measurement, or of health, such as the Social when available. The on) model performance

accuracy and precision in external validation for the composite of CVD (median C statistics ranging from 0.757–0.813; median calibration slopes ranging from 0.94–1.05).

- A validation study of the PREVENT equations among 6 612 004 US adults 30 to 79 years of age without known CVD observed that median C statistics for CVD were 0.794 (interquartile range, 0.763–0.809) in females and 0.757 (interquartile range, 0.727–0.778) in males.⁵⁵ The calibration slopes were 1.03 (interquartile range, 0.81–1.16) and 0.94 (interquartile range, 0.81–1.13) among females and males, respectively. Adding urine ACR, HbA1c, and Social Deprivation Index together to the base model slightly improved discrimination (ΔC statistic, 0.004 [interquartile range, 0.004–0.005] and 0.005 [interquartile range, 0.004–0.007] among females and males, respectively).

Calibration improved significantly when the urine ACR was added to the base model for those with marked albuminuria (>300 mg/g; 1.05 [interquartile range, 0.84–1.20] versus 1.39 [interquartile range, 1.14–1.65] in the base model without urine ACR; $P=0.01$).

- In a meta-analysis of studies assessing the performance of the FRS, ATP III score, and PCE score

Northern California between PCE overestimated ASCVD

- SCORE2, a risk prediction 45 cohorts in 13 European adults, 30 121 CVD events), the 10-year risk of fatal and adults 40 to 69 years of age betes or CVD, and C indices CI, 0.65–0.68) to 0.81 (95% the countries.⁵⁹ Furthermore, for predicting 10-year risk of CVD, the pooled ratio of observed number of CVD events within 10 years to the expected number of events varied in score/sex strata from 0.58 (95% CI, 0.43–0.73) for the FRS in males to 0.79 (95% CI, 0.60–0.97) for the ATP III score in females. In other words, these equations overestimated the number of events over 10 years by as little as 3% and as much as 57%, depending on sex and equation.⁵⁶
 - The addition of walking pace (change in C index: PCE score, +0.0031; SCORE, +0.0130), grip strength (PCE score, +0.0017; SCORE, +0.0047), or both (PCE score, +0.0041; SCORE, +0.0148) improved 10-year CVD risk prediction in the UK Biobank (N=406 834).⁵⁷
 - In an analysis of electronic health record data from

Persons risk prediction algorithm was developed to estimate 5- and 10- year risk of CVD among adults >65 years of age without preexisting ASCVD from the Cohort of Norway (28 503 individuals, 10 089 CVD events) with C indices ranging between 0.63 (95% CI, 0.61–0.65) and 0.67 (95% CI, 0.64–0.69) in 4 geographic risk regions in Europe.⁶⁰

- Among 6701 participants in MESA who were free of ASCVD during a median follow-up of 13.2 years for ASCVD and 12.5 years for ASCVD-CAC, 2 novel LDL-C calculations, LDL_{Martin} and LDL_{Sampson}, did not underestimate or overestimate ASCVD risk compared with the traditional LDL_{Friedewald} equation in primary prevention using AHA/ACC guidelines.⁶¹ However, the LDL_{Friedewald} equation underestimated ASCVD risk in adults who were at low risk.

- Higher LTPA promotes cardiovascular wellness. Higher LTPA was associated with lower ASCVD risk (aHR per 1-SD higher LTPA, 0.91 [95% CI, 0.86–0.96]). The addition of LTPA did not improve the performance of the PCE among 18 824 adults in 3 prospective cohort studies (MESA, ARIC, and CHS).⁶² There was no difference in PCE risk discrimination (C statistic, 0.76–0.78) and risk calibration (all $\chi^2 P > 0.10$) across 4 LTPA groups (inactive, less than guideline recommended, guideline recommended, and greater than guideline recommended).

- A pooled analysis of data from 4 cohort studies, 147 645 individuals from 21 countries in the PURE study and 40 countries in 3 prospective studies, demonstrated that the association between fish intake and risk of major CVD events varied by CVD status, with a lower risk found among those with established vascular disease but not in general populations (for major CVD, $I_2=82.6$, $P=0.02$; for death, $I_2=90.8$, $P=0.001$).⁶³ Furthermore, among 3 cohorts of patients with vascular disease, risk of major CVD (aHR, 0.84 [95% CI, 0.73–0.96]) was lower among those with intakes of ≥ 175 g/wk (or ≈ 2 servings/ wk) compared with ≤ 50 g/mo.

- Including a history of APO (placenta previa, pre-term delivery, placenta abruption, stillbirth, abortion, 56 130 Asian individuals pregnancy-induced hypertension/preeclampsia,

Filipino, Vietnamese, Japanese, and other Asian) and 19 760 Hispanic individuals

(Mexican, Puerto Rican, and other Hispanic) who received care in

gestational diabetes, and ectopic pregnancy) in the FRS enhanced the prediction of CVD among 4013 females in the Tehran Lipid and Glucose

Study compared with the original FRS that included traditional CVD risk factors (C statistic difference, 0.0053).⁶⁴ Females who had a history of multiple APOs had a higher CVD risk compared with those with 1 or no adverse pregnancy outcomes (1 APO: aHR, 1.22 [95% CI, 1.01–1.47]; 2 APOs: aHR, 1.94 [95% CI, 1.54–2.51]; ≥3 APOs: aHR, 2.48 [95% CI, 1.51–4.07]). Among 95 465 ever-gravid females who participated in the Nurses' Health risk for CVD (aHR, 1.21 [95% CI, 1.10–1.33]) over a mean follow-up of 23.10 years.⁶⁵

22 [Cardiomyopathy and Heart Failure], and 25 [Peripheral Artery Disease and Aortic Diseases]).• The performance of an ASCVD GRS for the pre- diction of ASCVD incidence has been evaluated.⁷⁰ In ancestrally diverse populations from the ARIC, MESA, and UK Biobank studies, improved pre- diction of ASCVD for White populations, African **Borderline Risk Factors/Subclinical/ Unrecognized Disease**

for self-identified White individuals, 2.5% (95% CI, 0.6%–4.3%) for Black/African American/Black Caribbean/Black African individuals, and 8.7% (95% CI, 3.1–14.4) for individuals of South Asian descent.

- Among 2119 participants in the Framingham Offspring Cohort study, the aHR for CVD events

Prevention

among those with concurrent high central pulse pressure and high carotid-femoral PWV compared with those with concurrent low central pulse pressure and low carotid-femoral PWV was 1.52 (95% CI, 1.10–2.11).⁶⁶

- Among 1005 patients with known CAD who had 2 CCTA scans in the PARADIGM study, those with a high ASCVD risk score (>20%) had a larger average annual increase in total plaque (1%) compared with those with an intermediate ASCVD risk score (7.5%–20% risk; 0.6% increase of total plaque; $P<0.001$) or low ASCVD risk score (<7.5% risk; 0.5% increase in total plaque; $P<0.001$).⁶⁷

- Among 1849 females participating in the Mexican Teachers' Cohort living in Chiapas, Yucatán, or Nuevo León who were sampled to be included in an ancillary study on CVD, having a family member incarcerated was associated with an

OR of 1.41 (95% CI, 1.04–2.00) for carotid atherosclerosis (mean left or right IMT ≥ 0.8 mm or plaque). This OR was adjusted for age, site, and demographic variables such as indigenous background, education, and marital status, as well as exposure to violence.⁶⁸ • Among individuals ≥ 45 years of age participating in the CORE-Thailand registry, having a low ABI <0.9 was associated with a 49% increased (OR, 1.49 [95% CI, 1.08–2.08]) risk of a decline in glomerular filtration rate >40%, eGFR <15 mL·min⁻¹·1.73 m⁻², doubling of serum creatinine, or initiation of dialysis.⁶⁹

Genetics and Family History

- Genetic contributors to the end points that make up total CVD are described elsewhere (see Chapters 8 [High Blood Pressure], 15 [Stroke (Cerebrovascular Diseases)], 21 [Coronary Heart Disease, Acute Coronary Syndrome, and

(See Chapter 2 [Cardiovascular Health] for more detailed statistics on healthy lifestyle and low risk factor levels.)

- Good adherence to CPAP use among adults with OSA is associated with an HR of 0.69 (95% CI, 0.52 with 0.92) compared to nonuse and poor adherence among adults with OSA for whom CPAP was recommended.⁷¹
- High adherence to a healthy reference diet, which emphasizes the intake of healthy foods, was associated with 14% and 12% lower risks of CVD (HR_{Q4vsQ1}, 0.86 [95% CI, 0.78–0.94]) and CHD (HR_{Q4vsQ1}, 0.88 [95% CI, 0.78–1.00]).⁷²
- According to data from NHANES, REGARDS, and RCTs on BP-lowering treatments, it is estimated that achieving the 2017 ACC/AHA BP goals could prevent 3.0 (uncertainty range, 1.1– 5.1) million CVD events (CHD, stroke, and HF) compared with achieving prior BP goals from the 2003 Seventh Joint National Committee Report and the 2014 Eighth Joint National Committee. However, achieving the 2017 ACC/AHA BP goals could also increase serious adverse events by 3.3 (uncertainty range, 2.2–4.4) million.⁷³
- Comparison of 3 healthy eating patterns over a total 52-week period in youths 9 to 18 years of age with BMI >95th percentile, including the AHA, Mediterranean, and plant-based diets, identified significant differences in compliance and CVD risk factors.⁷⁴ The plant-based diet was associated with best compliance (81% for plant-based compared with 62% for AHA and 56% for Mediterranean; $P<0.001$). At 52 weeks of follow-up, all 3 healthy eating patterns were associated with improvement in TC, LDL-C, fasting glucose, myeloperoxidase, and WC. Median changes in BMI were not significant at 52 weeks.

- A meta-analysis of the CVD abv has demonstrated DBP (WMD, -4.56 mm Hg -2.75] and WMD, -3.39 mm to -1.76], respectively), BMI [95% CI, -1.05 to -0.10], -0.14 [95% CI, -0.24 to (WMD, -7.59 mg/dL [95% CI,

CVD reported taking no prevention of CVD.⁷⁸

- Among 202 072 participants in the PURE study followed which included participants ORs for treatment with ondary prevention of CVD in with males varied by agent. in females compared with males was 0.65 (95%

CI, 0.69–0.72) for antiplatelet drugs, 0.93 (95% CI, 0.83–1.04) for β -blockers, 0.86 (95% CI, 0.77–

0.96) for ACE inhibitors or ARBs, and 1.56 (95% CI, 1.37–1.77) for diuretics. These ORs were adjusted for age, education, urban versus rural location, and INTERHEART risk score.⁷⁹

- Among 284 954 privately insured and Medicare Advantage enrollees from the OptumLab Data Warehouse database at least 21 years of age with an incident ASCVD event between 2007 and 2016, the use of statins increased modestly from 50.3% in 2007 to 59.9% in 2016; the use of high-intensity statins increased from 25% to 49.2% with an associated slight increase in statin intolerance from 4% in 2007 to 5% in 2016 among patients after stroke or TIA in receipt of high-intensity statin; the out-of-pocket costs for a 30-day supply of statins fell from \$20 to \$2; and the 1-year cumulative risk for a major cardiac adverse event decreased from 8.9% to 6.5%. However, among females and Black

[95% CI, -1.59 to -0.49]), as well as increased variability of SBP ($\beta=0.27$ [95% CI, 0.00–0.54]). No significant effect of intensive lifestyle intervention was found on the variability of DBP ($\beta=-0.08$ [95% CI, -0.22

Awareness, Treatment, and Control

- According to a systematic review and meta-analysis of the effects of α -linolenic acid supplementation (flaxseed, walnuts, perilla) on CVD risk, among 1183 individuals, compared with placebo, dietary α -linolenic acid supplementation significantly reduced CRP concentration (SMD, -0.38 mg/L [95% CI, -0.72 to -0.04]), tumor necrosis factor- α concentration (SMD, -0.45 pg/mL [95% CI, -0.73 to -0.17]), triglyceride in serum (SMD, -4.41 mg/dL [95% CI, -5.99 to -2.82]), and SBP (SMD, -0.37 mm Hg [95% CI, -0.66 to -0.08]) but led to a significant increase in LDL-C concentrations (SMD, 1.32 mg/dL [95% CI, 0.05–2.59]).⁷⁶ α -Linolenic acid supplementation had no significant effect on interleukin-6, DBP, TC, or HDL-C (all $P \geq 0.05$). Subgroup analysis revealed that α -linolenic acid

LDL-C according to a post hoc secondary analysis from the Look AHEAD study.⁷⁷ Intensive lifestyle intervention, 175 min/wk of supervised individual or group PA sessions among individuals 53 to 66 years of age, was associated with reduced variability of fasting blood glucose ($\beta=-1.49$ [95% CI, -2.39 to -0.59]), TC ($\beta=-1.12$ [95% CI, -1.75 to -0.48]), and LDL-C ($\beta=-1.04$

Mortality

(See Tables 14-1 through 14-3 and Charts 14-2 through 14-13)

ICD-10 I00 to I99 for CVD; C00 to C97 for cancer; C33 to C34 for lung cancer; C50 for breast cancer; J40 to J47 for chronic lower respiratory disease; G30 for AD; E10 to E14 for diabetes; and V01 to X59 and Y85 to Y86 for accidents.

to 0.05]).	• Deaths attributable to diseases of the heart
(Chart	
• Among 5246 individuals from rural China participating in the MIND-China study, the prevalence of CVD was 35%. CVD was defined as the presence of ischemic HD, HF, AF, or stroke from a combination of self-reported medical history, ECG, and a neurological examination. Among those with prevalent CVD, the most commonly used	therapies were calcium channel blockers (17.7%), traditional Chinese medicine products (16.7%), antithrombotic agents (14.0%), and lipid-lowering agents (9.4%). Approximately 50% of participants with prevalent

14-2) and CVD (Chart 14-3) in the United States increased steadily during the 1900s to the 1980s, declined into the 2010s, but increased again in the later 2010s to 2022.

- CHD (39.5%) was the leading cause of CVD death in the United States in 2022, followed by stroke (17.6%), other minor CVD causes combined (17.0%), HBP (14.0%), HF (9.3%), and diseases of the arteries (2.6%; Chart 14-4).
- In 2022, 941 652 US deaths were attributable to CVD (Table 14-1). The age-adjusted death rate

attributable to CVD did not change from 224.3 per 100 000 people in 2012 to 224.3 per 100 000 in 2022 (unpublished NHLBI tabulation using CDC WONDER⁸¹). The AAMRs for 2022 by sex, ethnicity, and race are available

- On the basis of 2022 mortality data (unpublished NHLBI tabulation using the NVSS⁸²):
 - HD and stroke currently claim more lives each year than cancer and chronic lower respiratory disease combined. In 2022, 206.8 of 100 000 people died of HD and stroke.
 - In 2022, 3 279 857 resident deaths were registered in the United States, which is 184 374 fewer deaths than in 2021. Of all registered deaths, the 10 leading causes accounted for 72.3%. The 10 leading causes of death in 2022 were the same as those in 2021. From 2021 to 2022, 9 of the 10 leading causes of death had an decrease in age-adjusted death rates. The age-adjusted rate decreased 3.8% for HD, 2.9% for cancer, 1.1% for unintentional injuries, 57.3% for COVID-19, 3.9% for stroke, 1.2% for chronic lower respiratory diseases, 6.8% for AD, 5.1% for diabetes, and 4.8% for chronic liver disease and cirrhosis.

The age-adjusted death rates increased 1.5% for kidney disease.⁸³

- CHD accounted for 371 506 (39.5%) of the total 941 652 CVD deaths in 2022 (unpublished age categories is shown in Table 14-2.
- The percentages of total deaths caused by CVD and other leading causes by race and ethnicity are presented in Charts 14-5 through 14-8.
- The number of CVD deaths per year for all males and females in the United States declined from 1980 to 2010 but increased in recent years from 783 475 in 2011 to 941 652 in 2022 (Chart 14-9).

2 to 3 times higher among individuals with stated additional risk factors than among individuals without additional stated risk factors. MACE rates are highest in the first 1 to 2 years after

Complications

- Among 392 participants in the National Health and Aging Trends Study who were at least 65 years of age and functionally independent at baseline, 23.8% of those with CVD at baseline experienced rapid functional decline compared with 16.2% of those without CVD at baseline. The Short Physical Performance Battery was used to assess physical function.⁸⁵
- In a meta-analysis of 18 studies (N=4858 patients) in patients with COVID-19 conducted from November 2019 through April 2020, the OR for severe COVID-19 in those with preexisting CVD compared with those without CVD was 3.14 (95% CI, 2.32–4.24). The meta-analysis included both cohort and case-control studies from China (16 studies) and the United States (2 studies).⁸⁶
- In a meta-analysis of 25 studies of individuals diagnosed with COVID-19 (65 484 individuals), the authors

Although the number of CVD deaths per year was greatest among females between 1984 and 2013, beginning in 2013, CVD deaths in males exceeded the number of CVD-related deaths in females.

- The age-adjusted death rates per 100 000 people for CVD, CHD, and stroke differ by US state (Table 14-3) and globally (Charts 14-10 through

Health Care Use: Hospital Discharges/ Ambulatory Care Visits

(See Chart 14-14)

- From 2011 to 2021, the number of inpatient discharges from short-stay hospitals with CVD as the principal diagnosis decreased from ≈5.2 million to 4.7 million. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *ICD-9* to *ICD-10*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years (unpublished NHLBI tabulation using HCUP⁸⁸).
14-13).
- Among individuals with additional risk factors associated with increased CVD risk (eg, patients with diabetes and target organ damage, CKD stages 3 to 4, index CVD-related event within 2 years after prior MI or ischemic stroke, and polyvascular disease), risk for MACEs (ie, composite of MI, ischemic stroke, and cardiovascular-related death) persists after initial MI or ischemic stroke despite the use of moderate- or high-intensity statins.⁸⁴ Compared with the overall population, risks for incident MI were

charges for CVD in the United States increased in the first decade and then began to generally decline in the second decade (Chart 14-14).

- In 2019, there were 106 381 000 physician office visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NAMCS⁸⁹).

In 2021, there were 6 867 805 ED visits and 4 741 970 hospital inpatient discharges with a primary diagnosis of CVD (unpublished NHLBI tabulation using HCUP⁸⁸).

- Between 2008 and 2018, there was an increasing trend in hospitalization to 5 million per year.⁹⁰ The hospitalization rates have been increasing in CVD hospitalization rates in adults and Hispanic US

Cost

(See Chapter 28 [Economic Cardiovascular Disease] for information.)

- The estimated direct and indirect costs of CVD in the United States from 2020 to 2021 was \$417.9 billion (NHLBI tabulation).
- Type 2 diabetes accounts for 10% of diabetes in the United States in adults >45 years of age.⁹² Health care costs were assessed with data from Analytics' MarketScan supplemental databases, between January 1, 2014, and December 31, 2018. Cost of CVD-related type 2 diabetes was \$15,000 with CVD in the type 2 diabetes group. Average all-cause health care costs baseline is \$38,985 with costs of \$35,260 per patient with type 2 diabetes experiencing a TIA, stroke).
- According to microsimulations modeling, underestimation of costs with higher health care costs for 1000 patients and 11.8 CVD deaths that might have been avoided.

454.0 [95% UI, 402.5–501.5]). In high-income Asia Pacific, the age-standardized rate of CVD was 431.0 [95% UI, 384.8–477.2], respectively. The highest age-standardized rate was in Uzbekistan (577.2 [95% UI, 501.5–652.9]), followed by Azerbaijan and Turkey with the lowest rate was 19.9–27.3], with a difference between the highest and

- A systematic review and meta-analysis of the global age-standardized CVD mortality.⁹⁵ The pooled rate of premature CVD was 96.04 per 100,000 (95% CI, 11.27–21.51). Subgroup analyses of standardized mortality rates (CI, 11.27–21.51) compared [95% CI, 8.09–18.91], males (23.69–59.37) compared with [95% CI, 9.61–25.81], and females (90.58 [95% CI, 56.40–114.66] with high-income countries (15.63–29.37)).
- Death rates for CVD, CHD, and stroke in selected countries in 2020 are 14–10 through 14–13.
- CVD mortality and prevalence in world regions. In 2021, based on territories⁹⁶:
–19.41 (95% UI, 17.78–20.67) were estimated for CVD to an increase of 18.51% (24.19%) from 2010. The death rate per 100,000 (95% UI, 214.64–250.52).

Global Burden

Table 14-1; Charts 14-10 through 14-13, 14-15, and 14-16; and Supplemental Material

- According to an updated analysis of the GBD Study 1990 to 2019, the age-standardized rates of DALYs and death attributed to metabolic disease decreased by 28% (95% UI, 23.8%–

32.5%) and 30.4% (95% UI, 26.6%–34.5%), respectively, from 1990 to 2019.⁹⁴ The age-standardized rate of DALYs for metabolic-attributed CVD was 3573.4 (95% UI, 3240.3–3870.5) per 100,000 population in 1990 and was 176.1 (95% UI, 156.2–192) per 100,000 popula-

- a decrease of –14.55% (95% UI, –18.73% to –10.55%) from 2010. There were 612.06 (95% UI, 570.32–649.81) million prevalent cases of CVD in 2021, an increase of 33.46% (95% UI, 30.72%–36.68%) compared with 2010. The age-standardized prevalence rate was 7178.73 (95% UI, 6696.15–7620.67) per 100,000, an increase of 1.38% (95% UI, –0.58% to 3.55%) from 2010. (Table 14-4).
- The highest mortality rates estimated for CVD among regions were for Central Asia and Eastern Europe, with high levels also seen for Oceania, North Africa and the Middle East, and central sub-Saharan Africa. Rates were lowest for high-income Asia Pacific and Australasia (Chart 14-15).
 tion in 2019, a 30.4% (95% UI, 26.6%–34.5%) decline. In 2019, the Central Asia region showed the highest age-standardized rates of DALYs and deaths (8507.1 [95% UI, 7677.8–9386.5] and

- CVD prevalence among regions was estimated as highest for North Africa and the Middle East followed by Eastern Europe and Central Asia.

Prevalence was lowest for high-income Asia Pacific and Southeast Asia (Chart 14-16).

- CVD represents 37% of deaths in individuals <70 years of age that are attributable to

• In 2019, 27% of the world's deaths were caused by CVD, making it the predominant cause of death globally.⁹⁷

- See the Supplemental Material for additional global and regional CVD

Table 14-1. CVDs in the United States

Population group	Total CVD prevalence,* 2017–2020: ≥20 y of	Prevalence, 2017–2020: ≥20 y of age†	Mortality, 2022: all ages‡	Age-adjusted mortality rates per 100 000 (95% CI),‡ 2022
Both sexes	127 900 000 (48.6%)	28 600 000 (9.9%)	941 652	224.3 (223.8–224.8)
Males	65 400 000 (52.4%)	14 800 000 (10.9%)	494 740 (52.5%)§	273.9 (273.1–274.7)
Females	62 500 000 (44.8%)	13 800 000 (9.2%)	446 912 (47.5%)§	183.1 (182.6–183.7)
NH White males	51.2%	11.3%	371 064	277.8 (276.9–278.7)
NH White females	44.6%	9.2%	338 610	186.2 (185.5–186.8)
NH Black males	58.9%	11.3%	64 606	379.7 (376.5–382.8)
NH Black females	59.0%	11.1%	58 860	246.9 (244.8–248.9)
Hispanic males	51.9%	8.7%	37 257	202.4 (200.2–204.6)
Hispanic females	37.3%	8.4%	30 676	133.0 (131.4–134.5)
NH Asian males	51.5%	6.9%	14 106	154.7 (152.1–157.3)
NH Asian females	38.5%	4.9%	13 150	104.9 (103.1–106.7)
NH American Indian/Alaska	...	...	4874	193.3 (187.8–198.9)
NH Native Hawaiian or			1421	245.8 (232.7–258.9)

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.⁹⁸

COVID-19 indicates coronavirus disease 2019; CVD, cardiovascular disease; ellipses (...), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Total CVD prevalence includes coronary heart disease, heart failure, stroke, and hypertension. CVD prevalence rates do not include peripheral artery disease (PAD) because the ankle-brachial index measurement used to ascertain PAD was discontinued after the NHANES 2003 to 2004 cycle.

†Prevalence excluding hypertension.

‡Mortality for Hispanic people, American Indian or Alaska Native people, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native decedents, Asian and Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

§These percentages represent the portion of total CVD mortality that is attributable to males versus females.

||Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES¹; Percentages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population estimates. Mortality (for underlying cause of CVD): Unpublished NHLBI tabulation using CDC Wonder⁸¹ and National Vital Statistics System.⁸² These data represent underlying cause of death only for *International Classification of Diseases, 10th Revision* codes I00 to I99 (diseases of the circulatory system).

Table 14-2. CVD and Other Major Causes of Death: All Ages, <85 Years of Age, and ≥85 Years of Age, by Sex, 2022

Cause	ICD-10 code	Total deaths	Deaths, <85 y of age
CVD	I00–I99	941 652	600 457
Males		494 740	361 069
Females		446 912	239 388
HD	I00–I09, I11, I13, I20–I51	702 880	454 071
Males		386 766	283 868
Females		316 114	170 203
Cancer	C00–C97	608 371	506 309
Males		319 336	269 772
Females		289 035	236 537
COVID-19	U07.1	186 552	133 481
Males		102 660	77 174
Females		83 892	56 307
Accidents	V01–X59, Y85–Y86	227 039	199 946
Males		151 629	140 159
Females		75 410	59 787
Stroke	I60–I69	165 393	97 683
Males		71 819	49 764
Females		93 574	47 919
CLRD	J40–J47	147 382	110 035
Males		69 004	54 086
Females		78 378	55 949

Deaths with age not stated are not included in the totals.

AD indicates Alzheimer disease; CLRD, chronic lower respiratory disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; HD, heart disease; and ICD-10, *International Classification of Diseases, 10th Revision*.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.⁸²

Table 14-3. Age-Adjusted Death Rates per 100 000 People for CVD, CHD, and Stroke, by US State, 2022

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change,	Rank	Death rate	% Change,	Rank	Death rate	% Change, 2012–2022
Alabama	49	307.1	4.3	15	76.6	–22.4	49	51.1	3.4
Alaska	7	195.5	2.7	10	71.2	–5.9	19	35.1	–17.5
Arizona	13	201.6	3.5	23	83.2	–17.8	17	34.5	15.4
Arkansas	48	290.0	2.0	51	126.3	–6.5	43	46.0	–6.4
California	15	203.2	–2.3	20	80.7	–21.1	29	39.8	12.5
Colorado	3	178.3	1.6	3	63.0	–13.7	15	33.8	3.6
Connecticut	5	183.1	–6.3	6	67.2	–22.3	9	30.1	11.5
Delaware	32	229.4	5.0	27	86.6	–21.8	51	56.9	48.9
District of Columbia	37	243.6	–8.7	46	109.8	–20.6	34	42.1	24.6
Florida	14	202.0	1.7	24	85.2	–16.4	41	45.1	46.9

(Continued)

Table 14-3. Continued

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change,	Rank	Death rate	% Change,	Rank	Death rate	% Change, 2012–2022
Georgia	39	246.8	2.6	8	68.1	–16.3	39	44.0	5.3
Hawaii	4	182.8	1.0	9	68.6	–0.6	28	39.5	12.1
Idaho	17	204.4	0.2	14	75.5	–11.3	16	34.4	–7.4
Illinois	30	225.5	0.0	13	75.4	–26.9	32	41.4	9.9
Indiana	38	244.9	–1.5	31	91.5	–18.9	33	41.9	–1.9
Iowa	31	228.2	2.8	37	99.6	–16.5	12	32.0	–6.0
Kansas	35	232.8	4.6	32	94.5	5.2	22	35.8	–9.1
Kentucky	44	270.7	0.2	43	105.2	–12.4	36	42.9	–3.1
Louisiana	47	288.1	5.2	42	103.2	–7.4	48	50.2	14.4
Maine	23	212.3	9.4	25	85.8	2.8	6	29.4	–14.1
Maryland	26	216.2	–4.2	22	81.6	–25.8	38	43.8	19.8
Massachusetts	1	171.8	–5.7	1	60.6	–25.2	2	25.6	–9.6
Michigan	43	269.4	6.3	47	113.2	–13.5	40	44.2	18.4
Minnesota	2	175.3	4.3	2	61.3	–7.8	11	31.8	–3.5
Mississippi	51	327.7	7.3	48	120.1	0.6	50	54.2	12.2
Missouri	40	254.3	1.1	44	105.7	–15.1	26	39.1	–7.5
Montana	19	207.0	3.8	35	96.8	14.2	3	26.5	–20.1
Nebraska	25	214.4	6.3	7	68.1	–11.6	20	35.1	0.8
Nevada	41	255.9	4.6	39	102.0	4.1	30	40.0	16.5
New Hampshire	6	191.4	1.9	11	74.3	–20.0	10	30.3	3.6
New Jersey	8	197.2	–10.7	12	75.0	–30.8	8	30.0	–8.4
New Mexico	22	209.3	8.5	41	103.0	6.3	25	38.1	25.9
New York	11	200.4	–12.6	40	102.6	–23.3	1	24.5	–7.8
North Carolina	34	231.5	2.5	26	86.1	–14.7	47	47.7	11.5
North Dakota	12	201.5	–3.3	16	78.3	–20.8	13	32.8	–12.0
Ohio	42	259.4	4.7	36	99.4	–14.5	45	46.5	12.8
Oklahoma	50	312.9	10.2	45	107.0	–27.6	27	39.5	–13.7
Oregon	24	212.4	14.2	4	65.1	–7.5	46	47.1	25.6
Pennsylvania	29	224.6	–2.4	28	87.0	–19.9	23	36.6	–2.3
Rhode Island	16	204.0	–1.2	33	94.7	–20.3	5	29.2	–4.5
South Carolina	36	241.6	–0.5	19	80.4	–19.2	42	45.6	–0.6
South Dakota	21	208.7	–0.7	38	101.7	–8.3	14	33.1	–11.4
Tennessee	46	284.8	6.6	50	124.7	–11.0	44	46.4	3.5
Texas	33	230.0	0.9	30	89.9	–12.0	35	42.3	1.3
Utah	20	207.7	6.8	5	65.1	–5.3	18	34.6	–8.3
Vermont	18	206.6	2.8	34	96.2	–2.0	4	27.1	–24.4
Virginia	27	216.4	0.8	18	80.3	–9.4	31	41.2	1.3
Washington	9	197.3	4.2	21	81.1	–7.2	24	36.7	6.9
West Virginia	45	273.5	–1.5	49	121.8	–6.6	37	43.4	–9.5
Wisconsin	28	218.8	3.1	29	88.9	–7.2	21	35.3	–2.1
Wyoming	10	200.3	–7.5	17	78.4	–21.3	7	29.8	–14.6
Total United		224.3	0.0		87.6	–16.9		39.5	7.2

Rates are per 100 000 people. *International Classification of Diseases, 10th Revision* codes used were I00 to I99 for CVD, I20 to I25 for CHD, and I60 to I69 for stroke. CHD indicates coronary heart disease; and CVD, cardiovascular disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.^{a2}

Table 14-4. Global Mortality and Prevalence of CVD by Sex, 2021

	Both sexes		Male	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	19.41 (17.78 to 20.67)	612.06 (570.32 to 649.81)	10.24 (9.52 to 10.97)	307.99 (286.99 to 328.53)
Percent change (%) in	57.46 (48.32 to 67.12)	111.38 (107.59 to 115.51)	68.27 (54.53 to 81.65)	114.40 (110.50 to 118.99)
Percent change (%) in	18.51 (12.42 to 24.19)	33.46 (30.72 to 36.68)	19.76 (11.27 to 28.62)	32.88 (29.79 to 36.31)
Rate per 100 000, age standardized, 2021	235.18 (214.64 to 250.52)	7,178.73 (6,696.15 to 7,620.67)	281.11 (259.77 to 301.13)	7,666.88 (7,159.91 to 8,166.57)
Percent change (%) in rate, age	−34.33 (−37.79 to −30.75)	0.88 (−0.64 to 2.69)	−30.05 (−35.23 to −24.87)	0.44 (−1.13 to 2.30)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. CVD indicates cardiovascular disease; GBD, Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁹⁶

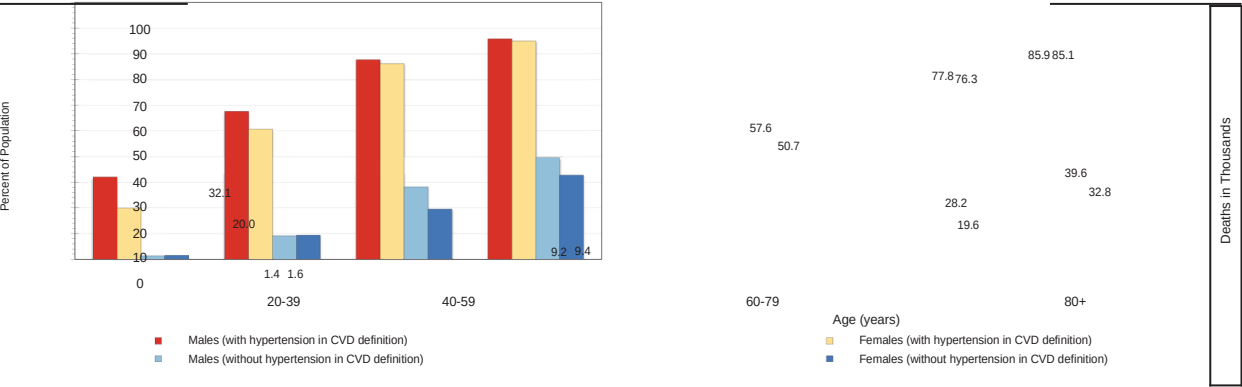


Chart 14-1. Prevalence of CVD in US adults ≥20 years of age, by age and sex (NHANES, 2017–2020).

These data include CHD, HF, stroke, and with and without hypertension. CHD indicates coronary heart disease; CVD, cardiovascular disease; HF, heart failure; and NHANES, National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.¹

Chart 14-2. Deaths attributable to diseases of the heart, United States, 1900 to 2022.

See Glossary (Chapter 30) for an explanation of diseases of the heart. In the years 1900 to 1920, the *ICD* codes were 77 to 80; for 1925, 87 to 90; for 1930 to 1945, 90 to 95; for 1950 to 1960, 402 to 404 and 410 to 443; for 1965, 402 to 404 and 410 to 443; for 1970 to 1975, 390 to 398 and 404 to 429; for 1980 to 1995, 390 to 398, 402, and 404 to 429; and for 2000 to 2019, I00 to I09, I11, I13, and I20 to I51. Before 1933, data are for a death registration area, not the entire United States. In 1900, only 10 states were included in the death registration area, and this increased over the years, so part of the increase in numbers of deaths is attributable to an increase in the number of states.

ICD indicates *International Classification of Diseases*.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.⁸²

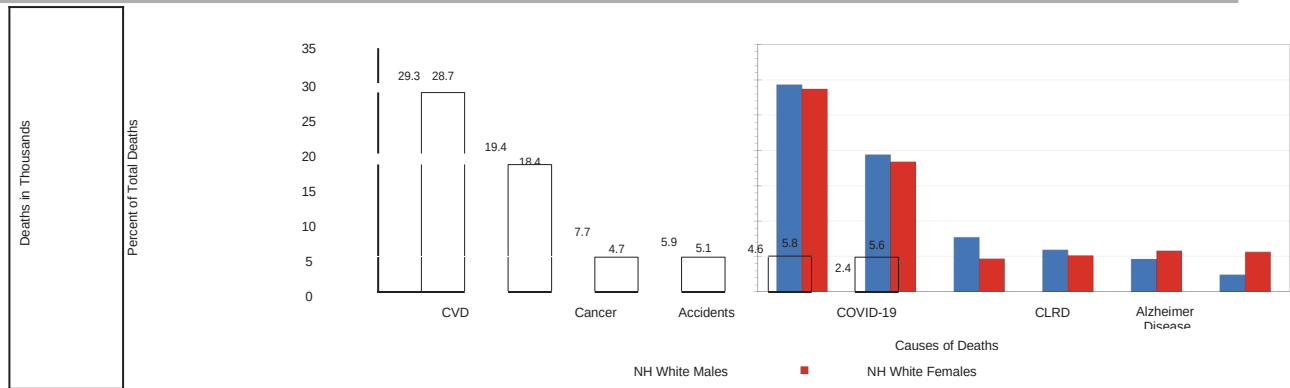


Chart 14-3. Deaths attributable to CVD, United States, 1900 to 2022.

Chart 14-5. CVD and other major causes of death for NH White males and females, United States, 2022.

Diseases included CVD (*ICD-10* codes I00–I99), cancer (C00–C97), CLRD (J40–J47), COVID-19 (U07.1), accidents (V01–X59 and Y85–Y86), and AD (G30).

tabulation using National Vital Statistics System.⁸²

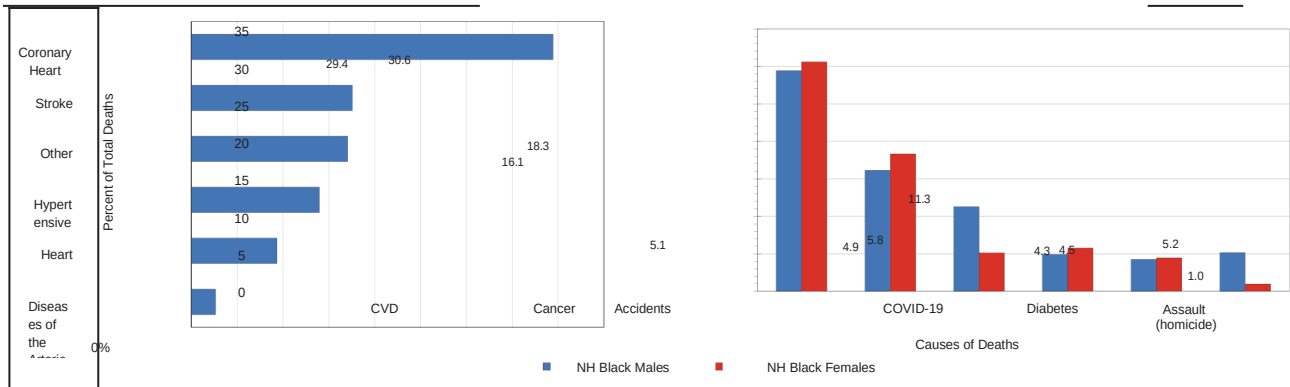


Chart 14-4. Percentage breakdown of deaths attributable to CVD, United States, 2022.

Total may not add to 100 because of rounding. CHD includes *ICD-10* codes I20 to I25; stroke, I60 to I69; HF, I50; HBP, I10 to I15; diseases of the arteries, I70 to I78; and other, all remaining *ICD-10* categories.

CHD indicates coronary heart disease; CVD, cardiovascular disease; HBP, high blood pressure; HF, heart failure; and *ICD-10*, *International*

Chart 14-6. CVD and other major causes of death for NH Black males and females, United States, 2022.

Diseases included CVD (<i>ICD-10</i> codes I00–I99), cancer (C00–C97), COVID-19 (U07.1), accidents (V01–X59, Y85, and Y86), assault (homicide; U01, U02, X85–Y09, and Y87.1), and diabetes (E10–E14). CLRD indicates chronic lower respiratory disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; <i>ICD-10</i> , <i>International Classification of Diseases, 10th Revision</i> ; and NH, non-Hispanic.	Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System. ⁸²
	Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System. ⁸²

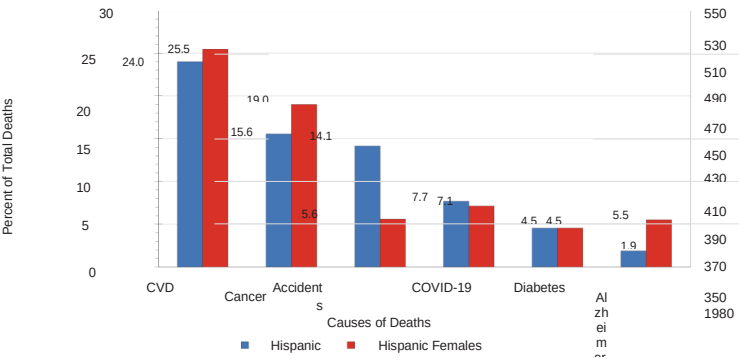
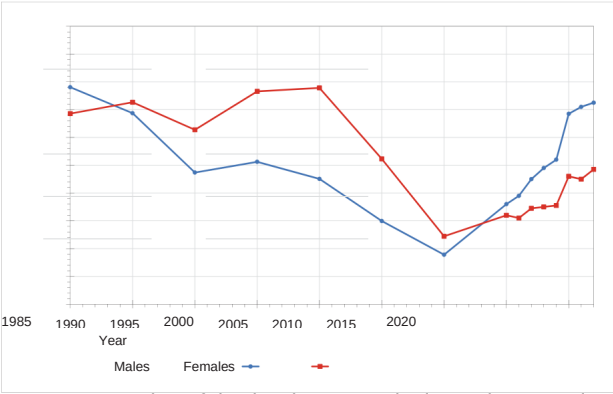


Chart 14-7. CVD and other major causes of death for Hispanic or Latino males and females, United States, 2022.



Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included CVD (*ICD-10* codes I00–I99), COVID-19 (U07.1), cancer (C00–C97), accidents (V01–X59 and Y85–Y86), diabetes (E10–E14), and AD (G30). AD indicates Alzheimer disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.⁸²

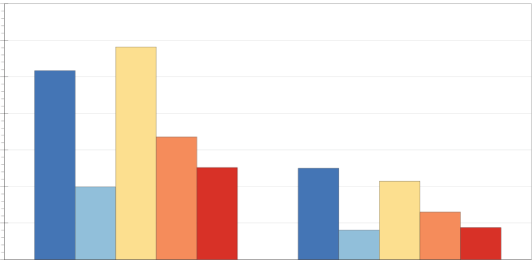
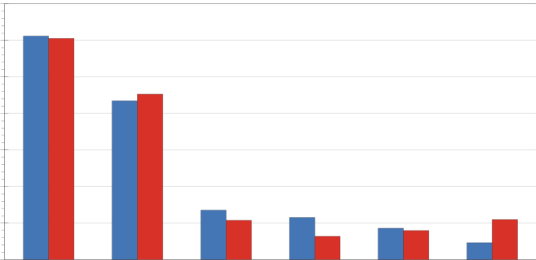


Chart 14-9. CVD mortality trends for US males and females, 1980 to 2022.

CVD excludes congenital cardiovascular defects (*ICD-10* codes I00–I99). The overall comparability for CVD between *ICD-9* (1979–1998) and *ICD-10* (1999–2015) is 0.9962. No comparability ratios were applied.

CVD indicates cardiovascular disease; *ICD-9*, *International Classification of Diseases, 9th Revision*; and *ICD-10*, *International Classification of Diseases, 10th Revision*.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.⁸²

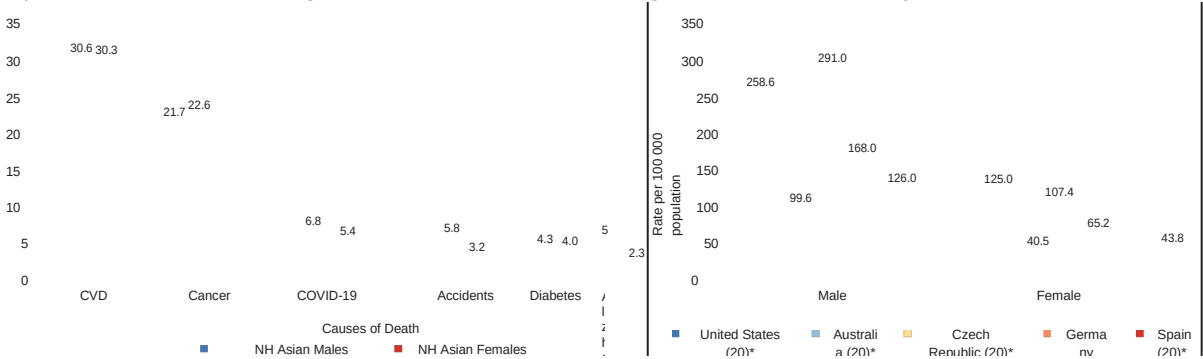


Chart 14-8. CVD and other major causes of death for NH Asian or Pacific Islander males and females, United States, 2022.

Asian or Pacific Islander is a heterogeneous category that includes people at high CVD risk (eg, South Asian people) and people at low CVD risk (eg, Japanese people). More specific data on these groups are not available. Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included CVD (*ICD-10* codes I00–I99), cancer (C00–C97), COVID-19 (U07.1), accidents (V01–X59, Y85, and Y86), diabetes (E10–E14), and AD (G30). AD indicates Alzheimer disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; *ICD-10*, *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.⁸²

Chart 14-10. Death rates per 100 000 population for CVD in selected countries for adults 35 to 74 years of age, 2020.

Rates are adjusted to the European Standard Population. *ICD-10* codes are I00 to I99 for CVD.
CVD indicates cardiovascular disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*.
*Number in parentheses indicates year of most recent data available (20 is 2020).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.⁹⁹

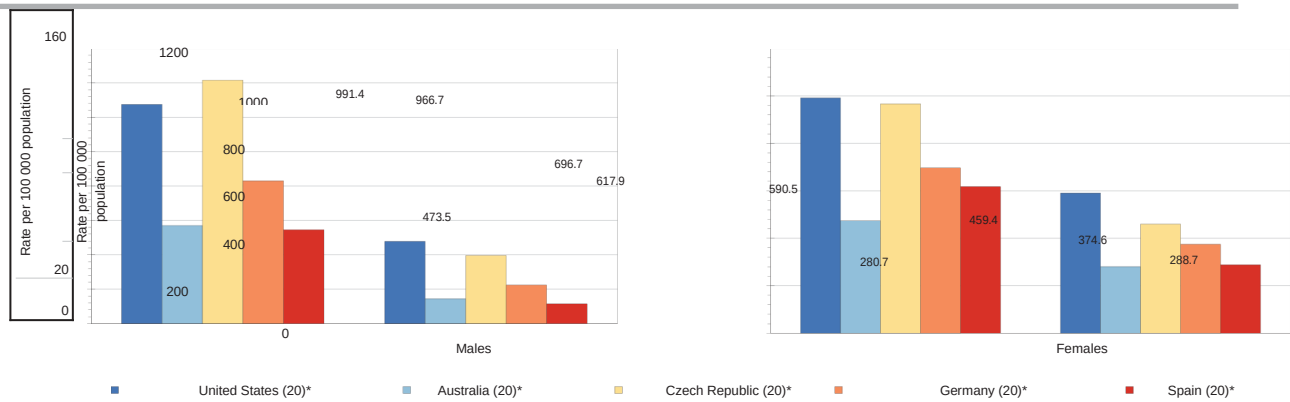


Chart 14-11. Death rates per 100 000 population for CHD in selected countries for adults 35 to 74 years of age, 2020.

Rates are adjusted to the European Standard Population. *ICD-10* codes are I20 to I25 for CHD. CHD indicates coronary heart disease; and *ICD-10*, *International Classification of Diseases, 10th Revision*. *Number in parentheses indicates year of most recent data available (20 is 2020). Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.⁹⁹

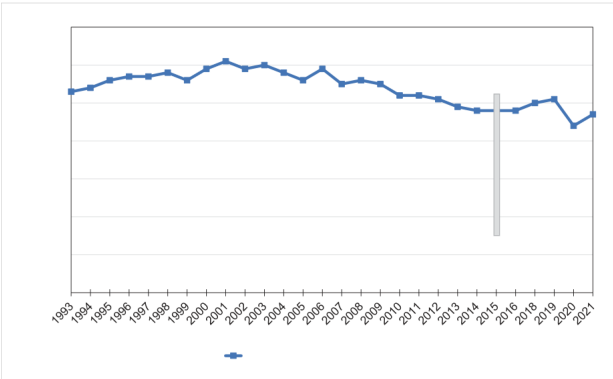
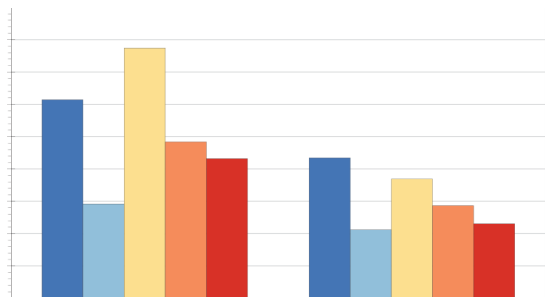


Chart 14-13. Death rates per 100 000 population for all causes in selected countries for adults 35 to 74 years of age, 2020.

Rates are adjusted to the European Standard Population.
ICD-10 codes are A00 to Y89 for all causes.
ICD-10 indicates *International Classification of Diseases, 10th Revision*. *Number in parentheses indicates year of most recent data available (20 is 2020).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.⁹⁹

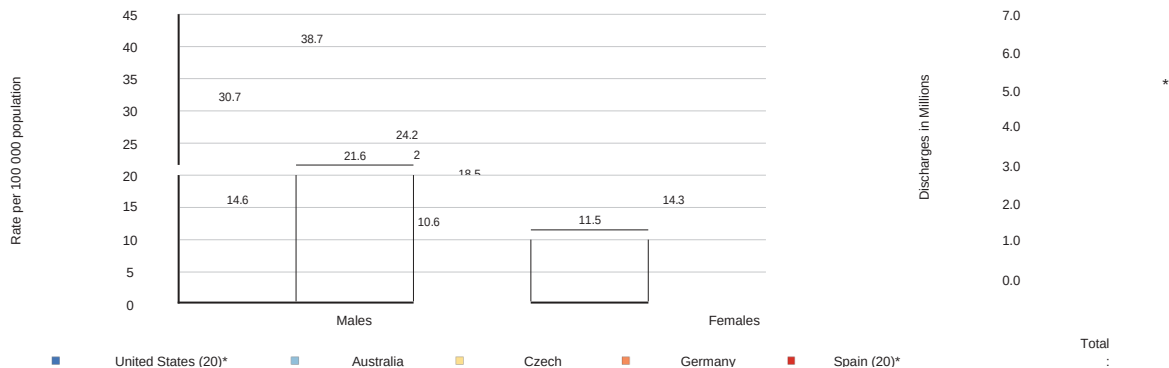


Chart 14-12. Death rates per 100 000 population for stroke in selected countries for adults 35 to 74 years of age, 2020.

Rates are adjusted to the European Standard Population. ICD-10 codes are I60 to I69 for stroke.
ICD-10 indicates *International Classification of Diseases, 10th Revision*.
*Number in parentheses indicates year of most recent data available (20 is 2020).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.⁹⁹

Chart 14-14. Hospital discharges for CVD, US adults, 1993 to 2021.

Hospital discharges include people discharged alive, dead, and status unknown. Data not available for males and females separately from 1993 to 1996 and after 2016.

CVD indicates cardiovascular disease.

*Data not available for 2015. Readers comparing data across

years should note that beginning October 1, 2015, a transition was made from *International Classification of Diseases, 9th Revision* to *International Classification of Diseases, 10th Revision*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.⁸⁸

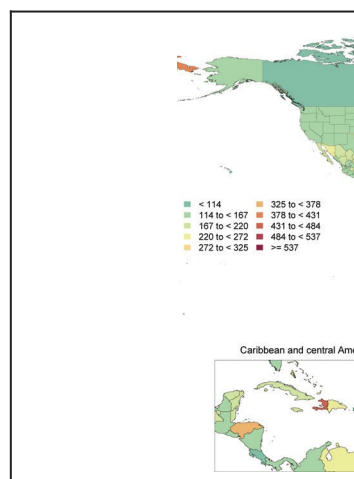


Chart 14-15. Age-standardized global mortality rates of CVDs per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

CVD indicates cardiovascular disease; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁹⁶

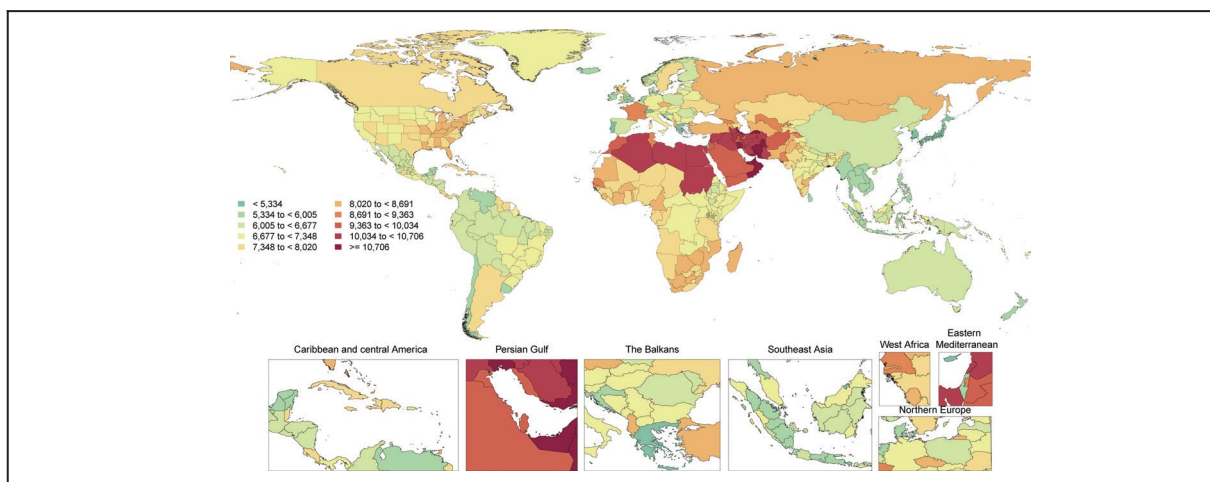


Chart 14-16. Age-standardized global prevalence rates of CVDs per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

CVD indicates cardiovascular disease; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁹⁶

REFERENCES

1. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2024.

2. Centers for Disease Control and Prevention and National Center for Health Statistics. Summary Health Statistics: National Health Interview Survey, 2018: table A-1. Accessed April 1, 2024.

3. Zhu H, Xi Y, Bao H, Xu X, Niu L, Tao Y, Cao N, Wang W, Zhang X. Assessment of cardiovascular disease risk in Northern China: a cross-sectional study. *Ann Hum Biol.* 2020;47:498–503. doi: 10.1080/03014460.2020.1779814

4. Irawati S, Wasir R, Florian Schmidt A, Islam A, Feenstra T, Buskens E, Wilffert B, Hak E. Long-term incidence and risk factors of cardiovascular events in Asian populations: systematic review and meta-analysis of population-based cohort studies. *Curr Med Res Opin.* 2019;35:291–299. doi: 10.1080/03007995.2018.1491149

5. Panagiotakos D, Chrysoshoou C, Damigou E, Barkas F, Liberopoulos E, Tsioufis C, Sfikakis PP, Pitsavos C; ATTICA Study Group. Prediction of life-time risk for cardiovascular disease, by risk factors

17. Tith RM, Paradis G, Potter BJ, Low N, Healy-Profítós J, He S, Auger N. Association of bulimia nervosa with long-term risk of cardiovascular disease and mortality among women. *JAMA Psychiatry.* 2020;77:44–51. doi: 10.1001/jamapsychiatry.2019.2914

18. Kurth T, Rist PM, Ridker PM, Kotler G, Bubes V, Buring JE. Association of migraine with aura and other risk factors with incident cardiovascular disease in women. *JAMA.* 2020;323:2281–2289. doi: 10.1001/jama.2020.7172

19. Erqou S, Clougherty JE, Olafiran O, Magnani JW, Aiyer A, Tripathy S, Kinnee E, Kip KE, Reis SE. Particulate matter air level: the ATTICA epidemiological cohort study (2002-2022). *Ann Epidemiol.* 2023;87:17–24. doi: 10.1016/j.annepidem.2023.09.010

6. Livingstone S, Morales DR, Fleuriot J, Donnan PT, Guthrie B. External validation of the QLifetime cardiovascular risk prediction tool: population cohort study. *BMC Cardiovasc Disord.* 2023;23:194. doi: 10.1186/s12872-023-03209-8

7. Bundy JD, Ning H, Zhong VW, Paluch AE, Lloyd-Jones DM, Wilkins JT, Allen NB. Cardiovascular health score and lifetime risk of car-

- 10-year atherosclerotic cardiovascular disease risk in a large rural Chinese adult population: a cross-sectional study. *Environ Int.* 2020;140:105819. doi: 10.1016/j.envint.2020.105819
21. Wang Y, O'Neil A, Jiao Y, Wang L, Huang J, Lan Y, Zhu Y, Yu C. Sex differences in the association between diabetes and risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality: a systematic review and meta-analysis of 5,162,654 participants. *BMC Med.* 2019;17:136. doi: 10.1186/s12916-019-1355-0
22. Wang YJ, Yeh TL, Shih MC, Tu YK, Chien KL. Dietary sodium intake and risk of cardiovascular disease: a systematic review and dose-response meta-analysis. *Nutrients.* 2020;12:2934. doi: 10.3390/nu12102934
23. Filippini T, Naska A, Kasdagli MI, Torres D, Lopes C, Carvalho C, Moreira P, Malavolti M, Orsini N, Whelton PK, et al. Potassium intake and blood pressure: a dose-response meta-analysis of randomized controlled trials. *J Am Heart Assoc.* 2020;9:e015719. doi: 10.1161/JAHA.119.015719
24. Shan Z, Li Y, Baden MY, Bhupathiraju SN, Wang DD, Sun Q, Rexrode KM, Rimm EB, Qi L, Willett WC, et al. Association between healthy eating patterns and cardiovascular disease: the Cardiovascular Lifetime Risk Pooling study. *Circ Cardiovasc Qual Outcomes.* 2020;13:e006450. doi: 10.1161/CIRCOUTCOMES.119.006450
8. Vasan RS, Enserro DM, Xanthakis V, Beiser AS, Seshadri S. Temporal trends in the remaining lifetime risk of cardiovascular disease among middle-aged adults across 6 decades: the Framingham study. *Circulation.* 2022;145:1324–1338. doi: 10.1161/CIRCULATIONAHA.121.057889
9. Gali B, Eyawo O, Hull MW, Samji H, Zhang W, Sereda P, Lima VD, McGrail K, Montaner JSG, Hogg RS, et al; COAST Study Team. Incidence of select

2020;180:1090–1100. doi: 10.1001/jamainternmed.2020.2176

25. Cunha CM, Costa PRF, de Oliveira LPM, Queiroz VAO, Pitangueira JCD, Oliveira AM. Dietary patterns and cardiometabolic risk factors among adolescents: systematic review and meta-analysis. *Br J Nutr*. 2018;119:859–879. doi: 10.1017/S0007114518000533
26. Song Q, Sun D, Zhou T, Li X, Ma H, Liang Z, Wang H, Cardoso MA, Heianza Y, Qi L. Perinatal exposure to maternal smoking and adult- hood smoking behaviors in predicting cardiovascular diseases: a chronic prospective cohort study. *Atherosclerosis*. 2021;328:52–59. doi:

individuals receiving highly active antiretroviral therapy. *Curr Med Res Opin*.

2019;35:1955–1963. doi: 10.1080/03007995.2019.1645999

10. Glenn AJ, Guasch-Ferre M, Malik VS, Kendall CWC, Manson JE, Rimm

EB, Willett WC, Sun Q, Jenkins DJA, Hu FB, et al. Portfolio diet score and risk of cardiovascular disease: findings from 3 pro-

10.1016/j.atherosclerosis.2021.05.009

27. Gao M, Jebb SA, Aveyard P, Ambrosini GL, Perez-Cornago A, Carter J, Sun X, Piernas C. Associations between dietary patterns and the incidence of total and fatal cardiovascular disease and all-cause mortality in 116,806 individuals from the UK Biobank: a prospective cohort study. *BMC Med.* 2023;148:1750– doi: 2021;19:83.

10.1161/CIRCULATIONAHA.123.065551

11. Alhassan HA, Akunor H, Howard A, Donohue J, Kainat A, Onyeaka HK, Aiyer A. Comparison of atherosclerotic cardiovascular risk factors and cardiometabolic profiles between current and never users of marijuana. *Circ*

Cardiovasc Qual Outcomes. 2023;16:e009609. doi:

10.1161/CIRCOUTCOMES.122.009609

12. Li H, Wang Y, Sonestedt E, Borne Y. Associations of ultra-processed food consumption, circulating protein biomarkers, and risk of cardiovascular dis-

28. Pollevick ME, Xu KY, Mhango G, Federmann EG, Vedanthan R, Busse P, Holguin F, Federman AD, Wisnivesky JP. The relationship between asthma and cardiovascular disease: an examination of the Framingham Offspring Study. *Chest*. 2021;159:1338–1345. doi: 10.1016/j.chest.2020.11.053
29. Shen Y, Zhou J, Shi L, Nauman E, Katzmarzyk PT, Price-Haywood EG, Horswell R, Bazzano AN, Nigam S, Hu G. Association between visit-to-visit HbA1c variability and the risk of cardiovascular disease in patients with type 2 diabetes. *Diabetes Obes Metab*. 2021;23:125–135. doi: 10.1111/dom.14201
13. Bertomeu-Gonzalez V, Cordero A, Ruiz-Nodar JM, Sanchez-Ferrer F, Lopez-Pineda A, Quesada JA. Risk factors for major adverse cardiovascular events in postmenopausal women: UK Biobank pro-

30. Guasch-Ferré M, Li Y, Willett WC, Sun Q, Sampson L, Salas-Salvadó J, Martínez-González MA, Stampfer MJ, Hu FB. Consumption of olive oil and risk of total and cause-specific mortality among U.S. adults. *J Am Coll*
spective cohort study. *Atherosclerosis*. 2023;386:117372. doi: *Cardiol*.

31. Gan ZH, Cheong HC, Tu YK, Kuo PH. Association between plant-based dietary patterns and risk of cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. *Nutrients*. 2021;13:3952. doi: 10.3390/nu13113952
- physical activity and sedentary behavior with incident cardiovascular disease, myocardial infarction, and ischemic stroke: the Women's Health Study. *J Am Heart Assoc*. 2023;12:e028180. doi: 10.1161/JAHA.122.028180
15. Khawaja T, Linge J, Leinhard OD, Al-Kindi SG, Rajagopalan S, Khera A, de Lemos JA, Joshi P, Neeland IJ. Coronary artery calcium, hepatic steatosis, and atherosclerotic cardiovascular disease risk in patients with type 2 diabetes mellitus: results from the Dallas Heart Study. *Prog Cardiovasc Dis*. 2023;78:67–73. doi: 10.1016/j.pcad.2023.03.002
16. Ye L, Zhang C, Duan Q, Shao Y, Zhou J. Association of magnesium depletion score with cardiovascular disease and its association with longitudinal mortality in patients with cardiovascular disease. *J Am Heart Assoc*. 2023;12:e030077. doi: 10.1161/JAHA.123.030077

32. Wan Z, Geng T, Li R, Chen X, Lu Q, Lin X, Chen L, Guo Y, Liu L, Shan Z, et al. Vitamin D status, genetic factors, and risks of cardiovascular disease among individuals with type 2 diabetes: a prospective study. *Am J Clin Nutr*. 2022;116:1389–1399. doi: 10.1093/ajcn/nqac183
33. Oliver-Williams C, Stevens D, Payne RA, Wilkinson IB, Smith GCS, Wood A. Association between hypertensive disorders of pregnancy and later risk of cardiovascular outcomes. *BMC Med*. 2022;20:19. doi: 10.1186/s12916-021-02218-8
34. Debras C, Chazelas E, Sellem L, Porcher R, Druetne-Pecollo N, Esseddik Y, de Edelenyi FS, Agaësse C, De Sa A, Lutchia R, et al. Artificial sweeteners and risk of cardiovascular diseases: results from

- the prospective NutriNet-Santé cohort. 10.1136/hmi-2022-071204
35. Yang B, Glenn AJ, Liu O, Madsen T, Allison Chan KHK, Wu WC, Li J, et al. Added and artificially sweetened beverages and findings from the Women's Health Initiative prospective studies. *Nutrients*.
 36. Jacobs DR Jr, Woo JG, Sinaiko AR, Daniels Kartiosuo N, Lehtimäki T, Magnussen CG. cardiovascular risk factors and adult 2022;386:1877–1888. doi: 10.1016/j.jamcardio.2023.3990
 37. Mannani JW, Nino H, Wilkins JT. Lloyd-attainment and lifetime risk of 2024;9:45–54. doi: 10.1001/jamcardio.2023.3990
 38. Dong T, Harris K, Freedman D, Janus S, Griggs S, Iyer Y, Nasir K, Neeland IJ, Rajagopalan S, Al-Kindi SG. Food insecurity and atherosclerotic cardiovascular disease risk in adults with diabetes. *Nutrition*. 2023;106:111865. doi: 10.1016/j.nut.2022.111865
 39. Nejatnamini S, Campbell DJT, Godley J, Minaker LM, Sajobi TT, McCormack GR, Olstad DL. The contribution of modifiable risk factors to socioeconomic inequities in cardiovascular disease morbidity and mortality: a nationally representative population-based cohort study. *Prev Med*. 2023;171:107497. doi: 10.1016/j.ypmed.2023.107497
 40. Xiao Q, Berrigan D, Powell-Wiley TM, Matthews CE. Ten-year change in neighborhood socioeconomic deprivation and rates of total, cardiovascular disease, and cancer mortality in older US adults. *Am J Epidemiol*. 2018;187:2642–2650. doi: 10.1093/aje/kwy181
 41. Palacio A, Mansi R, Seo D, Suarez M, Garay S, Medina H, Tang F, Tamariz L. Social determinants of health score: does it help identify those at higher cardiovascular risk? *Am J Manag Care*. 2020;26:e312–e318. doi: 10.1093/eurinc/zwac232
 54. Khan SS, Coresh J, Pencina MJ. 2023;171:107497. doi: 10.1016/j.ypmed.2023.107497
- the Multi-Ethnic Study of 2023;16:e009304. doi: 10.1093/eurinc/zwac232
52. Dang K, Wang X, Hu J, Zhang Y. The association between with obesity indicators and *Cardiovasc Diabetol*. 2024;23:8. doi: 10.1093/eurinc/zwac232
 53. Ostergaard HB, Hagaman SHJ, Read S, Petitjean C, Xu Z, Shi F, McEvoy time risk of incident cardiovascular tes: an update and geographical perspective model (DIAL2). *Eur J Prev* 10.1093/eurinc/zwac232
 54. Khan SS, Coresh J, Pencina MJ 2023;171:107497. doi: 10.1016/j.ypmed.2023.107497

SL, Palaniappan LP, Sperling LS, Virani SS, Ho JE, et al; on behalf of the American Heart Association. Novel prediction equations for absolute risk assessment of total cardiovascular disease incorporating cardiovascular-kidney-metabolic health: a scientific statement from the American Heart Association. *Circulation*. 2023;148:1982–2004. doi: 10.1161/CIR.0000000000001191

55. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Ciemins E, et al; on behalf of the Chronic Kidney Disease Prognosis Consortium and the American Heart Association Cardiovascular-Kidney-Metabolic Science Advisory Group. Development and validation of the American Heart Association's PREVENT Equations [published correction appears in *Circulation*. 2024;149:e956]. *Circulation*. 2024;149:430–449. doi: 10.1161/CIRCULATIONAHA.123.067626

56. Damen JA, Pajouheshnia R, Heus P, Moons KGM, Reitsma JB, Scholten R, Hooft L, Debray TPA. Performance of the Framingham risk models and Pooled Cohort Equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. *BMC Med*. 2019;17:109. doi: 10.37765/ajmc.2020.88504

42. Chen R, Zhan Y, Pedersen N, Fall K, Valdimarsdóttir UA, Hägg S, Fang F. Marital status, telomere length and cardiovascular disease risk in a Swedish prospective cohort. *Heart*. 2020;106:267–272. doi: 10.1136/heartjnl-2019-315629

43. Xiao Q, Heiss G, Kucharska-Newton A, Bey G, Love SM, Whitsel EA. Life-course neighborhood socioeconomic status and cardiovascular events in Black and White adults in the Atherosclerosis Risk in Communities study. *Am J Epidemiol*. 2022;191:1470–1484. doi: 10.1186/s12916-019-1340-7

57. Welsh CE, Celis-Morales CA, Ho FK, Brown R, Mackay DF, Lyall DM, et al. Walking pace and cardiovascular disease risk prediction in 406,834 UK Biobank participants. *Mayo Clin Proc.* 2020;95:879–888. doi: 10.1016/j.mayocp.2019.12.032
58. Rodriguez F, Chung S, Blum MR, Coulet A, Basu S, Palaniappan LP. Atherosclerotic cardiovascular disease risk prediction in disaggregated Asian and Hispanic subgroups using electronic health records. *J Am Heart Assoc.* 2019;8:e011874. doi: 10.1161/JAHA.118.011874
44. Al Rifai M, Jia X, Pickett J, Hussain A, Navaneethan SD, Birtcher KK, Ballantyne C, Petersen LA, Virani SS. Social determinants of health and comorbidities among individuals with atherosclerotic cardiovascular disease: the Behavioral Risk Factor Surveillance System Survey. *Popul Health Manag.* 2022;25:39–45. doi: 10.1089/pop.2021.0084
45. Kyalwazi AN, Locco EC, Brewer LC, Ofili EO, Xu J, Song Y, Maddox KEJ, Yeh RW, Wadhera RK. Disparities in cardiovascular mortality between Black and White adults in the United States, 1999 to 2019. *Circulation.* 2022;146:211–228. doi: 10.1161/CIRCULATIONAHA.122.060199
46. Vassou C, Chrysoschoou C, Skoumas J, Georgousopoulou EN, Yannakoulia M, Pitsavos C, Cropley M, Panagiotakos DB. Irrational beliefs, depression and anxiety, in relation to 10-year cardiovascular disease risk: the ATTICA epidemiological study. *Anxiety Stress Coping.* 2023;36:199–213. doi: 10.1080/10615806.2022.2062331
47. Golaszewski NM, LaCroix AZ, Godino JG, Allison MA, Manson JE, King JJ, Weitlauf JC, Bea JW, Garcia L, Kroenke CH, et al. Evaluation of social isolation, loneliness, and cardiovascular disease among older women in the US. *JAMA Netw Open.* 2022;5:e2146461. doi: 10.1001/jamanetworkopen.2021.46461
48. Barger SD, Struve GC. Association of depression with 10-year and life-time cardiovascular disease risk among US adults, National Health and Nutrition Examination Survey, 2005–2018. *Prev Chronic Dis.* 2022;19:E28. doi: 10.5888/pcd19.210418
49. Rossom RC, Hooker SA, O'Connor PJ, Crain AL, Sperl-Hillen JM. Cardiovascular risk for patients with and without schizophrenia, schizoaffective disorder, or bipolar disorder. *J Am Heart Assoc.* 2022;11:e021444. doi: 10.1161/JAHA.121.021444
50. Hooker SA, O'Connor PJ, Sperl-Hillen JM, Crain AL, Ohnsorg K, Kane S, Rossom R. Depression and cardiovascular risk in primary care patients. *J Psychosom Res.* 2022;158:110920. doi: 10.1016/j.jpsychores.2022.110920
51. Hammoud A, Chen H, Ivanov A, Yeboah J, Nasir K, Cainzos-Achirica M, Bertoni A, Khan SU, Blaha M, Herrington D, et al. Implications of social disadvantage score in cardiovascular outcomes and risk assessment: findings from

59. SCORE2 Working Group and ESC Cardiovascular Risk Collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*. 2021;42:2439–2454. doi: 10.1093/eurheartj/ehab309
60. SCORE2-OP Working Group and ESC Cardiovascular Risk Collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. *Eur Heart J*. 2021;42:2455–2467. doi: 10.1093/eurheartj/ehab312
61. Cao J, Remaley AT, Guan W, Devaraj S, Tsai MY. Performance of novel low-density lipoprotein-cholesterol calculation methods in predicting clinical and subclinical atherosclerotic cardiovascular disease risk: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2021;327:1–4. doi: 10.1016/j.atherosclerosis.2021.04.018
62. Pandey A, Mehta A, Paluch A, Ning H, Carnethon MR, Allen NB, Michos ED, Berry JD, Lloyd-Jones DM, Wilkins JT. Performance of the American Heart Association/American College of Cardiology Pooled Cohort Equations to estimate atherosclerotic cardiovascular disease risk by self-reported physical activity levels. *JAMA Cardiol*. 2021;6:690–696. doi: 10.1001/jamacardio.2021.0948
63. Mohan D, Mente A, Dehghan M, Rangarajan S, O'Donnell M, Hu W, Dagenais G, Wielgosz A, Lear S, Wei L, et al; PURE, ONTARGET, TRANSCEND, and ORIGIN Investigators. Associations of fish consumption with risk of cardiovascular disease and mortality among individuals with or without vascular disease from 58 countries. *JAMA Intern Med*. 2021;181:631–649. doi: 10.1001/jamainternmed.2021.0036
64. Saei Ghare Naz M, Sheidaei A, Aflatounian A, Azizi F, Ramezani Tehrani F. Does adding adverse pregnancy outcomes improve the Framingham Cardiovascular Risk Score in Women? Data from the Tehran Lipid and Glucose Study. *J Am Heart Assoc*. 2022;11:e022349. doi: 10.1161/JAHA.121.022349
65. Wang YX, Minguez-Alarcon L, Gaskins AJ, Wang L, Ding M, Missmer SA, Rich-Edwards JW, Manson JE, Chavarro JE. Pregnancy loss and risk of cardiovascular disease: the Nurses' Health Study II. *Eur Heart J*. 2022;43:190–199. doi: 10.1093/eurheartj/ehab737

66. Niiranen TJ, Kalesan B, Mitchell GF, Vasan RS. Relative contributions of pulse pressure and arterial stiffness to cardiovascular disease. *Hypertension*. 2019;73:712–717. doi: 10.1161/HYPERTENSIONAHA.118.12289
67. Han D, Berman DS, Miller RJH, Andreini D, Budoff MJ, Cademartiri F, Chinnaiyan K, Choi JH, Conte E, Marques H, et al. Association of cardiovascular disease risk factor burden with progression of coronary atherosclerosis assessed by serial coronary computed tomographic angiography. *JAMA Netw Open*. 2020;3:e2011444. doi: 10.1001/jamanetworkopen.2020.11444
68. Connors K, Flores-Torres MH, Stern D, Valdimarsdottir U, Rider JR, Lopez-Ridaura R, Kirschbaum C, Cantu-Brito C, Catzin-Kuhlmann A, Rodriguez BL, et al. Family member incarceration. *Psychology* (2012-2016). *Am J Public Health*. 2020;110:S71–S77. doi: 10.2105/AJPH.2019.305397
69. Aiumtrakul N, Supasynh O, Krittayaphong R, Phrommintikul A, Satirapoj
81. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.
82. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
83. Kochanek KD, Murphy SL, Xu J, Arias E. Mortality in the United States, 2022. *NCHS Data Brief*. 2022;1–8.
84. Hagstrom E, Sorio Vilela F, Svensson MK, Hallberg S, Soreskog E, Villa G. Cardiovascular event rates after myocardial infarction or ischaemic stroke in patients with additional risk

10.1007/s12325-021-01852-1

85. Keeney T, Fox AB, Jette DU, Jette A. Functional trajectories of persons with cardiovascular disease in late life. *J Am Geriatr Soc*. 2019;67:37–42. doi: 10.1111/jgs.15584
- B. Ankle-brachial index predicts renal outcomes and all-cause mortality in high cardiovascular risk population: a nationwide prospective cohort study in CORE project. *Int Urol Nephrol*. 2022;54:1641–1652. doi: 10.1007/s11255-021-03049-5
70. Weale ME, Riveros-Mckay F, Selzam S, Seth P, Moore R, Tarran WA, Gradovich E, Giner-Delgado C, Palmer D, Wells D, et al. Validation of an integrated risk tool, including polygenic risk score, for atherosclerotic cardiovascular disease in multiple ethnicities and ancestries. *Am J Cardiol*. 2021;148:157–164. doi: 10.1016/j.amjcard.2021.02.032
71. Sanchez-de-la-Torre M, Gracia-Lavedan E, Benitez ID, Sanchez-de-la-Torre A, Moncusi-Moix A, Torres G, Loffler K, Woodman R, Adams R, Labarca G, et al. Adherence to CPAP treatment and the risk of recurrent cardiovascular events: a meta-analysis. *JAMA*. 2023;330:1255–1265. doi: 10.1001/jama.2023.17465
72. Colizzi C, Harbers MC, Vellinga RE, Verschuren WMM, Boer JMA, Biesbroek S, Temme EHM, van der Schouw YT. Adherence to the EAT-2017 Lancet healthy reference diet in relation to risk of cardiovascular events and environmental impact: results from the EPIC-NL cohort. *J Am Heart Assoc*. 2023;12:e026318. doi: 10.1161/JAHA.122.026318
73. Bress AP, Colantonio LD, Cooper RS, Kramer H, Booth JN 3rd, Odden MC, Bibbins-Domingo K, Shimbo D, Whelton PK, Levitan EB, et al. Potential cardiovascular disease events prevented with adoption of the 2017 American College of Cardiology/American Heart

86. Aggarwal G, Cheruiyot I, Aggarwal S, Wong J, Lippi G, Lavie CJ, Henry BM, Sanchis-Gomar F. Association of cardiovascular disease with coronavirus disease 2019 (COVID-19) severity: a meta-analysis. *Curr Probl Cardiol.* 2020;45:100617. doi: 10.1016/j.cpcardiol.2020.100617
87. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. *PLoS One.* 2020;15:e0238215. doi: 10.1371/journal.pone.0238215
88. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024.
89. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed November 1, 2024.
90. Akhabue E, Rua M, Gandhi P, Kim JH, Cantor JC, Setoguchi S. Disparate cardiovascular hospitalization trends among young and middle-aged adults within and across race and ethnicity groups in four states in the United States. *J Am Heart Assoc.* 2023;12:e7978. doi: 10.1161/JAHA.122.027342
91. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2024.
- Association blood pressure guideline. *Circulation.* 2019;139:24–36. doi: 10.1161/CIRCULATIONAHA.118.035640
74. Macknin M, Stegmeier N, Thomas A, Worley S, Li L, Hazen SL, Tang WHW. Three healthy eating patterns and cardiovascular disease risk markers in 9 to 18 year olds with body mass index >95%: a randomized trial. *Clin Pediatr*

92. Meyers J, Hoog M, Mody R, Yu M, Davis K. The health care resource utilization and costs among patients with type 2 diabetes and either cardiovascular disease or cardiovascular risk factors an analysis of a US Health Insurance Database. *Clin Ther*. 2021;43:1827–1842. doi: 10.1016/j.clinthera.2021.09.003
75. Isath A, Kanwal A, Virk HUH, Bandyopadhyay D, Wang Z, Kumar A, Kalra A, Naidu SS, Lavie CJ, Virani SS, et al. The effect of yoga on cardiovascular disease risk factors: a meta-analysis. *Curr Probl Cardiol*. 2023;48:101593. doi: 10.1016/j.cpcardiol.2023.101593
76. Yin S, Xu H, Xia J, Lu Y, Xu D, Sun J, Wang Y, Liao W, Sun G. Effect of alpha-linolenic acid supplementation on cardiovascular disease risk profile in individuals with obesity or overweight: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr*. 2023;14:1644–1655. doi: 10.1016/j.advnut.2023.09.010
77. He L, Liu M, Zhuang X, Guo Y, Wang P, Zhou Z, Chen Z, Peng L, Liao X. Effect of intensive lifestyle intervention on cardiovascular risk factors: analysis from the perspective of long-term variability. *J Am Heart Assoc*. 2024;13:e030132. doi: 10.1161/JAHA.123.030132
78. Cong L, Ren Y, Hou T, Han X, Dong Y, Wang Y, Zhang Q, Liu R, Xu S, Wang L, et al. Use of cardiovascular drugs for primary and secondary prevention of cardiovascular disease among rural-dwelling older Chinese adults. *Front*

93. Fonseca R, Palmer AJ, Picone DS, Cox IA, Schultz MG, Black JA, Bos WJW, Cheng HM, Chen CH, Cremer A, et al. Cardiovascular and health cost impacts of cuff blood pressure underestimation and overestimation of invasive aortic systolic blood pressure. *J Hypertens*. 2023;41:1585–1594. doi: 10.1097/HJH.0000000000003510
94. Wu S, Xu W, Guan C, Lv M, Jiang S, Jinhua Z. Global burden of cardiovascular disease attributable to metabolic risk factors, 1990-2019: an analysis of observational data from a 2019 Global Burden of Disease study. *BMJ Open*. 2023;13:e069397. doi: 10.1136/bmjopen-2022-069397
95. Hasani WSR, Muhamad NA, Hanis TM, Maamor NH, Chen XW, Omar MA, Cheng Kueh Y, Abd Karim Z, Hassan MRA, Musa KI. The global estimate of premature cardiovascular mortality: a systematic review and meta-analysis of age-standardized mortality rate. *BMC Public Health*. 2023;23:1561. doi: 10.1186/s12889-023-16466-1
96. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed July 1, 2024. *Pharmacol*. 2020;11:608136. doi: 10.3389/fphar.2020.608136
79. Walli-Attaei M, Joseph P, Rosengren A, Chow CK, Rangarajan S, Lear SA, AlHabib KF, Davletov K, Dans A, Lanas F, et al. Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2020;396:97–109. doi: 10.1016/S0140-6736(20)30543-2
97. World Health Organization. Cardiovascular diseases (CVDs). Accessed March 22, 2024. Assessment of trends in statin therapy for secondary prevention of atherosclerotic cardiovascular disease in US adults from 2007 to 2016. *JAMA Netw Open*. 2020;3:e2025505. doi: 10.1001/jamanetworkopen.2020.25505
80. Yao X, Shah ND, Gersh BJ, Lopez-Jimenez F, Noseworthy PA.

98. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, Fryar CD, Gu S, Examination Survey 2017–March 2020 prepandemic data files: development of files Hales CM, Hughes JP, et al. National Health and Nutrition and prevalence estimates for selected health outcomes. *Natl Health Stat Rep*. 2021;158:1–21. doi: 10.15620/cdc:106273
99. World Health Organization. WHO mortality database. Accessed March 22, 2024. www.who.int/healthinfo/mortality_data/en/

15. STROKE Diseases)

*ICD-9 430 to 438; ICD-10 I60 to
through 15-7 and Charts 15-1
through 15-15*

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Stroke Prevalence

(See Table 15-1 and Chart 15-1)

- Stroke prevalence estimates may differ slightly between studies because each study selects and recruits a sample of participants to represent the target study population (eg, state, region, or country).
- An estimated 9.4 million Americans ≥ 20 years of age self-report having had a stroke (NHANES 2017–2020 data). Overall stroke prevalence during this period was an estimated 3.3% (Table 15-1).
- Prevalence of stroke in the United States increases with advancing age in both males and females (Chart 15-1).
- According to BRFSS₁ 2022 data (unpublished NHLBI tabulation), stroke prevalence in adults was 3.4% (median) in the United States with the lowest prevalence in Puerto Rico (1.8%) and South Dakota (2.1%) and the highest prevalence in Arkansas (4.8%).
- Projections show that by 2030 an additional 3.4 million US adults ≥ 18 years of age, representing 3.9% of the adult population, will have had a stroke, a 20.5% increase in prevalence from 2012.² The highest increase (29%) is projected to be in White Hispanic males.

and NINDS data for 1999 unpublished estimates

- Of all strokes, 87% are and 3% are SAHs unpublished NHLBI
- According to the GBD strokes accounted for strokes in 2019 (7.63 ICH accounted for 27.9% 3.91] million), and SAH accounted for 9.7% (1.18 [95% CI, 1.01–1.39] million).³

Secular Trends

Stroke Incidence

(See Table 15-1)

- Each year, $\approx 795\ 000$ people experience a new or recurrent stroke (Table 15-1). Approximately 610 000 of these are first attacks and 185 000 are recurrent attacks (GCNKSS, NINDS, and NHLBI; GCNKSS

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- An analysis of data from the GBD Study 2019 found that from 1990 to 2019, the absolute number of incident strokes increased by 70.0% (95% CI, 67.0%–73.0%), and the age-standardized incidence rate for total stroke decreased by 17.0% (95% CI, 15.0%–18.0%).³ The age-standardized incidence rate for ischemic stroke decreased by 10% (95% CI, 8.0%–12.0%) and ICH decreased by 29% (95% CI, 28.0%–30.0%) during the same period.
- A population-based cohort study from Ontario, Canada, assessed the influence of age on the association between sex and the incidence of stroke or TIA from January 1, 2003, to March 31, 2018.⁴ The study followed up 9.2 million adults for a median of 15 years and observed 280 197 incident stroke or TIA events. Females had an overall lower adjusted hazard of stroke or TIA than males (HR, 0.82 [95% CI, 0.82–0.83]), which held true for all stroke types except SAH (HR, 1.29 [95% CI, 1.24–1.33]). A U-shaped association between age and sex differences in the incidence of stroke or TIA was seen with the hazard of stroke being higher in females among those ≤30 years of age (HR, 1.26 [95% CI, 1.10–1.45]), lower among those between 40 and 80 years of age (40–49 years of age: HR, 0.84 [95% CI, 0.82–0.87]; 50–59 years of age: HR, 0.69 [95% CI, 0.68–0.70]; 60–69 years of age: HR, 0.69 [95% CI, 0.68–0.70]; and 70–79 years of age: HR, 0.80 [95% CI, 0.79–0.81]), and similar among those ≥80 years of age (HR, 0.99 [95% CI, 0.98–1.01]).
- A population-based incidence study conducted in Oxfordshire, England, from April 2002 to March 2018 found that between 2002 to 2010 and 2010 to 2018, stroke incidence increased significantly among subjects <55 years of age (IRR, 1.67 [95% CI, 1.31–2.14]) but fell significantly among those ≥55 years of age (IRR, 0.85 [95% CI, 0.78–0.92]; $P<0.001$ for difference).⁵
- A systematic review found among 50 studies in 20 countries that temporal trends in stroke incidence are diverging by age in high-income countries, with

less favorable trends at younger versus older ages (pooled relative temporal rate ratio, 1.57 [95% CI, 1.42–1.74]).⁶ The overall relative temporal rate ratio was consistent by sex (males, 1.46 [95% CI, 1.34–1.60]; females, 1.41 [95% CI, 1.28–1.55]) and by stroke subtype (ischemic, 1.62 [95% CI, 1.44–1.83]; ICH, 1.32 [95% CI, 0.91–1.92]; SAH, 1.54 [95% CI, 1.00–2.35]) but was greater in studies reporting trends solely after 2000 (1.51 [95% CI, 1.12–1.24]) and was highest in population-based studies in which the most recent reported period of ascertainment started after 2010 (1.87 [95% CI, 1.55–2.27]).

in young females (pooled relative temporal trend ratio, 3.08 [95% CI, 1.18– 4.97]; $P_{\text{heterogeneity}} < 0.001$). • A study assessing stroke registry data in Iran among hospitalized patients with first or recurrent stroke found that stroke rates had increased over time, ranging from 6.59 to 8.91 per 10 000 cases from April 2001 to March 2022 to 11.17 to 13.82 per 10

- In the multicenter ARIC study of Black adults and White adults, stroke incidence rates decreased by 32% (95% CI, 23%–40%) per 10 years during

ranged from 1.56% (95% CI, 0.14%–2.97%) to 2.67% (95% CI, 1.25%–4.09%). A similar trend for the whole reference population was seen for stroke incidence rate based on WHO-MONICA with an average annual change of 2.5% (95% CI, 1.28%–3.72%) to 3.64% (95% CI, 2.47%–4.82%).

the 30-year period from 1987 to 2017 in adults ≥ 65 years of age. The decreases varied across

Stroke Risk Factors

groups but were similar across sex and race.⁷ Data from the Danish Stroke Registry and the Danish National Patient Registry showed that the incidence rate per 100 000 PY in 2005 and 2018 of ischemic stroke (20.8 versus 21.9, respectively; average annual percentage change, -0.6 [95% CI, -1.5 to 0.3]) and ICH (2.2 versus 2.5, respectively; average annual percentage change, 0.6 [95% CI, -1.0 to 2.3]) remained steady in younger adults (18–49 years of age), but in older adults (>50 years of age), rates of ischemic stroke and ICH declined (-1.5 [95% CI, -1.9 to -1.1] and -1.2 [95% CI, -1.9 to -0.6], respectively), especially in those ≥ 70 years of age.⁸

- In a US nationwide study of mortality among Asian American individuals from 2003 to 2017, age-standardized cerebrovascular disease mor-

tality declined by an average of 2.2%/y (95% CI, 1.1%/y–3.2%/y) among Asian American females and 2.4%/y (95% CI, 1.3%/y–3.6%/y) among Asian American males.⁹ There was heterogeneity among Asian American ethnic subgroups. Average annual percent decline in cerebrovascular mortality was fastest among Japanese American individuals (decline of 3.1 %/y [95% CI, 2.0%/y–4.2%/y] among females and decline of 3.2%/y [95% CI, 1.9%/y–4.5%/y] among males).

- A meta-analysis assessing temporal trends in stroke incidence between January 1997 and December 2021 by age and sex in Latin America and the Caribbean region found unfavorable changes in stroke incidence in younger people (<55 years of age) with a higher incidence rate after 2010 compared with before 2010 (IRR, 1.37 [95% CI, 1.23–1.50]).¹⁰ The overall relative temporal trend ratio was 1.65 (95% CI, 1.50–1.80) in the younger compared with older age group with a greater increase

For prevalence and other information on any of these specific risk factors, refer to the specific risk factor chapters.

- In analyses using data from the GBD Study, 87% of the stroke risk could be attributed to modifiable risk factors such as HBP, obesity, hyperglycemia, hyperlipidemia, and renal dysfunction, and 47% could be attributed to behavioral risk factors such as smoking, sedentary lifestyle, and an unhealthy diet. Globally, 30% of the risk of stroke was attributable to air pollution.^{12,13}
- The FINGER trial in 1259 adults 60 to 77 years of age found that a 2-year multidomain intervention with diet, PA, cognitive activity, and vascular monitoring compared with general health advice resulted in a reduced incidence of stroke (HR, 0.71 [95% CI, 0.51–0.99]).¹⁴

High BP

(See Chapter 8 [High Blood Pressure] for more information.)

(See Tables 15-2 and 15-3 and Charts 15-2 and 15-3)

Observational Studies

- High BP is associated with stroke mortality. Among 430 977 adults 30 to 79 years of age in China with 5168 stroke deaths during a median follow-up of 10 years, stroke mortality rates per 100 000 PY in BP groups were 39 in the normal BP, 71 in the prehypertension-low, 83 in the prehypertension-high, 283 in the isolated systolic hypertension, 82 in the isolated diastolic hypertension, and 375 in the systolic-diastolic hypertension groups. Compared with normal BP, multiadjusted HRs for stroke mortality were 1.20 (95% CI, 1.06–1.36) in the prehypertension-low, 1.53 (95% CI, 1.37–1.70) in the prehypertension-high, 2.52 (95% CI, 2.28–2.78)

in the isolated systolic CI. 1.94–3.21) in the isolated sion, and 5.60 (95% CI. 5.06–diastolic hypertension groups. relative to normal BP. HRs for mortality were larger than mortality.¹⁵

- Higher SBP and DBP are stroke. Among 36 352 adults recruited from rural areas of

Province, China, the overall rate of stroke over a median of 12.5 years was 7.0%. A 20– mm Hg increment in SBP was associated with 1.28 times the risk for stroke (95% CI, 1.22–1.34), and a 10– mm Hg increment in DBP was associated with 1.14 times the risk for stroke (95% CI, 1.09–1.19) after adjustment for demographic, clinical, and behavioral

characteristics.¹⁶ Ideal BP for lower stroke risk varied by BMI: At BMI <24 kg/m², stroke risk was elevated (HR >1) in those with BP >130/80 mm Hg, whereas at BMI ≥24 kg/m², stroke risk was elevated (HR >1) in those with BP >120/80 mm Hg. • Higher pulse pressure is associated with incident stroke. In a longitudinal cohort study of 11 848 adult participants in 12 countries in Europe, Asia, and South America undergoing 24-hour ambulatory BP assessment with a median follow-up of 13.7 years and 846 stroke events, the rate of stroke was 5.2 per 1000 PY. A 1-SD increment in mean pulse pressure (10.0 mm Hg) was independently associated with stroke risk.¹⁷ For participants ≤40 years of age, a 1-SD increment in mean ambulatory pulse pressure was associated with a 3-fold higher risk of stroke (aHR per SD, 3.06 [95% CI, 1.03–9.09]). The aHRs per SD were 1.40 (95% CI, 0.76–2.58) for 40 to 50 years of age, 1.51 (95% CI, 1.14–1.99) for 50 to 60

of ischemic stroke (HR, 1.37 and ICH (HR, 1.71 [95% CI. mendelian randomization of age in the multiancestry sortium, a 1-SD increment in pulse pressure was ischemic stroke (aOR, 1.23 independently of genetically pressure, and this result was Biobank.²⁰

years of age, 1.44 (95% CI, 1.24–1.67) for 60 to 70 years of age, and 1.18 (95% CI, 1.09– 1.28) for >70 years of age.

- However, SBP/DBP combinations are associated with stroke risk in nonlinear patterns that do not simply reflect pulse pressure. Among 33 357 adults in ALLHAT with 936 strokes during a median follow-up of 4.4 years, heat map plotting of stroke risk at all SBP and DBP combinations showed that stroke risk was lowest in the SBP/DBP range of <110/<60 mm Hg (HRs <0.90 relative to BP of 120/80 mm Hg) and stroke risk was highest in the SBP/DBP range of 170 to 190/85 to 100 mm Hg (HRs >2.00 relative to BP of 120/80 mm Hg; Chart 15-2).¹⁸

- Genetically predicted higher BP measures are associated with incident ischemic stroke. In a mendelian randomization study of 86 060 adults 40 to 79 years of age in China, a 10–mm Hg increment in genetically predicted SBP was associated with higher risk

- High SBP and DBP are associated with incident ICH and SAH. Among 947 378 adults 20 to 64 years of age in the Korean National Health Insurance Service Database who had stable BP levels during 10 years of observation, with 355 ICH and 566 SAH cases, ICH and SAH incidence rates increased across BP categories among both males and females (Table 15-2).²¹ Among 500 598 adults 40 to 69 years of age in the UK Biobank, with 539 cases of SAH over a mean of 4.5 years of follow-up, SBP and DBP analyzed as continuous variables were positively associated with SAH risk (HR per 10 mm Hg of SBP, 1.10 [95% CI, 1.05–1.15]; HR per 10 mm Hg of DBP, 1.17 [95% CI, 1.07–1.27]; Chart 15-3).²² The authors also meta-analyzed the UK Biobank results for SBP categories with 4 additional studies for a total of 809 983 participants and 1465 SAH cases, showing increasing SAH incidence rates across BP categories among both males and females (Table 15-3).

Interventional Studies

- In a meta-analysis of 66 trials of SBP-lowering 11 437 strokes over an average follow-up of 3.3 lower odds (95% CI, 15%–26% lower) of stroke types, SBP lowering was associated with 14% ischemic stroke (6 trials), 28% lower odds (95% CI, and 28% lower odds (95% CI, 19%–39% lower) of
- In a meta-analysis of 14 randomized trials comparing 60 870 participants and 1323 strokes over an average follow-up of 3.95 years, more intensive BP control was associated with a lower risk of stroke (OR, 0.79 [95% CI, 0.67–0.93]).²⁴ The trials differed in the specific BP targets, and the average achieved SBP reduction in the more intensive treatment was 7.69 mm Hg (95% CI, 7.64–7.71 mm Hg).

High BP and Stroke Prognosis

- In a meta-analysis of 26 studies including 56 513 patients undergoing intravenous thrombolysis for

AIS, elevated pretreatment (aOR, 1.08 [95% CI, 1.01–1.16]) and posttreatment (aOR, 1.13 [95% CI, 1.01–1.25]) SBP levels were associated with increased risk of symptomatic ICH.²⁵ Higher pre-treatment (aOR, 0.91 [95% CI, 0.84–0.98]) and posttreatment (aOR, 0.70 [95% CI, 0.57–0.87]) SBP values were associated with lower likelihood of 3-month functional independence.

(See Chapter 9 [Diabetes] for more information.) **Observational Studies**

- In a meta-analysis of 64 cohort studies involving 775 385 individuals and 12 539 incident strokes, diabetes was associated with stroke risk in females (aRR, 2.28 [95% CI, 1.93–2.69]) and in males (aRR, 1.83 [95% CI, 1.60–2.08]).²⁶ The magnitude of the RR was greater in females (ratio of female aRR/male aRR, 1.27 [95% CI, 1.10–1.46]), suggesting that diabetes is a more potent risk factor for stroke among females.
- Prediabetes, defined as impaired glucose tolerance or impaired fasting glucose, is associated with a modestly increased risk of stroke. A meta-analysis of 53 prospective cohort studies including 1 611 339 participants, of which 18 studies reported the association between prediabetes and stroke, revealed that impaired glucose

fatal stroke by 19% (HR, 0.81 [95% CI, 0.62–1.08]), and total stroke by 16% (HR, 0.84 [95% CI, 0.76–0.93]).³¹

- SGLT-2 inhibitors reduce blood glucose through reducing renal glucose reabsorption. In a meta-analysis of 5 RCTs that included 46 969 patients with type 2 diabetes,

Diabetes and Stroke Prognosis

- Diabetes is an independent risk factor tolerance was associated with a 20% increased risk of stroke (aRR, 1.20 [95% CI, 1.00–1.45]).²⁷ Impaired fasting glucose, defined as FPG of 100 to 125 mg/dL, was associated increased stroke risk (aRR, 1.06 [95% CI, 1.01–1.11]).

Interventional Studies

- In a meta-analysis of 11 RCTs that included 56 161 patients with type 2 diabetes and 1835 cases of stroke, intensive blood glucose control did not reduce stroke risk compared with conventional glucose control (RR, 0.94 [95% CI, 0.84–1.06]).²⁸ An RCT of intensive or standard blood glucose control in patients with AIS with hyperglycemia (80% with diabetes) did not demonstrate a difference in favorable functional outcome (aRR, 0.97 [95% CI, 0.87–1.08]) at 90 days.²⁹ A meta-analysis of 19

recurrence. A meta-analysis of 27 studies involving 274 631 participants with prior ischemic stroke demonstrated that diabetes was an independent risk factor for stroke recurrence (pooled HR, 1.50 [95% CI, 1.36–1.65]).³³

- In the GWTG-Stroke registry involving 409 060 United States, diabetes was associated with a higher risk of adverse outcomes 3 years after ischemic stroke, including all-cause mortality (46.0% versus 44.2%, a difference of 1.8 per 100; aHR, 1.24 [95% CI, 1.23–1.25]), all-cause hospital readmission (71.3% versus 63.7%, a difference of 7.6%; aHR, 1.22 [95% CI, 1.21–1.23]), a composite of mortality and cardiovascular readmission (69.5% versus 64.3%, a difference of 5.2%; aHR, 1.19 [95% CI, 1.18–1.20]), and ischemic stroke/TIA (25.7% versus 13.1%; aOR, 2.51 [95% CI, 1.65–3.82]) after adjustment for age, sex, and other confounding factors that varied by study.³⁵

ing 274 631 participants with prior ischemic stroke risk factor for stroke recurrence (pooled HR, 1.50

participants ≥65 years of age from 1690 sites in the higher risk of adverse outcomes 3 years after ischemic stroke, including all-cause mortality (46.0% versus 44.2%, a difference of 1.8 per 100; aHR, 1.24 [95% CI, 1.23–1.25]), all-cause hospital readmission (71.3% versus 63.7%, a difference of 7.6%; aHR, 1.22 [95% CI, 1.21–1.23]), a composite of mortality and cardiovascular readmission (69.5% versus 64.3%, a difference of 5.2%; aHR, 1.19 [95% CI, 1.18–1.20]), and ischemic stroke/TIA (25.7% versus 13.1%; aOR, 2.51 [95% CI, 1.65–3.82]) after adjustment for age, sex, and other confounding factors that varied by study.³⁵

patients with AIS, hyperglycemia (random blood glucose >140 mg/dL) at stroke admission was associated with higher risk of symptomatic ICH (9.3% versus 5.5%; aOR, 1.80 [95% CI, 1.30–2.50]), higher odds of poor clinical outcome at 90 days (61.0% versus 47.2%; aOR, 1.82 [95% CI, 1.52–2.19]), and higher odds of all-cause mortality at 90 days (25.7% versus 13.1%; aOR, 2.51 [95% CI, 1.65–3.82]) after adjustment for age, sex, and other confounding factors that varied by study.³⁵

Disorders of Heart Rhythm

(See Chapter 18 [Disorders of Heart Rhythm] for

RCTs with 155 027 participants with type 2 diabetes demonstrated that GLP1-RA treatment was

more information.)

Atrial Fibrillation

associated with reduced stroke risk (RR, 0.84 [95% CI, 0.77–0.93]).³⁰

- Glucagon-like peptide 1 agonists reduce blood glucose through multiple mechanisms, including stimulating insulin secretion, blocking

glucagon secretion, slowing digestion, and increasing satiety. In a meta-analysis of 7 RCTs that included 56 004 patients with type 2 diabetes, treatment with glucagon-like peptide 1 agonists reduced the risk of nonfatal stroke by 15% (HR, 0.85 [95% CI, 0.76–0.94]),

- In an international multicenter prospective cohort of patients with cryptogenic stroke or TIA who had a continuous cardiac monitor placed (N=250), 43% had a probable cardiac cause identified at 12 months of follow-up. The most common causes identified were AF and atrial flutter (29%).³⁶
- The 12-month prevalence of AF in patients with stroke attributed to large- or small-vessel disease was 12.1% in the STROKE-AF RCT with continuous cardiac monitoring versus 1.8% with usual care;

median time respectively. predictors of continuous HF (HR, enlargement

- Biomarkers NT-proBNP, kin-6, and associated with

in AF after adjustment for traditional vascular risk factors (hypertension, diabetes, HF, CAD).^{39,40}

randomization, the cumulative incidence of recurrent stroke at 1 year was 7% (95% CI, 5.2%–8.7%), and the cumulative incidence of mortality at 3 months was 12.4% (95% CI, 10.5%–14.4%).⁴⁷ The risk of recurrent stroke in this population of patients with AF and ischemic stroke remained similar even when accounting for the competing risk of death.

- In STROKESTOP, an RCT in participants 75 to 76 years of age, an invitation to AF screening (defined as twice-daily handheld electrocardiogram)
- In a meta-analysis of 26 studies of patients with AF

recordings over 2 weeks) was found to be cost-effective with 65 QALYs gained per 1000 individuals invited for screening and \$1.92 million saved per

and prior stroke (N=23 054 patients), nonparoxysmal AF compared with paroxysmal AF was associated with a higher risk of recurrent stroke (OR, 1.47 [95% CI, 1.08–1.99]).⁴¹

- In a meta-analysis of 35 studies (N=2 458 010 patients), perioperative or postoperative AF was associated with an increased risk of early stroke (OR, 1.62 [95% CI, 1.47–1.80]) and later stroke (HR, 1.37 [95% CI, 1.07–1.77]). This risk was found in patients undergoing both noncardiac surgery (HR, 2.00 [95% CI, 1.70–2.35]) and cardiac surgery (HR, 1.20 [95% CI, 1.07–1.34]).⁴²

- In a meta-analysis of 28 studies (N=2 612 816 patients), AF after noncardiac surgery was associated with a ≈3-fold increased risk of stroke at 1 month (OR, 2.82 [95% CI, 2.15–3.70]) and ≈4-fold increase in long-term risk of stroke (OR, 4.12 [95% CI, 3.32–5.11]).⁴³ For the choice of anticoagulant postoperatively, a study from the STS database of 26 522 patients with AF after cardiac surgery (36.8% on DOAC and 36.2% on

1000 individuals.⁴⁸

vitamin K antagonist) showed no association between type of oral anticoagulant and 30-day outcomes (major bleeding, stroke/TIA, or mortality) but did show a half-day reduction in length of stay (B=–0.47 [95% CI, –0.62 to –0.33]).⁴⁴

- In a meta-analysis of 21 national cohort studies including 9.7 million global participants eligible for oral anticoagulants, the prevalence of DOAC use increased from 0.00 (95% CI, 0.00–0.00) in 2010 to 0.45 (95% CI, 0.45–0.46) in 2018.⁴⁵ On the other hand, the prevalence of vitamin K antagonist use decreased from 0.42 (95% CI, 0.22–0.65) in 2010 to 0.32 (95% CI, 0.32–0.32) in 2018. Nine percent of participants in 2018 were treated with

Other Arrhythmias

- In an analysis of inpatient and outpatient claims ≥66 years of age (2008–2014), atrial flutter was 0.69 [95% CI, 0.60–0.79]; *P*<0.05).⁴⁹
- In a meta-analysis of 5 studies (N=7545 patients), as the presence of either ≥30 premature atrial contractions, was associated with an increased
- In a French longitudinal cohort study of 1 692 157 matching, isolated sinus node disease was associated with AF (HR, 0.77 [95% CI, 0.73–0.82]) but a higher 1.27 [95% CI, 1.19–1.35]).⁵¹

High Blood Cholesterol and Other Lipids

(See Chapter 7 [High Blood Cholesterol and Other Lipids] for more information.)

LDL Cholesterol

- Evidence from RCTs, mendelian randomization analyses, and population-based cohort studies supports a direct and causal relationship between serum LDL-C and atherosclerotic ischemic stroke risk.
- A meta-analysis of LDL-C–lowering drug treatment trials has demonstrated that every 1–mmol/L (≈39–mg/dL) reduction in LDL-C is associated with a 20% lower risk of ischemic stroke (RR, 0.80 [95% CI, 0.76–0.84]) but a 17% increased risk of ICH (RR, 1.17 [95% CI, 1.03–1.32]).⁵²
- In an analysis of 2046 patients admitted with AIS who had AF, mean heart rate during the AIS period was not associated with stroke recurrence but was associated with higher mortality.⁴⁶
- In an analysis using individual participant data from 5 randomized trials of oral antithrombotic therapy in AF, among 1163 patients with AF and a stroke after

- In an RCT that enrolled individuals with prior ischemic stroke/TIA and evident atherosclerosis, achieving an LDL-C <70 mg/dL (versus an LDL-C target range of 90–110 mg/dL) was associated with a lower risk of subsequent cardiovascular events (HR, 0.78 [95% CI, 0.61–0.98]) without increased risk of ICH.⁵³

- A meta-analysis of 39 primary and secondary prevention trials including 287 651 participants did not demonstrate an association between lipid-lowering therapy and ICH risk (OR, 1.12 [95% CI, 0.98–1.28]).⁵⁴ Another meta-analysis of 8 trials did not demonstrate a difference in the incidence of hemorrhagic stroke among those receiving intensive lipid-lowering therapy (achieved LDL-C <55 mg/dL) and those receiving less intensive treatment (OR, 1.05 [95% CI, 0.85–1.31]).⁵⁵
- A mendelian randomization study demonstrated that every 1-mmol/L reduction in genetically predicted LDL-C was associated with a 25% reduced

Remnant Cholesterol

- Remnant cholesterol is defined as the cholesterol content of triglyceride-rich lipoproteins, including chylomicron remnants, very low-density lipoproteins, and intermediate-density lipoproteins. Remnant cholesterol can be measured in the laboratory or calculated (TC-[HDL-C+LDL-C]). Remnant cholesterol is associated with inflammation, oxidative stress, and accelerated atherosclerosis. In a meta-analysis (N=7 studies), compared with low concentrations of remnant cholesterol, elevated

higher risk of hemorrhagic stroke after full multivariable adjustment (HR, 1.25 [95% CI, 1.03–1.52]).

HDL Cholesterol

- A meta-analysis of 62 prospective cohort studies including 900 501 participants and 25 678 strokes demonstrated that a 1-mmol/L increase in HDL-C level was associated with an 18% lower risk of total stroke (RR, 0.82 [95% CI, 0.76–0.89]); the RR for ischemic stroke was 0.75 (95% CI, 0.69–0.82) but was 1.21 (95% CI, 1.04–1.42) for ICH.⁵⁶
- Genetic predisposition to higher HDL-C has been associated with lower risk of small-vessel ischemic stroke in mendelian randomization analyses.^{57,58}

HDL/LDL Ratio

- Among 384 093 participants in the UK Biobank, compared with an HDL-C/LDL-C ratio of 0.4 to 0.6, an HDL-C/LDL-C ratio <0.4 was associated with a higher risk of ischemic stroke (HR, 1.12 [95% CI, 1.02–1.22]) after full multivariable adjustment.⁵⁹ An HDL-C/LDL-C ratio >0.6 was associated with

Triglycerides

- In a population-based cohort study of 5 688 055 Korean young adults (20–39 years of age) with a median follow-up of 7.1 years, serum triglyceride concentration was associated with an increased risk of stroke (comparing Q4 vs Q1: HR, 2.53 [95% CI, 2.34–2.73]).⁶⁰
- Low triglyceride levels have been associated with an increased risk of hemorrhagic stroke. In the WHS, compared with females in the highest quartile of triglyceride levels, those in the lowest quartile had an increased risk of hemorrhagic stroke (RR, 2.00 [95% CI, 1.18–3.39]).⁶¹
- In an RCT of 8179 participants in 11 countries with established CVD or diabetes, other vascular risk factors, and elevated serum triglycerides despite the use of statin therapy, icosapent ethyl treatment reduced nonfatal stroke risk compared with placebo (HR, 0.71 [95% CI, 0.54–0.94]).⁶²

individuals, remnant cholesterol was associated with stroke risk after adjustment for multiple stroke risk factors and lipid therapy but not other lipid levels (compared with those in the lowest quartile, adjusted HR for those in highest quartile, 1.26 [95% CI, 1.06–1.50]).⁶⁴ The association was nonlinear with a point of inflection for remnant cholesterol <1.78 mmol/L: Remnant cholesterol concentrations were associated with increased risk of stroke when remnant cholesterol was <1.78 mmol/L (HR, 1.25 [95% CI, 1.09–1.44]) but not when remnant cholesterol was ≥1.78 mmol/L (HR, 0.89 [95% CI, 0.74–1.08]).[•] In a mendelian randomization study among 958 434 participants drawn from several large-scale genome-wide association databases designed to strengthen causal inference, genetic variants associated with remnant cholesterol levels were associated with increased risk of total stroke (OR, 1.23 [95% CI, 1.12–1.35]; $P=3.72\times10^{-6}$).⁶⁵ Effects on stroke were not independent of effects of LDL-C, although they were for CAD end points.

Smoking/Tobacco Use

(See Chapter 3 [Smoking/Tobacco Use] for more information.)

- Current smoking is associated with an increased prevalence of MRI-defined subclinical brain infarcts.⁶⁶
- A meta-analysis of 141 cohort studies showed that low cigarette consumption (≈1 cigarette/d) carries an RR of developing stroke of 1.52 (95% CI, 1.10–2.10) compared with the RR associated with high cigarette consumption (≈20 cigarettes/d) of 2.90 (95% CI, 1.54–2.35).⁶⁷ The risk associated with low cigarette consumption is much higher than what would be predicted from a linear or log-linear dose-response relationship between smoking and risk of stroke.⁶⁷
- A comprehensive search included 6 studies with 1 024 401 participants in observational studies that

- assessed the association of electronic nicotine delivery stroke compared with nicotine delivery systems use significant increased risk of CI, 1.17–1.97) compared with ciation was found between tine delivery svstems use and 1.03 [95% CI, 0.87–1.21]).
- A post hoc analysis of the SPS3 rate of persistent smoking after ischemic stroke and its association with a MACE composite of n=6 observational studies), from 33% to 66% with combined with behavioral 46% with pharmacological ioral interventions.^{.74}
 - In a meta-analysis of 18 participants with CHD who time of diagnosis, smoking ated with a lower risk of 0.61 [95% CI, 0.49–0.75]).^{.75} A stroke (ischemic hemorrhagic), MI, and mortality.^{.69}
- and
and

including 9 studies and 11 352 participants showed that smoking cessation was associated with a lower risk of nonfatal stroke (HR, 0.70 [95% CI,

Among 2874 patients included in the study, 570 (20%) were smokers at enrollment, 408 (71.5%) continued to smoke, and 162 (28.4%) quit smoking by 3 months. Rates of MACEs were higher in the persistent smokers compared with never smokers (18.4% versus 14.2%), as was death (7.7% versus 6.3%, respectively). In an

0.53–0.90]).

adjusted analysis, the risk of MACEs and death was higher in the persistent smokers compared with never smokers (HR for MACE, 1.56 [95% CI, 1.16–2.09]; HR for death, 2.0

- In a cross-sectional study from 2016 to 2018 of the US CDC BRFSS survey of stroke survivors (N=6 867 786 stroke survivors), the estimated prevalence of cigarette use was 23.6% (95% CI, 22.7%–24.5%) and prevalence of e-cigarette use was 13.5% (95% CI, 11.8%–15.3%).⁷⁶ In a meta-analysis of studies from Europe, North America, and Asia, adult ever users of smokeless tobacco had a higher risk of fatal stroke (OR, 1.39 [95% CI, 1.29–1.49]).⁷⁷ The risk of stroke and MI did not differ according to smoking status.
- Exposure to secondhand smoke, also called passive smoking or secondhand tobacco smoke, is a risk

- A cross-sectional study of BRFSS between 2016 and 2020 assessed the association between cannabis use (the number of days in the past 30 factor for stroke.
 - A systematic review of 24 articles on the association between secondhand smoke and multiple outcomes found that the RR for both sexes combined was 1.35 (95% CI, 1.22–1.50) for stroke with higher risk in females (1.43 [95% CI, 1.28– 1.61]) than in males (1.40 [95%

days marijuana or hashish was used) and car-
CI, 1.09–1.81]).⁷⁰— A study using
NHANES data sampled from
1988 to 1994 and 1999 to
2012 found that individuals

diovascular outcomes. The association between daily cannabis use and the composite outcome of CHD, MI, and stroke was an aOR of 1.16 (95% CI, 0.98–1.38) and stroke was an aOR of 1.28 (95% CI, 1.13–1.44).⁷⁸ Among nontobacco smokers, daily cannabis use was associated with the composite outcome (aOR, 1.77 [95% CI, 1.31–2.40]) and stroke (aOR, 2.16 [95% CI,

with a prior stroke have greater odds of having been exposed to secondhand smoke (OR, 1.46 [95% CI, 1.05–2.03]), and secondhand smoke exposure was associated with a 2-fold increase in mortality among stroke survivors compared with stroke survivors without the

1.43–3.25]).

PA/Inactivity

exposure (AAMR, 96.4±20.8 per 100 PY versus 56.7±4.8 per 100

(See Chapter 4 [Physical Activity and Sedentary Behavior] for more information.)

- The GBD Study 2019 estimated that low PA PY; $P=0.026$).⁷¹
- The FINRISK study found a strong association between current smoking and SAH compared with nonsmoking (HR, 2.77 [95% CI, 2.22–3.46]) and reported a dose-dependent and cumulative association with SAH risk that was highest in females who were heavy smokers.⁷² A meta-analysis of 75 studies from 32 countries found that for every 1% decrease in population accounted for 1.7% of stroke-related disability globally (95% CI, 0.3%–4.5%) and 2.9% in high-smoking prevalence (mean, 19.3%, range, 0.3%–72.9%), SAH incidence declined by 2.4% (95% CI, 1.6%–3.3%).⁷³
- In a systematic review of efficacy of smoking-cessation pharmacotherapy after stroke (n=2 trials and

income countries (95% CI, 0.5%–8.0%).³

- A prospective study among 437 318 participants in China found that physical inactivity was associated with an increased risk of incident total stroke (aHR, 1.52 [95% CI, 1.37–1.70]), ischemic stroke (aHR, 1.49 [95% CI, 1.33–1.67]), and hemorrhagic stroke (aHR, 1.83 [95% CI, 1.30–2.59]).⁷⁹
- In the REGARDS study, sedentary time was independently associated with higher stroke risk (HR per 1-h/d increase in sedentary time, 1.14 [95% CI, 1.02–1.28]) independently of PA levels.⁸⁰ Light-intensity PA associated with reduced risk of incident

stroke (HR per 1-h/d increase, 0.86 [95% CI, 0.77–0.97]).

- In a case-control study of NHANES participants, self-reported recent moderate-intensity activity (OR, 0.8 [95% CI, 0.7–0.9]), vigorous-intensity activity (OR, 0.6 [95% CI, 0.5–0.8]), and muscle-strengthening exercises (OR, 0.6 [95% CI, 0.5–0.8]) were associated with lower odds of stroke.⁸¹

PA and Stroke Severity/Prognosis

- In a systematic review of 7 observational studies that included 41 800 stroke survivors, prestroke PA was associated with lower stroke severity at hospital admission.⁸²
- In a longitudinal cohort study of 3472 stroke survivors, prestroke physical inactivity was associated with higher odds of dependency for activities of daily living 3 months after stroke (OR, 2.30 [95% CI, 1.89–2.80]).⁸³
- In an observational analysis of 1367 stroke survivors (median, 72 years of age, [95% CI, 1.72–3.75]) compared with poststroke decreasing PA becoming inactive over 6 months.⁸⁴ The association was consistently observed across many demographic and comorbidity subgroups.

Cardiorespiratory Fitness

- In the UK Biobank cohort study (N=66 438; 40–69 years of age), higher cardiorespiratory fitness measured by a treadmill test was associated with lower ischemic stroke (highest tertile versus lowest: HR, 0.71 [95% CI, 0.57–0.89]) but not with hemorrhagic stroke (HR, 0.96 [95% CI, 0.68–1.37]).⁸⁵ Similarly, in the REGARDS study (N=24 162; ≥45 years of age), an association of non-exercise-estimated cardiorespiratory fitness with incident ischemic stroke was observed among

16.13 strokes per 1000 PY; HR, 0.28 [95% CI, 0.15–0.50]).

- Improved cardiorespiratory fitness over time is associated with lower stroke risk. In the Oslo Ischemia Cohort Study (N=1403 males; 40–59 years of age), individuals with an improvement in cardiorespiratory fitness assessed by a bicycle electrocardiographic test between baseline and >7 years later from unfit (below median) to fit (above the median) had 66% lower risk (95% CI, 33%–83%) of incident stroke over 23.6 years compared with those who declined from fit to unfit. Those who declined to unfit had 2.35 times (95% CI, 1.49–3.63) greater risk of incident stroke compared with those who were continuously fit.⁸⁸ Similarly, in the Henry Ford FIT Project (N=9496 male and female individuals; mean age, 55 years), improved

cardiorespiratory fitness was associated with lower stroke risk among White participants (highest tertile versus lowest: HR, 0.54 [95% CI, 0.43–0.69]) but not in Black participants (HR, 1.00 [95% CI, 0.74–1.37]), and there was no association with hemorrhagic stroke in either race group.⁸⁶ Similar results were observed among Chinese individuals in the China Health and Retirement Longitudinal Study (N=10 507; median age, 56 years), in which higher estimated cardiorespiratory fitness at baseline was associated with lower stroke risk (highest quartile, 4.65 strokes per 1000 PY versus lowest quartile, 16.92 strokes per 1000 PY; HR, 0.45 [95% CI, 0.32–0.63]).⁸⁷ The association was observed in males (highest quartile, 6.23 strokes per 1000 PY versus lowest quartile, 17.79 strokes per 1000 PY; HR, 0.61 [95% CI, 0.40–0.95]) and in females (highest quartile, 3.19 strokes per 1000 PY versus lowest quartile,

(See Chapter 5 [Nutrition].)

Kidney and Liver Disease

(See Chapter 12 [Kidney Disease] for more information.)

- A meta-analysis of 38 studies comprising 1 735 390 participants (n=26 405 stroke events) showed that any level of proteinuria was associated with greater stroke risk even after adjustment for cardiovascular risk factors (aRR, 1.72 [95% CI, 1.51–1.95]).⁹⁰ The association did not substantially attenuate with further adjustment for hypertension.
- COMBINE-AF evaluated the safety and efficacy of DOACs versus warfarin across continuous CrCl.⁹¹ Among 71 683 patients, the mean CrCl was 75.5±30.5 mL/min. The incidence of stroke and systemic embolism, major bleeding, ICH, and death increased significantly with worsening kidney function. Major bleeding did not differ between patients randomized to standard-dose DOACs and those randomized to warfarin across continuous CrCl values down to 25 mL/min ($P_{\text{interaction}}=0.61$). Compared with warfarin, standard-dose DOAC use resulted in a significantly lower hazard of ICH (–6.2% in HR per 10-mL/min decrease in CrCl; $P_{\text{interaction}}=0.08$). Compared with warfarin, standard-dose DOAC resulted in significantly lower hazard of stroke and systemic embolism (–4.8% in HR per 10-mL/min decrease in CrCl; $P_{\text{interaction}}=0.01$).
- In a study from the multicenter Japan Stroke Data Bank including 10 392 adult participants with an acute stroke occurring between October 2016 and December 2019, lower eGFR was associated with

high risk of cardioembolic decrease in eGFR, 1.20 [95% lower risk of small-vessel per 1-SD decrease in eGFR, 0.94]).⁹² In addition, eGFR and proteinuria were of an unfavorable functional an mRS score of 3 to 6 at embolic stroke (OR, 1.30 3.18 [95% CI, 2.03–4.98].

vessel occlusion (OR, 1.44 [95% CI, 1.01–2.07] and 2.08 [95% CI, 1.08–3.98], respectively).

- The AXADIA–AFNET 8 trial randomized patients with AF on chronic hemodialysis to either apixaban (2.5 mg twice daily) or a vitamin K antagonist.⁹³ The primary efficacy outcome was a composite of isch-emic stroke, all-cause death, MI, and DVT or PE. There were no differences in safety or efficacy out-comes. Patients with AF on hemodialysis who were on oral anticoagulation remained at high risk of car-diovascular events.
- Among 232 236 patients in the GWTG-Stroke registry, admission eGFR was inversely associated with mortality and poor functional outcomes. After adjust- ment for potential confounders, lower eGFR was associated with increased mortality, with the highest mortality among those with eGFR <15 mL·min⁻¹·1.73 m⁻² without dialysis (aOR, 2.52 [95% CI, 2.07–3.07]) compared with those with eGFR ≥60 mL·min⁻¹·1.73 m⁻². Lower eGFR was also associated with decreased likelihood of being discharged home.⁹⁴
- In a retrospective observational cohort study (N=85 116 patients with incident nonvalvular AF), stroke rates increased from 1.04 events per 100 PY in stage 1 CKD to 3.72 in stage 4 to 5 CKD.⁹⁵ In CRIC, a prospective cohort study of 1778 females

MASLD was associated with 1.2–2.1), MI (1.6 [95% CI, 1.2–2.3]), and maior cerebrovascular events (2.3 [95%

Stroke After Procedures and

- In a meta-analysis of 13 underaoidng TAVR, including 8 and 5 observational studies embolic protection device use and 2161 males with CKD, no significant sex differ- ences in the risk of stroke were found (aHR, 0.83 [95% CI, 0.54–1.28]).⁹⁶ Notably, the mean±SD eGFR was 43.9±17.4 mL·min⁻¹·1.73 m⁻² in females (22% had an eGFR <30 mL·min⁻¹·1.73 m⁻²) and 45.7±16.4 mL·min⁻¹·1.73 m⁻² in males (18% had an eGFR <30 mL·min⁻¹·1.73 m⁻²).
- In the ARIC study cohort (N=12 588 participants; median follow-up time, 24.2 years), those in the top quartile of concentration of the liver enzyme γ-glutamyl transpeptidase compared with those in the lowest quartile were at increased risk of stroke after adjustment for age, sex, and race (aHR, 1.94 [95% CI, 1.64–2.30] for all incident stroke; aHR, 2.01 [95% CI, 1.68–2.41] for ischemic stroke).⁹⁷ There was a dose-response association ($P_{\text{linear trend}} < 0.001$).
- A systematic review of 33 studies (N=10 592 851) examined whether MASLD was associated with cardiovascular events.⁹⁸ The pooled OR found that

a reduction in risk of stroke (OR, 0.84 [95% CI, 0.74–0.95]) and disabling stroke (OR, 0.37 [95% CI, 0.21–0.67]) but not nondisabling stroke (OR, 0.94 [95% CI, 0.65–1.37]).^{.99}

- In a study from the STS National Adult Cardiac Surgery Database, the incidence of postoperative stroke after type A aortic dissection repair was 13%.^{.100} Axillary cannulation (OR, 0.60 [95% CI, 0.49–0.73]) and retrograde cerebral perfusion (OR, 0.75 [95% CI, 0.61–0.93]) were associated with lower risk of postoperative stroke.
- In a meta-analysis of 11 controlled studies (N=3667 patients) of patients undergoing Stanford type B thoracic aortic dissection repair, the endovascular approach was associated with lower risk of stroke than open surgery (3.7% versus 5.0%; RR, 0.71 [95% CI, 0.51–0.98]).^{.101}
- In a retrospective observational registry analysis using the Nationwide Readmissions Database, among 42 114 admissions for LAAO, early stroke (during index admission or within 90 days) occurred in 0.63% of patients; 67% of readmissions with strokes occurred <45 days after implantation.^{.102} Rates of early stroke after LAAO declined from 2016 to 2019 (0.64% versus 0.46%; $P_{\text{trend}} < 0.001$).
- In a meta-analysis of 14 published real-world cohorts of patients undergoing cardiac catheterizations (N=2 188 047 catheterizations), the pooled incidence of perioperative stroke was 193 (95% CI, 105–355) per 100 000.^{.103} Transradial access was associated with a lower risk of perioperative stroke than transfemoral access in adjusted analyses (OR, 0.66 [95% CI, 0.49–0.89]) and in the subgroup limited to prospective cohorts (OR, 0.67 [95% CI, 0.48–0.94]). No independent predictors of periprocedural stroke risk were identified.
- In the PRECOMBAT trial evaluating the long-term outcomes of PCI with drug-eluting stents compared with CABG for unprotected left main CAD, the 10-year incidence of ischemic stroke was not significantly different (HR, 0.71 [95% CI, 0.22–2.23]; incidence rate, 1.9% in the PCI arm [n=300] and 2.2% in the CABG arm [n=300]).^{.104}
- In a meta-analysis among 22 studies of patients undergoing LVAD implantation (N=53 227 patients; 24.2% female), females had a higher risk of total

stroke (OR, 1.32 [95% CI, 1.06–1.66]), ischemic stroke (OR, 1.80 [95% CI, 1.22–2.64]), and hemorrhagic stroke (OR, 1.72 [95% CI, 1.09–2.70]).¹⁰⁵ In a nationwide prospective cohort study from Denmark (N=78 096 patients ≥65 years of age undergoing hip fracture surgery), patients with a CHA₂DS₂-VASc score >5 had a higher risk of ischemic stroke at 1 year compared with those with a score of 1 among those both with [95% CI, 1.37–22.24]; for those without AF: 1.6% versus 7.6%; aHR, 4.91 [95% CI, 3.40–7.10]).¹⁰⁶

Risk Factor Issues Specific to Females

- In a meta-analysis of 11 studies of stroke incidence published between 1990 and January 2017, the pooled crude rate of pregnancy-related stroke was 30.0 per 100 000 pregnancies (95% CI, 18.8–47.9).

The crude rates per 100 000 pregnancies were 18.3 (95% CI, 11.9–28.2) for antenatal/perinatal stroke and 14.7 (95% CI, 8.3–26.1) for postpartum stroke.¹⁰⁷

- Among 80 191 parous females in the WHI Observational Study, those who reported breastfeeding for at least 1 month had a 23% lower risk of stroke than those who never breastfed (HR, 0.77 [95% CI, 0.70–0.83]). The strength of the association increased with increasing breastfeeding duration (1–6 months: HR, 0.81 [95% CI, 0.74–0.90]; 7–12 months: HR, 0.75 [95% CI, 0.66–0.85]; ≥13 months: HR, 0.74 [95% CI, 0.65–0.83]; $P_{\text{trend}} < 0.01$).

- In a prospective cohort study in Japan (N=74 928 adults), weight gain during midlife was associated with an increased risk of stroke in females (aHR, 1.61 [95% CI, 1.36–1.92] for weight gain ≥5 kg) but not in males.¹¹²

- In a population-based matched cohort study in the United Kingdom (n=56 090 females with endometriosis

The strongest association was observed among NH Black females (HR, 0.54 [95% CI, 0.37–0.71]).¹⁰⁸

- In a systematic review and meta-analysis of 78 studies including >10 million participants, any HDP, including gestational hypertension, preeclampsia, or eclampsia, was associated with a greater risk of ischemic stroke; late menopause (55 years of age) and gestational hypertension were associated with a greater risk of hemorrhagic stroke; and oophorectomy, HDP, PTB, and stillbirth were associated with a greater risk of any stroke.¹⁰⁹

- In a systematic review and meta-analysis of 16 cohort studies and 2 case-control studies including 7.8 million participants, females who had a miscarriage or stillbirth had a higher risk of stroke (HR, 1.07 [95% CI, 1.00–1.14] and 1.38 [95% CI, 1.11–1.71], respectively). This increased with each additional miscarriage and stillbirth.¹¹⁰

- In an analysis from the FHS of 1435 females with at least 1 pregnancy before menopause, hysterectomy, or 45 years of age, females with a history of preeclampsia had a higher risk of stroke in later life compared with females without a history of preeclampsia after adjustment for time-varying covariates (RR, 3.79 [95% CI, 1.24–11.60]).¹¹¹

- (aHR, 1.19 [95% CI, 1.04–1.36]) compared with females without endometriosis.¹¹³
- In a case-control analysis of data from the Longitudinal Health Insurance Database 2000 of the Taiwan National Health Research Institutes, among 24 955 females 15 to 49 years of age with dysmenorrhea, nonsteroidal anti-inflammatory drug use and duration of use were associated with increased incidence of stroke. The aHR for nonsteroidal anti-inflammatory drug use was 1.47 (95% CI, 0.93–2.32).¹¹⁴ The aHR for nonsteroidal anti-inflammatory drug use ≥ 24 d/mo was 2.29 (95% CI, 1.36–3.84).
 - In a retrospective cohort study in the Taiwan National Health Insurance Research Database, among females 40 to 65 years of age treated with postmenopausal hormone therapy, the incidence of ischemic stroke was 1.17-fold higher in females treated with conjugated equine estrogen than in those treated with estradiol (4.24 per 1000 PY versus 3.61 per 1000 PY; aHR, 1.23 [95% CI, 1.05–1.44]).¹¹⁵
 - Among people living with HIV, females had a higher incidence of stroke or TIA than males, especially at younger ages.¹¹⁶ Compared with females without HIV, females living with HIV had a 2-fold higher incidence of ischemic stroke.¹¹⁷
 - In a record linkage study among 487 767 primiparous females 15 to 44 years of age with singleton pregnancies giving birth in New South Wales, Australia, from 2003 to 2015, a history of stroke before pregnancy was associated with early-term delivery (37–38 weeks; RR, 1.49 [95% CI, 1.17–1.90]) and a prelabor caesarean delivery (RR, 2.83 [95% CI, 2.20–3.63]).¹¹⁸ There were no differences in other APOs for females with a history of stroke.

SDB and Sleep Duration

(See Chapter 13 [Sleep] for more information.)

- Among 6214 participants without history of stroke in the ELSA dataset, over 8 years of follow-up, compared with those with good sleep quality, poor baseline sleep quality was associated with long-term stroke risk (HR, 2.37 [95% CI, 1.44–3.91]).¹¹⁹ Worsened sleep quality was associated with stroke risk among those with baseline good (HR, 2.08

[95% CI, 1.02–4.26]) and [95% CI, 1.16–3.98]) sleep quality was associated with among those with baseline 0.31 [95% CI, 0.15–0.61]).

- Among 4785 Chinese adults >65 the 2011 CHARLS, short and were not associated with reported good general health als who reported poor health normal sleep duration (7–8 tion (aOR, 2.11 [95% CI, sleep duration (aOR, 1.86, were associated with
- In a mendelian randomization Biobank data (N=446 118 was associated with an bolic stroke (OR, 1.33 [95% long sleep increased the risk (OR, 1.41 [95% CI, 1.02– were not significant after comparisons.¹²¹
- In a mendelian randomization 40 585 stroke cases and 406 using 36 SNPs associated as instrumental variables, associated with large-artery CI, 1.49–30.57]) but not with emic stroke, cardioembolic stroke.¹²²

Psychosocial Factors

Psychological Distress

- In the INTERSTROKE case-control study of 26 919 participants from 32 countries, participants with psy- chological distress had a >2-fold (OR, 2.20 [95% CI, 1.78–2.72]) greater odds of having a stroke than control participants.¹²³
- In a prospective cohort study in Australia (N=221 677 participants; average follow-up, 4.7 years), high psychological distress was associated with increased risk of fatal and nonfatal stroke in females (HR 1.56 [95% CI, 1.26–1.93]) and males (HR, 1.19 [95% CI, 0.96–1.48]) compared with a low level of psychological distress.¹²⁴
- Among 20 688 adults with hypertension in the

Depression and Depressive

- In a meta-analysis of 17 involving 57 761 participants, depressive symptoms were stroke risk (HR, 1.39 [95% CI,
- In INTERSTROKE there was acute stroke in people with compared with those without (OR, 1.46 [95% CI, 1.34– stroke increased as the symptoms increased.¹²⁸
- In REGARDS (N=16 368; ≥45 sistently elevated depressive ciated with higher risk of participants without diabetes 1.48–4.72]) but not in White diabetes (HR, 1.06 [95% CI,
- In REGARDS, depressive by the 4-item Center for Depression scale was stroke.¹³⁰ Participants with 1.27 [95% CI, 1.11–1.43]) and 1.25 [95% CI, 1.03–1.51]) had risk compared with symptoms, with no differential
- Among 1 068 117 older adults System for Research in antidepressant medication increased risk for stroke [95% CI, 1.02–1.06]; recent

China Stroke Primary Prevention Trial, those who reported high levels of psychological stress had 1.40 times the risk of first stroke (95% CI, 1.01–1.94) and 1.45 times the risk of first ischemic stroke (95% CI, 1.01–2.09) compared with those who reported low levels of psychological stress.¹²⁵

- In a meta-analysis of 8 cohort studies involving 3.7 million participants, having posttraumatic stress disorder was associated with higher risk for stroke (HR, 1.59 [95% CI, 1.36–1.86]).¹²⁶

CI, 3.27–3.41]; and past users: HR, 2.06 [95% CI, 2.02–2.10]) compared with antidepressant nonusers.¹³¹

- Among 7108 CHARLS participants followed up for 8 years, those with depressive symptoms but no chronic diseases had 1.66 times the risk of incident stroke (95% CI, 0.95–2.90), those with depressive symptoms and 1 chronic disease had 1.94 times the risk of incident stroke (95% CI, 1.17–3.24), and those with depressive symptoms and at least 2 chronic diseases had 3.00 times the risk of incident stroke (95% CI, 1.85–4.88) compared with those with no depressive symptoms and no chronic diseases.¹³²

Social Isolation and Loneliness

- In the UK Biobank cohort study (N=479 054; mean follow-up, 7.1 years), social isolation (HR, 1.39 [95% CI, 1.25–1.54]) and loneliness (HR, 1.36 [95% CI, 1.20–1.55]) were associated with a higher risk of incident stroke in analyses adjusted for demographic characteristics. However, after adjustment for biological factors, health behaviors, depressive symptoms, socioeconomic factors, and chronic diseases, these relationships were no longer statistically significant. In fully adjusted analyses, social

isolation, but not loneliness, was associated with increased risk of mortality after stroke (HR, 1.32 [95% CI, 1.08–1.61]).¹³³

Social Determinants of Health/Health Equity

- A meta-analysis of cohort and case-control studies between January 2000 and May 2022 examined the association between SES and health-related quality of life after stroke and found that across all SES indicators, people stroke who have lower SES have poorer overall health-related quality of life than those with higher SES. In the “global” meta-analysis combining different SES indicators in 17 studies, health-related quality of life among survivors of stroke was lower in the low-SES group than in the high-SES group (SMD, –0.36 [95% CI, –0.52 to –0.20]; $P<0.0001$). Similar results were found when education and income indicators were used separately (low- versus high-education SMD, –0.38 [95% CI, –0.57 to –0.18]; $P<0.0001$; low-
- Females have a higher lifetime risk of stroke than males. In the Framingham original cohort, lifetime risk of stroke among those 55 to 75 years of age was 1 in 5 for females (95% CI, 20%–21%) and ≈1 in 6 for males (95% CI, 14%–17%).¹³⁸
- In the GCNKSS, sex-specific ischemic stroke incidence rates between 1993 to 1994 and 2015 declined versus high-income SMD, –0.39 [95% CI, –0.59 to –0.19]; $P<0.0001$).¹³⁴
- A cohort study of 3024 Black adult participants in the JHS without prevalent CVD at visit 1 (2000–2004) assessed the association of economic food insecurity and risk of incident CHD, HF, and stroke. In an analysis adjusted for cardiovascular risk and socioeconomic factors, economic food insecurity (defined as receiving food stamps or self-reported not enough money for groceries) was associated with higher risk of incident CHD (HR, 1.76 [95% CI,

females, the decline was from 229 (95% CI, 215–242) to 174 (95% CI, 163–185) per 100 000. This trend was not observed for ICH or SAH.¹³⁹

- A cohort study of cardiovascular events in trans-2118 transmasculine participants with a mean follow-up of 4.0 and 3.6 years, respectively.¹⁴⁰ Incident strokes occurred in 54 transfeminine participants or 4.8 events (95% CI, 3.7–6.3) per 1000 PY and 16 transmasculine participants or 2.1 events per 1000 PY. The adjusted cumulative incidence rate of ischemic stroke among transfeminine women who initiated estrogen therapy compared with cisgender men (95% CI, –2.7% to 50.7%). A systematic review examined the risk of CVD in transgender people.¹⁴¹ The meta-analysis of 10 studies of stroke (95% CI, 1.0–1.8) compared to cisgender stroke (95% CI, 1.0–1.6) compared with cisgender stroke (95% CI, 1.06–2.91]) and incident HFrEF (HR, 2.07 [95% CI, 1.16–3.70]) but not stroke.¹³⁵
- In a multi-institutional, retrospective cohort study of consecutively hospitalized patients with radiographically confirmed stroke and SARS-CoV-2 presenting from March through November 2020, 159 patients across 5 Comprehensive Stroke Centers in metropolitan Chicago, IL, were assessed to determine whether household income was

242) to 174 (95% CI, 163–185) per 100 000. This

gender individuals enrolled 2842 transfeminine and low-up of 4.0 and 3.6 years, respectively.¹⁴⁰ Incident or 4.8 events (95% CI, 3.7–6.3) per 1000 PY and 1000 PY. The adjusted cumulative incidence rate of initiated estrogen therapy compared with cisgender 62.8%) and increased by 27.2% compared with tematic review examined the risk of CVD in trans- showed that transwomen had 1.3 times higher risk der men and transmen had 1.3 times higher risk of

women.

associated with functional outcomes after stroke and COVID-19.

Ischemic stroke occurred in 115 patients (72.3%; median NIHSS score, 7; interquartile range, 0.5–18.5) and hemorrhagic stroke in 37 (23.7%). When age, sex, severe COVID-19, and NIHSS score were controlled for, patients with ischemic stroke and household income above the Chicago median were more likely to have a good functional outcome at discharge (OR, 7.53 [95% CI, 1.61–45.73];

- A systematic review conducted between January 2008 and July 2021 looked at sex differences in ischemic strokes among young adults (18–45 years of age).¹⁴² Overall, in young adults ≤35 years of age, the estimated effect size favored more ischemic strokes in females (IRR, 1.44 [95% CI, 1.18–1.76]; $I^2=82\%$) and a nonsignificant sex difference in young adults 35 to 45 years of age (IRR, 1.08 [95% CI, 0.85–1.38]; $I^2=95\%$).
- A systematic review and meta-analysis through 2020 in Latin America and the Caribbean focused on individuals ≥18 years of age and found a higher stroke incidence among males than females.¹⁴³ The overall pooled stroke incidence was 255 (95% CI, 217–293) per 100 000 PY, with higher incidence rates in males (261 [95% CI, 221–301]) compared with females (217 [95% CI, 184–250]) per 100 000 PY. $P=0.016$).¹³⁶
- In the United States in 2019, males had a lower relative burden of stroke mortality, which ranked fifth and accounted for 4.4% of deaths, compared with females, for whom it ranked third and accounted for 6.2% of deaths.¹³⁷

- In NOMAS, among 3298 stroke-free participants recruited between 1993 and 2001, the greatest incidence rate was observed in Black individuals (13/1000 PY) followed by Hispanic individuals (10/1000 PY), and lowest rate was seen in White

individuals (9/1000 PY).¹⁴⁴ of age, the greatest incidence individuals. The increased individuals was largely and insurance status but females ≥ 70 years of age 1.13–1.93).

- A cohort study compared Black White participants in the groups in the observational

whether clinical trial participation mitigated disparities in stroke risk.¹⁴⁵ The risk of stroke between self-reported White participants in SPRINT and ARIC was not significantly different (inverse propensity-weighted HR 0.78 [0.52–1.19]). Black ARIC participants were twice as likely to have a stroke as White ARIC participants (inverse propensity-weighted HR, 1.96 [95% CI, 1.41–2.71]), but Black SPRINT participants did not have higher stroke risk compared with self-reported White SPRINT or White ARIC participants (inverse propensity-weighted HR, 0.99 [95% CI, 0.68–1.77]

Pacific Islander, American undetermined race than White 26.9%; $P < 0.0001$); to arrive EMS (32.7% versus 16.1%; NIHSS score < 6 (68.7% and to present from a Area Deprivation Index was nearer to the hospital ≤ 7.7 miles; $P = 0.0032$). American race. Asian. Pacific and 0.95 [95% CI, 0.57–1.59], respectively). Black SPRINT participants in the intensive BP control group had a lower risk of stroke compared with Black ARIC participants (inverse propensity-weighted HR, 0.39 [95% CI, 0.20–0.75]). The authors concluded that the absence of the racial disparity in stroke incidence in SPRINT indicated that aspects of the disparity are

Indian or Alaska Native, or undetermined race (OR, 1.083 [95% CI, 1.039–1.127]); Area Deprivation Index by units of 10 (OR, 1.022 [95% CI, 1.020–1.024]); arrival by means other than EMS (OR, 1.193 [95% CI, 1.145–1.124]); and an NIHSS score <6 (OR, 1.085 [95% CI, 1.041–1.129]) were associated with late presentation.

- In a study of NH White females and Black females from the WHI (N=126 018, 9% Black females) followed up through 2010, Black females had a greater risk of total stroke than White females (age-adjusted HR, 1.47 [95% CI, 1.33–1.63]).¹⁴⁸ Adjustment for socioeconomic factors and stroke risk factors attenuated this association, although the higher risk for Black females remained statistically significant in those 50 to <60 years of age (HR, 1.76 [95% CI, 1.09–2.83]).
- In an analysis of pooled SHS and ARIC data, there were 2842 stroke events (7.6%) among 3182 American Indian participants without prior stroke
modifiable.
 - A retrospective cohort of Black participants and White participants in the ARIC, MESA, and REGARDS studies (1983–2019) compared the performance of stroke-specific algorithms with PCE developed for ASCVD for the prediction of new-onset stroke.¹⁴⁶ The study looked at 62 482 participants who were at least 45 years of age and free of stroke or TIA. Significant differences in discrimination were observed by race: C indexes were 0.76 for all 3 models in White females versus 0.69 in Black females (all $P<0.001$) and between 0.71 and 0.72 in White males and between 0.64 and 0.66 in Black males (all $P>0.001$). All algorithms exhibited worse discrimination in Black individuals than in White individuals, suggesting a need to expand the pool of risk factors and improve modeling techniques to address observed racial disparities and improve model performance.
 - A retrospective observational study of patients pre-senting to the Yale New Haven Hospital with AIS from 2010 to 2020 classified patients as presenting early (within 4.5 hours from last known well) or late (beyond 4.5 hours).¹⁴⁷ A total of 2643 patients with AIS were included (36.6% presented early and 63.4% presented late). Patients presenting late were more likely to be Black or African American, Asian,

followed up from 1988 to 2008; there were 613 stroke events (5.9%) among 10 413 White participants from 1987 to 2011. American Indian participants had higher stroke rates in unadjusted analyses. Results were attenuated after adjustment for vascular risk factors, which may be on the causal pathway for this association.¹⁴⁹

- A retrospective study of 34 596 patients admitted to 43 hospitals from January 2016 to September 2020 assessed racial disparities in mechanical thrombectomy in 26 640 NH White individuals (77.0%) and 7956 Black individuals (23.0%) and found that Black individuals with stroke underwent mechanical thrombectomy less frequently than White individuals (aOR, 0.65 [95% CI, 0.54–0.76]), in part because of longer times from last known well to hospital arrival and a lower rate of documented acute large-vessel occlusion (see Organization of Stroke Care section).¹⁵⁰

TIA: Incidence and Prognosis

- Among 14 059 participants in the FHS (1948–2017), the incidence of TIA was 1.19 per 1000 PY.¹⁵¹ In those with a TIA (median follow-up, 8.9 years), 29.5% had a stroke with a median time to

stroke of 1.64 years (interquartile range, 0.07–6.6 years). Compared with age- and sex-matched control subjects without TIA, participants who experienced a TIA were at a higher risk of stroke (aHR, 4.37 [95% CI, 3.30–5.71]) after TIA was 16.7% in the period of 1948 to 1985, 11.1% between 1986 and 1999, and 5.9% from 2000 to 2017 (HR for 90-day risk of stroke for the epoch 2000–2017 compared with 1948–1985, 0.32 [95% CI, 0.14–0.75]).

- TIA confers a substantial short-term risk of stroke, hospitalization for CVD events, and death. In a meta-analysis of 68 studies from 1971 to 2019, the estimated risk of subsequent ischemic stroke

(95% CI, 10–28; $P<0.0001$) of cognitive aging and those with TIA experienced 3 years (95% CI, 0–6; $P=0.021$) of cognitive aging, whereas MI ($P=0.60$) and other

Recurrent Stroke: Incidence, Race and Ethnicity, and Risk Factors

- In a meta-analysis of 10 studies including 13 after a TIA was 2.4% (95% CI, 1.8%–3.2%) within 2 days, 3.8% (95% CI, 2.5%–5.4%) within 7 days, 4.1% (95% CI, 2.4%–6.3%) within 30 days, and 4.7% (95% CI, 3.3%–6.4%) within 90 days.¹⁵² When

stroke survivors and 1428 recurrent strokes during follow-up ranging from 1 to 5 years, hypertension was associated with 67% higher odds of recurrent stroke (95% CI, 45%–92%).¹⁵⁷ Among 17 916 patients in the

PROFESS trial, every 10-point increment in SBP variability, defined as the SD across repeated measurements, was associated with 15% higher hazard (95% CI, 2%–32%) of recurrent stroke.¹⁵⁸

studies were categorized according to date of pub-

lication (before 1999, 1999–2007, after 2007), the risk of subsequent ischemic stroke slightly declined

- Among 1701 community-living participants in the Rotterdam Study who had a first stroke between over time.
- In the Oxford Vascular Study, acute lesions on MRI were identified in 13% of participants with TIA.¹⁵³ In age- and sex-adjusted analyses, participants with acute MRI lesions had a higher

1990 and 2020, the overall 10-year recurrence risk of recurrent ischemic stroke compared with individuals with TIA and a negative MRI (HR, 2.54 [95% CI, 1.21–5.34];

was 18.0% (95% CI, 16.2%–19.8%), 19.3% (95% CI, 16.3%–22.3%) in males, and 17.1% (95% CI, 14.8%–19.4%) in females.¹⁵⁹ Recurrent stroke risk declined substantially over time, with a 10-year risk of 21.4% (95% CI, 17.9%–24.9%) between 1990 and 2000 and 11.0% (95% CI, 8.3%–13.8%) ($P=0.014$).

- In a substudy of the SpecTRA multicenter cohort of participants with transient neurological symptoms, MRI diffusion-weighted imaging performed within 7 days of an event identified a

between 2010 and 2020.

lesion in 35.1% of participants.¹⁵⁴ Among participants with focal symptoms, increased duration of symptoms (up to 24 hours) was directionally proportional to the probability of identifying a lesion (ranging from 30% at <1

- Among 396 patients 18 to 55 years of age with 2007 to 2010, the cumulative 10-year incidence any recurrent cerebrovascular event.¹⁶⁰
- A meta-analysis of 13 cohorts with 59 919 par-higher risk of recurrent stroke (RR, 1.46 [95% CI, hour duration to 72% at 24 hours). This relationship was not present among those with mixed or nonfo-cal symptoms, in whom the predicted probability of a lesion was 35%.
- Among patients with TIA enrolled in the POINT trial, 188 of 1964 patients (9.6%) enrolled with TIA had an mRS score <1 (some disability) at 90 days.¹⁵⁵ In multivariable analysis, age, subsequent ischemic stroke, serious adverse

ischemic stroke or TIA from 3 European centers in rate per 1000 PY was 14.9 (95% CI, 11.3–19.3) for

ticipants found that MetS was associated with

1.07–1.97]).¹⁶¹

events, and major bleeding were significantly associated with disability in TIA. • TIA also may be associated with cognitive decline.

In an individual participant meta-analysis of 6 RCTs testing various interventions among patients with or at risk of vascular disease (N=64 106 patients) in which cognitive performance was measured

- The IPSS compared outcomes after posterior cir-culation arterial ischemic stroke and anterior cir-culation arterial ischemic stroke in neonates and children with AIS up to 18 years of age.¹⁶² Recurrent ischemic events were more frequent in posterior circulation arterial ischemic stroke than anterior cir-culation arterial ischemic stroke (30% versus 22%; $P=0.02$) despite similar rates of secondary preven-tive antithrombotic treatment. Multivariable logistic regression analysis found that posterior circulation arterial ischemic stroke (OR, 1.69 [95% CI, 1.08–2.65]; $P=0.02$) and cervicocephalic artery dissec-tions (OR, 2.39 [95% CI, 1.36–4.22]; $P=0.003$) were risk factors for recurrent ischemic events in before and after outcome events, cognitive aging children. was estimated from normalized neuropsychologi-cal test scores.¹⁵⁶ Compared with those with no event, patients with stroke experienced 18 years

- Clinical features associated with recurrent stroke among participants enrolled in the RE-SPECT ESUS trial were assessed.¹⁶³ A total of 384 of

5390 participants had rate, 4.5%) over a median. Multivariable models revealed before the index event (HR, 2.821), creatinine clearance [95% CI, 1.23–2.321], male [1.27–2.02]), and CHA₂DS₂-VAsC scores of 4 (HR, 1.55 CI, 1.21–2.26]) versus CHA₂DS₂-VAsC scores of 2 stroke.

- A post hoc cohort study was conducted using data from the CNSR from 2007 to 2018 and included patients with ischemic stroke who were enrolled in CNSR in phases I or III within 7 days of symptom onset.¹⁶⁴ Over 10 years, the adjusted cumulative incidence of recurrent stroke within 12 months decreased from 15.5% (95% CI, 14.8%–16.2%) to 12.5% (95% CI, 11.9%–13.1%; $P<0.001$). Although the stroke recurrence rate in China decreased significantly, ≈12.5% of patients still experienced stroke recurrence within 12 months.
- Among 128 789 Medicare beneficiaries from 1999 to 2013, the incidence of recurrent stroke per 1000 PY was 108 (95% CI, 106–111) for White people and 154 (95% CI, 147–162) for Black people. Mortality after recurrence was 16% (95% CI, 15%–18%) for White people and 21% (95% CI, 21%–22%) for Black people. Compared with

associated with long-term. Compared with those treated the risk was increased for 180 minutes (HR, 1.25 [95% for those treated at 181 to 270 [95% CI, 1.12–1.61]).

- In a study in China (N=9022), line-based secondary stroke lower risk of recurrent stroke 0.74–0.991) at 12 months adherence.¹⁶⁹

White people, Black people had higher 1-year risk of recurrent stroke (aHR, 1.36 [95% CI, 1.29–1.44]).¹⁶⁵ In a meta-analysis of publications through September 2017, MRI findings of multiple lesions (pooled RR, 1.7 [95% CI, 1.5–2.0]), multiple-stage lesions (pooled RR, 4.1 [95% CI, 3.1–5.5]), multiple-territory lesions (pooled RR, 2.9 [95% CI, 2.0–4.2]), prior infarcts (pooled RR, 1.5 [95% CI, 1.2–1.9]), and isolated cortical lesions (pooled RR, 2.2 [95% CI, 1.5–3.2]) were associated with increased risk of ischemic stroke recurrence. A history of stroke

- Data from 2015 to 2019 in 1458 hospitals in China found that an increase of $10 \mu\text{g}/\text{m}^3$ in PM₁ (particles with aerodynamic diameter $<1 \mu\text{m}$) was associated with a 1.64% increment in stroke recurrence.¹⁷⁰• In a multicenter Japanese registry (N=12 576 patients with ischemic stroke), both eGFR $<45 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ (aHR compared with eGFR $\geq 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$, 1.22 [95% CI, 1.09–1.37]) and severe proteinuria (aHR, 1.25 [95% CI, 1.07–1.46]) were independently associated with increased risk of recurrent stroke (overall rate of recurrent stroke was 48.0 per 1000 patient-years).¹⁷¹
- In a meta-analysis of 52 studies (N=21 473 patients with stroke), of which 19 studies were adjusted for potential confounding variables, high D-dimer concentrations within 24 hours of stroke (compared with normal for each study) were associated with stroke recurrence (OR, 1.23 [95% CI, 1.11–1.36]) and early neurological deterioration (OR, 1.79 [95% CI, 1.12–2.87]).¹⁷² High fibrinogen concentrations were associated with stroke recurrence (OR, 1.23 [95% CI, 1.17–1.42]) and early neurological deterioration (OR, 2.38 [95% CI, 1.16–4.9]).
- In an individual participant meta-analysis (10 prospective studies, N=8420 patients with ischemic stroke/TIA), interleukin-6 (RR, 1.09 [95% CI, 1.00–1.19]) and high-sensitivity CRP (RR, 1.05 [95% CI, 1.00–1.11]) were marginally associated with recurrent stroke after adjustment for risk factors and treatment.¹⁷³ or TIA was also associated with higher risk (pooled RR, 2.5 [95% CI, 2.1–3.1]). Risk of recurrence was lower for small- versus large-vessel stroke (pooled RR, 0.3 [95% CI, 0.1–0.7]) and for stroke resulting from an undetermined cause versus large-artery atherosclerosis (pooled RR, 0.5 [95% CI,

- In a meta-analysis of 4 studies (N=2452 patients independently associated with risk of recurrent strokes),^{.166} with ischemic stroke), uric acid concentrations were stroke (pooled OR, 1.80 [95% CI, 1.47–2.20]).^{.174}
- In a nationwide Danish registry study of individuals after stroke from 2003 to 2012 (n=60 503
- A meta-analysis of 104 studies with 71 298 patients with ischemic stroke found that moderate to severe WMH burden was associated with increased risk of any recurrent stroke (RR, 1.65 [95% CI, 1.36–2.01]) and recurrent ischemic stroke (RR, 1.90 [95% CI, 1.26–2.88]).^{.167}
- In a nationwide cohort study of Danish patients with first ischemic stroke treated with intravenous tPA, time from symptom onset to treatment was

income was inversely related to long-term, but not short-term, mortality for all causes of death.¹⁷⁵ There was a 5.7% absolute difference ($P<0.05$) in mortality between the lowest- and highest-income groups at 5 years after stroke.

- Employment status was linked to outcomes in a study of 377 symptomatic patients with stroke from the Jisei stroke registry in Tokyo. Patients with regular employment compared with those with nonregular

employment were more likely to have a hyperacute stroke on Monday in reference to Sunday (OR, 2.56 [95% CI, 1.00–6.54]; $P=0.049$) but were also more likely to have a favorable outcome defined as an mRS score of 0 to 2 at 3 months (OR, 2.89 [95% CI, 1.38–6.05]; $P=0.005$).¹⁷⁶

- In the WHO MONICA-psychological program, among a random sample from a Russian/Siberian population 25 to 64 years years of follow-up, the risk of stroke in people with a low level of social network was 3.4 times higher for males (95% CI, 1.28–5.46) and 2.3 times higher for females (95% CI, 1.18–4.49).¹⁷⁷

Genetics and Family History

- Ischemic stroke is heritable, although heritability estimates vary by ischemic stroke subtype.¹⁷⁸ A study of $n=3752$ patients with ischemic strokes and $n=5972$ control subjects estimated ischemic stroke heritability to be 37.9%. Estimated heritability was higher for large-vessel disease (40.3%) and lower for small-vessel disease (16.1%).
- Rare monogenic causes of stroke include Fabry disease, sickle cell disease, homocystinuria, Marfan syndrome, vascular Ehlers-Danlos syndrome (type IV), pseudoxanthoma elasticum, retinal vasculopathy with cerebral leukodystrophy and systemic manifestations, and mitochondrial myopathy, encephalopathy, and lactic acidosis.¹⁷⁹
- Recognizing stroke disparities in African populations, GWASs in African populations are emerging. The first (and only) GWAS of ischemic stroke in indigenous African populations ($N=1683$ cases) identified 2 risk-reducing loci at or near *AADACL2* and *MIR5186*.¹⁸² It is interesting that neither locus was observed in stroke GWASs
 - The largest multiancestry GWAS of stroke conducted to date reported 32 genetic loci for any stroke or stroke subtypes.¹⁸⁰ These loci point to a major role of cardiac mechanisms beyond established sources of cardioembolism. Approximately half of the stroke genetic loci share genetic associations with other vascular traits, most notably BP. The identified loci were also enriched for targets of antithrombotic drugs, including alteplase and cilostazol.
 - Because previous multiancestry stroke GWASs were conducted primarily in European ancestral populations, GWASs in populations with proportionately greater representation of non-European participants also have been conducted.¹⁸¹ One study in 5 ancestries (33% non-European) with $n=110\,182$ cases and $n=1\,503\,898$ controls identified 61 novel independent loci for stroke and stroke subtypes. Putative causal genes included *SH3PXD2A*, *FURIN*, *GRK5*, and *NOS3*, and lead variant effect sizes were highly correlated across ancestral populations. Cross-ancestry and ancestry-specific GRSS predicted ischemic stroke in African populations, East Asian populations, and European populations independently of risk factors.

vessel disease stroke subtype.

- Some stroke genetic loci may be subtype specific.¹⁸⁰ For example, *EDNRA* and *LINC01492* were associated exclusively with large-artery stroke. However, shared genetic influences between stroke subtypes were also evident. For example, *SH2B3* showed shared influence on large-artery and small-vessel stroke, and *ABO* shared influence on large-artery and cardioembolic stroke; *PMF1-SEMA4A* has been associated with both nonlobar ICH and isch-emic stroke.
- A GWAS of ICH suggests that 15% of this heritability is attributable to genetic variants in the *APOE* gene and 29% is attributable to non-*APOE* genetic variants.¹⁸³ Other genes strongly implicated in ICH are *PMF1* and *SLC25A44*, which have been linked to ICH with small-vessel disease.^{184,185}
- A multiancestry GWAS of SAH in 10 754 cases and 306 882 controls of European and East Asian ancestry identified 17 risk loci, 11 of which were not previously reported.¹⁸⁶
- An initial GWAS of small-vessel stroke from the International Stroke Consortium (n=4203 cases and n=50 728 controls) identified a novel association with a region on chromosome 16q24.2.¹⁸⁷ A follow-up study that included n=7338 cases and n=254 798 controls identified 5 loci in European or transethnic meta-analysis (*ICA1L-WDR12-CARF-NBEAL1, ULK4, SPI1-SLC39A13-PSMC3-RAPSN, ZCCHC14, and ZBTB14-EPB41L3*).¹⁸⁸ By extending analyses to simultaneously consider cerebral WMHs and small-vessel stroke, multitrait GWASs identified an additional 7 loci (*SLC25A44-PMF1-BGLAP, LOX-ZNF474-LOC100505841, FOXF2-FOXQ1, VTA1-GPR126, SH3PXD2A, HTRA1-ARMS2, and COL4A2*). Two of these loci (*COL4A2* and *HTRA1*) are implicated in monogenic forms of small-vessel stroke.
- GWASs also have examined early-onset ischemic stroke. One study of participants 18 to 59 years of age (n=16 730 cases and n=599 237 controls from 48 studies) identified 2 independent variants at *ABO*, a known stroke locus.¹⁸⁹ Low-frequency genetic variants (ie, allele frequency <5%) also may contribute to risk of large- and small-vessel

stroke. *GUCY1A3*, for frequency in the lead SNP of ated with large-vessel the α 1-subunit of soluble plays a role in both nitric tion and platelet inhibition and with early MI. Low-frequency may affect ischemic stroke at *ABO*, *TPTE*, *MEP1A*, and the rarity of these variants has challenging.

- Stroke GWASs are now being extended to evaluate genetic correlates of recovery.^{192,193} For example, in the VISP study (N=488), suggestive ($P<5\times 10^{-6}$) evidence of association with motor improvement was identified for 115 new loci.

immediately calling 9-1-1 control at baseline). This rate among intervention control subjects.²⁰⁰

- A retrospective ecological Face, Arm, Speech, Time public health messaging) paions in the general vations of EMS for potential Canada, from 2015 to 2019.²⁰¹ naions of median duration 9

These suggestive loci included variants with putative roles in neuronal repair and did not overlap with loci previously identi-

daily EMS calls increased by 28% ($P<0.001$) for any suspected stroke and by 61% ($P<0.001$) for stroke with symptom onset <5 hours compared with 10.1% for headache (negative control; $P=0.012$). Three of the 5 individual campaigns led to increases in daily EMS calls for stroke (high-est OR, 1.26 [95% CI, 1.11–1.43]). There were no significant changes in calls after individual campaigns for suspected stroke with symptom onset <5 hours.

- Genetically determined higher levels of monocyte chemoattractant protein-1/chemokine (C-C motif) ligand 2 concentrations were associated with high risk of any stroke, including associations with large-artery stroke, ischemic stroke, and cardioembolic stroke, but not small-vessel stroke or ICH. These results implicate inflammation in stroke pathogenesis.¹⁹⁴
- Genetic determinants of coagulation factors, including factor XI and factor VII, have been implicated in the pathogenesis of ischemic stroke.^{195,196}

- Genetic correlation analyses suggest genetic overlaps between ischemic stroke and PA, cardiometabolic factors, smoking, and lung function. Genetic predisposition to higher concentration of small LDL particles was associated with risk of large-artery stroke (OR, 1.31 [95% CI, 1.09–1.56]; $P=0.003$).¹⁹⁷

Stroke Mortality

(See Table 15-1 and Charts 15-4 through 15-6)

- In 2022 (unpublished NHLBI tabulations using CDC WONDER₂₀₂ and the NVSS₂₀₃):
 - On average, someone died of a stroke every 3 minutes 11 seconds.
 - Stroke accounted for ≈1 of every 20 deaths in the United States.
 - When considered separately from other CVDs, stroke ranks fifth among all causes of death, behind diseases of the heart, cancer, unintentional injuries/accidents, and COVID-19.
 - The number of deaths with stroke as an under-

Awareness

lying cause was 165 393 (Table 15-1); the age-

- Awareness of stroke symptoms and signs among US adults improved in NHIS from 2009 to 2014. In 2014, 68.3% of survey respondents were able to recognize 5 common stroke symptoms, and 66.2% demonstrated knowledge of all 5 stroke symptoms and the importance of calling 9-

1-1.¹⁹⁸
• In the 357 participants who completed the South Asian Health Awareness About Stroke program from 2014 to 2017, those ≤60 years of age had

cause of death was 39.5 per 100 000, whereas the age-adjusted rate for any mention of stroke as a cause of death was 71.6 per 100 000.

- Approximately 65% of stroke deaths occurred outside of an acute care hospital.
- More females than males die of stroke each year because of the higher prevalence of elderly females compared with males. Females accounted for 56.6% of US stroke deaths in 2022.
 - a 2.9-point greater increase in score on educational questionnaires than those >60 years of age ($P<0.0001$) after a culturally specific educational presentation on stroke awareness.¹⁹⁹
 - among seniors from underrepresented races and ethnicities found that participants would respond
- A study of a community-partnered intervention

- Conclusions about changes in stroke death rates from 2012 to 2022 are as follows²⁰²:
 - The age-adjusted stroke death rate increased 7.0% (from 36.9 per 100 000 to 39.5 per 100 000), whereas the actual number of stroke deaths increased 28.7% (from 128 546 to 165 393 deaths) to only half of presented stroke symptoms by

- Age-adjusted stroke death rates increased 9.2% for males and 5.8% for females.
- Crude stroke death rates remained the same among people 25 to 34 years of age (0.0%; from 1.3 to 1.3 per 100 000) and increased among people 35 to 44 years of age (14.0%; from 4.3 to 4.9 per 100 000), 45 to 54 years of age (7.8%; from 12.8 to 13.8 per 100 000), 55 to 64 years of age (17.4%; from 28.7 to 33.7 per 100 000), and >85 years of age (12.1%; from 931.2 to 1043.9 per 100 000). In comparison, the crude stroke death rates declined among those 75 to 84 years of age (–2.6%; 272.2 to 265.0 per 100 000). There has been a recent flattening of or increase in death rates among most age groups (Charts 15-4 and 15-5).
- There are substantial geographic disparities in stroke mortality, with higher rates in the southeastern United States known as the Stroke Belt (2018–2020; Chart 15-6). This area is usually defined to include the 8 southern states of North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Historically, the overall average stroke mortality has been ≈30% higher in the Stroke Belt than in the rest of the nation and ≈40% higher in the Stroke Buckle (North Carolina, South Carolina, and Georgia).²⁰⁴

Racial and Ethnic Disparities

(See Chart 15-7)

- In 2022, NH Black males and females had higher

1 year, 39.8% at 5 years, and 58.4% at the end of 24 years of follow-up. Mortality rates were higher after an incident hemorrhagic stroke (67.9%) than after ischemic stroke (57.4%). Age-adjusted mortality after an incident stroke decreased over time (absolute decrease, 8.1 deaths per 100 strokes after 10 years), which was attributed mainly to the decrease

age-adjusted death rates for stroke than NH White males and females, NH Asian males and females, NH Native Hawaiian or Other Pacific Islander males and females, NH American Indian or Alaska Native males and females, and Hispanic males and females in the United States (except NH Native Hawaiian or Other Pacific Islander females, who had the highest age-adjusted death rate among females; Chart 15-7).

- Age-adjusted stroke death rates increased among all racial and ethnic groups; however, in 2022, rates remained higher among NH Black people (57.2 per 100 000; change since 2018, 7.9%) than among NH White people (38.3 per 100 000; change since 2018, 6.4%), NH Asian people (30.3 per 100 000; change since 2018, 3.8%), NH Native Hawaiian or Other Pacific Islander (52.7 per 100 000; change since 2018, 13.1%), NH American Indian or Alaska Native people (30.3 per 100 000; change since 2018, –1.3%), and Hispanic people (35.3 per 100 000; change since 2018, 10.3%).²⁰²
- Data from the ARIC study (1987–2011; 4 US cities) showed that the cumulative all-cause mortality rate after a stroke was 10.5% at 30 days, 21.2% at

Complications and Recovery

Disability

- In 125 548 Medicare fee-for-service beneficiaries discharged from inpatient rehabilitation facilities after stroke, individuals who had a paid caregiver before their stroke had a lower odds of being discharged with potential to recover to full independence after discharge than those who lived with a caregiver or family (OR for walking, 0.59 [95% CI, 0.51–0.69]).²⁰⁵
- In the Swedish Stroke Registry (Riksstroke) of 11 775 patients with first ischemic stroke who were functionally independent before stroke, the number of chronic comorbidities was associated with a poor outcome (dead or dependent; mRS score ≥ 3) at 12 months²⁰⁶: no comorbidity, 24.8%; 1 comorbidity, 34.7%; 2 to 3 comorbid conditions, 45.2%; and ≥ 4 comorbid conditions, 59.4%. At 5 years, these proportions were 37.7%, 50.3%, 64.3%, and 81.7%, respectively. There were substantial negative effects of dementia, kidney disease, and HF.
- In a meta-analysis of 22 studies including 5125 participants, the prevalence of lateropulsion (pusher syndrome) after stroke was 55.1% (95% CI, 35.9%–74.2%).²⁰⁷ This decreased from 52.8% (95% CI, 40.7%–65%) in the acute phase to 37% (95% CI, 26.3%–47.7%) in the early subacute phase and 22.8% (95% CI, 0%–46.3%) in the late subacute phase.
- In a meta-analysis of 55 studies, 56.7% (95% CI, 48.3%–65.1%) of people returned to work after stroke at 1 year and 66.7% (95% CI, 60.2%–73.2%) returned at 2 years in population-based studies.²⁰⁸

Comorbid Complications

- In a systematic review of 47 studies (N=139 432 patients; mean age, 68.3 years; mean NIHSS score, 8.2), the pooled frequency of poststroke pneumonia was 12.3% (95% CI, 11%–13.6%). The frequency was lower in stroke units (8% [95% CI, 7.1%–9%]) than other locations ($P_{\text{interaction}}=0.001$). The frequency of poststroke urinary tract infection was 7.9% (95% CI, 6.7%–9.3%) and of any poststroke infection was 21% (95% CI, 13%–29.3%).²⁰⁹

- In a meta-analysis of 9 studies (7 *Depression* reduced motor function in the [95% CI, 1.40–5.61]), 1.16–3.78]), and a history of 2.78 [95% CI, 1.29–5.97]) ican risk factors for the shoulder pain within the first
- In a meta-analysis of 26 366 studies, the prevalence of was 42%.²¹¹ Poststroke ated with high risk of pneumonia (OR, 4.08 [95% CI, 2.13–7.79]) and mortality (OR, 4.07 [95% CI, 2.17–7.63]). Factors associated with increased risk of poststroke dysphagia include hemorrhagic stroke type (OR, 1.52 [95% CI, 1.13–2.07]), prior stroke (OR, 1.40 [95% CI,
- In a retrospective cohort study beneficiaries admitted for July 1, 2016, to December 31, (n=90 474) were 20% more stroke depression over 1.5 males (n=84 427) in adjusted [95% CI, 1.17–1.23]).²¹⁶
- In a secondary analysis of a center, placebo-controlled trial 1.18–1.67]), severe stroke (OR, 1.38 [95% CI, 1.17–1.61]), female sex (OR, 1.25 [95% CI, 1.09–1.43]), and diabetes (OR, 1.24 [95%

with spontaneous intracranial hemorrhage who completed the Center for Epidemiologic Studies Depression Scale, poststroke depression occurred in 36% of patients at 180 days.²¹⁷ Correlates of depression included female sex (aOR, 1.93, [95% CI, 1.07–3.48]), Hispanic ethnicity (aOR, 3.05 [95% CI, 1.19–7.85]), intraventricular hemorrhage (aOR, 1.88 [95% CI, 1.02–3.45]), right-sided lesions (aOR, 3.00 [95% CI, 1.43–6.29]), impaired cogni-

- Among 938 patients with ischemic stroke in the Spanish Stroke-Chip study, 19 patients (2%) had

tion at day 30 (aOR, 2.50 [95% CI, 1.13–5.54]), and not being at home at day 30 (aOR, 3.17 [95% CI, 1.05–9.57]).

acute decompensated HF, and a 3-biomarker panel including vascular adhesion protein-1 >5.67, NT-proBNP >4.98, and D-dimer >5.38 predicted this outcome with a sensitivity of 89.5% and specificity of 71.7%.²¹² Eighty-six patients (9.1%) had respiratory tract infections, and a panel of inter-leukin-6 >3.97, von Willebrand factor >3.67, and D-dimer >4.58 predicted respiratory tract infection with a sensitivity of 82.6% and specificity of 59.8%.

The addition of the panel to clinical predictors significantly improved the AUCs of receiver-operating characteristic curves for both outcomes.

- In a 2019 meta-analysis of 89 studies (N=7096 patients; 54 studies performed within 1 month of stroke, 23 at 1–3 months, and 12 after 3 months), the prevalence after stroke of SDB with AHI >5 episodes/h was 71% (95% CI, 66.6%–74.8%) and with AHI >30 episodes/h was 30% (95% CI, 24.4%–35.5%).²¹³ Severity and prevalence of SDB were similar at all time periods after stroke.

- In the BASIC project, Mexican American people had a higher prevalence of poststroke SDB, defined as an AHI ≥10, than NH White people (68.5% versus 49.5%) after adjustment for confounders (PR, 1.21 [95% CI, 1.01–1.46]).²¹⁴

- In a meta-analysis of 75 studies including 8670 patients with stroke, the prevalence of sleep apnea was nominally higher in those with hemorrhagic (82.7% [95% CI, 64.4%–92.7%]) compared with patients with ischemic (67.5% [95% CI, 63.2%–71.5%]; $P=0.098$) stroke and in those with supratentorial (64.4% [95% CI, 56.7%–71.4%]) compared with infratentorial (56.5% [95% CI, 42.2%–60.0%]; $P=0.171$) stroke.²¹⁵

- Poststroke depression is associated with higher mortality. Among 15 prospective cohort studies (N=250 294 participants), poststroke depression was associated with an increased all-cause mortality (HR, 1.59 [95% CI, 1.30–1.96]).²¹⁸
- In a secondary analysis of the AFFINITY trial including 1221 participants recruited within 2 weeks of stroke and randomized to fluoxetine or placebo, 36.6% of participants developed depression in the year after their stroke (17.9% had early, 7.4% had late, and 11.4% had persistent depression).²¹⁹ Increased stroke severity, defined as doubling of the measured NIHSS score, was associated with increased risk of early (RR, 2.08 [95% CI, 1.65–2.62]), late (RR, 1.53 [95% CI, 1.14–2.06]), and persistent (RR, 2.50 [95% CI, 1.89–3.32]) depression. In addition, history of depression and having a partner were associated with increased risk of persistent depression (RR, 6.28 [95% CI, 2.88–13.71] and 3.94 [95% CI, 2.42–6.41], respectively).

Functional Impairment

Functional and cognitive impairment and dementia are common after stroke, with the incidence increasing with duration of follow-up.

- In secondary analysis of the AFFINITY RCT evaluating the use of fluoxetine after stroke, improvement in the mRS score was observed in 95% of participants at 12 months.²²⁰ Functional recovery was associated with younger age (<70 years of age at time of stroke); absence of prestroke history of diabetes, CHD, or ischemic stroke; prestroke history of depression, relationship with a partner, living with

others, independence, or paid employment; absence of fluoxetine intervention; ischemic stroke (versus hemorrhagic stroke); and lower baseline NIHSS and Patient Health Questionnaire-9 scores.

- In the EFFECTS cohort of 1367 participants with stroke, there were 2 distinct PA trajectories observed within the first 6 months after a stroke: those who increased their PA and sustained it, and those who decreased their PA and eventually became inactive.⁸⁴ In this cohort, increased PA within the first 6 months after a stroke was associated with functional recovery at 6 months (aOR, 2.54 [95% CI, 1.72–3.75]).
- In a substudy of the prehospital FAST-MAG RCT, ultraearly rapid neurological improvement, defined as an improvement of ≥ 2 on the Los Angeles Motor Scale between prehospital and early after the ED, in ischemic stroke or TIA occurred in 31% of patients (N=1245).²²¹ In addition, compared with those without, any ultraearly rapid neurological improvement was associated with an overall improved recovery (mRS score, 0–1 in 65% versus 35.4%; $P < 0.001$), increased probability of being discharged

Cognitive Impairment and Dementia

- In a study among 4 centers in Shanghai (N=383 patients with AIS), the prevalence of cognitive impairment (MoCA score < 22) was 49.6% at 2 weeks and 34.2% at 6 months.²²² Age, lower level of education, higher glucose level,

Stroke in Infants and Children

- Strokes occurring in childhood and the perinatal period (≤ 28 days of age) are considered distinct entities because of differences in their treatment, diagnostic workup, risk factors, and secondary pre-vention measures.²²⁵

Perinatal Stroke Incidence

- In neonates (≤ 28 days of age), the annual incidence of arterial ischemic stroke is 18.51 per 100 000 live births (95% CI, 12.70–26.97) according to a meta-analysis of 11 neonatal stroke studies.²²⁶ The reported incidence of arterial ischemic stroke in neonates was ≈ 6 times higher than in older children in a large population-based Canadian study (neonates, 10.2/100 000 live births; childhood, 1.72/100 000 PY).²²⁷ In a cohort of Northern California Kaiser members, the prevalence of perinatal hemorrhagic stroke was 6.2 in 100 000 live births (95% CI, 3.8–9.6), presenting with encephalopathy (100%) and

and severe stroke were correlates of poststroke cognitive impairment, and LDL-C level was associated with higher cognitive scores. The DREAM-LDL score had an AUC of the receiver-operating curve of 0.93 for predicting cognitive impairment at 6

emic stroke compared across studies published before and after 2011 remained stable over time. Ischemic strokes are more common in Black children (2.62 per 100 000) than White children (1.01 per 100 000), according to a California-wide hospital discharge database (RR, 2.59 [95% CI, 2.17–3.09])²²⁹ and a population-based cohort in southern England (RR, 2.28 [95% CI, 1.00–4.60]),²³⁰ and are also more common in Asian children (2.92 [95% CI, 1.60–4.90] per 100 000) than White children (1.36 [95% CI, 1.06–1.74] per 100 000; RR, 2.14

months.

- Among 109 patients with ischemic stroke, NIHSS score ($\beta = -0.54$ [95% CI, -0.99 to -0.89]) and preexisting leukoaraiosis severity ($\beta = -1.45$ [95% CI, -2.86 to -0.03]) independently predicted functional independence, primarily through an

[95% CI, 1.11–3.85]).²³⁰ Most of the increased risk effect on cognitive rather than motor scores.²²³

- In a multicenter cohort study of 912 patients with lacunar strokes and 425 control subjects, vascular cognitive impairment was identified in 38.8% of patients with lacunar strokes versus 13.4% of con-

of ischemic stroke in Black children is explained by sickle cell disease, which increased stroke risk >200 times (238 per 100 000 [95% CI, 78–556]) compared with those without (0.83 per 100 000) according to 18 childhood stroke cases captured in the Baltimore–Washington, DC, area.²³¹ Almost half of childhood strokes are hemorrhagic (49%), which includes ICH (33%) and SAH (16%), with a total estimated annual incidence of 1.1 hemorrhagic strokes per 100 000 children 0 to 19 years

trol subjects.²²⁴ Factors associated with vascular cognitive impairment included diabetes (aOR, 1.98 [95% CI, 1.40–2.80]) and higher BMI (aOR, 1.03 [95% CI, 1.00–1.05]). On the other hand,

of age.²²⁹

years of full-time education was found to be associated with lower risk of vascular cognitive impairment (aOR, 0.92 [95% CI, 0.86–0.99]).

- Reported incidence was higher in newborns than in older children (1/3500 live births/y ver-sus 1–2/100 000 live births/y) with a ratio of ≈ 6 times higher.²³² A multicenter prospective study in Beijing included all live births from 17 representa-tive maternal delivery hospitals from March 1, 2019,

to February 29, 2020.²³³ A total of 27 cases were identified, and the incidence of perinatal stroke in Beijing was 1 in 2660 live births, including 1 in 5985 for ischemic stroke and 1 in 4788 for hemorrhagic stroke.

Risk Factors

Perinatal

- Both maternal and neonatal factors are associated with perinatal strokes. A case-control study of 40 perinatal strokes and 120 controls nested in a cohort of 199 176 births in Kaiser Northern California found that history of infertility (OR, 7.5 [95% CI, 1.3–45.0]), oligohydramnios (OR, 5.4 [95% CI, 0.9–31.3]), preeclampsia (OR, 5.3 [95% CI, 1.3–22.0]), prolonged rupture of membranes (OR, 3.8 [95% CI, 1.1–12.8]), cord abnormality (OR, 3.6 [95% CI, 1.0–12.7]), chorioamnionitis (OR, 3.4 [95% CI, 1.1–10.5]), and primiparity (OR, 2.5 [95% CI, 1.0–6.4]) were significantly associated with perinatal strokes.²³⁴ The risk of perinatal strokes increases with multiple risk factors (≥ 1 risk factor: OR, 4.2 [95% CI, 1.4–14.8]; ≥ 2 risk factors: OR, 6.5 [95% CI, 2.6–16.5]; ≥ 3 risk factors: OR, 25.3 [95% CI, 7.9–87.1]).
- An Australian study compared 66 perinatal stroke cases with Australian general population data and found that 87% (52/60) of perinatal strokes had multiple risk factors.²³⁵ The following risk factors were more common among perinatal strokes than the general population: cesarean delivery (50% versus 32%; $P=0.04$), 5-minute Apgar score <7 (16.7% versus 2.0%; $P<0.01$), neonatal resuscitation (45.5% versus 19%; $P<0.01$), and primiparity (64.8% versus 43%; $P<0.01$).
- In a multicenter prospective study in Beijing that included 27 cases of perinatal stroke and 108 controls drawn from among 17 817 live births from 17 representative maternal delivery hospitals in 2019 to 2020, risk factors include primiparity (56% versus 33%; $P=0.045$), placental or uterine abruption/acute chorioamnionitis (7% versus 1%; $P=0.025$), intrauterine distress (59% versus 27%; $P=0.002$), asphyxia/resuscitation (44% versus 8%; $P<0.001$), and severe infection (15% versus 2%; $P=0.015$).²³³

Childhood

- The causes of childhood stroke can be categorized into 3 broad groups: (1) structural genetic predisposition (congenital HD, genetic arteriopathies, collagen defect), (2) hematologic genetic predisposition (hereditary thrombophilia, sickle cell disease), and (3) acquired exposures (infection, trauma, radiation, drugs).²³⁶
- One study reviewed vascular imaging of 355 pediatric ischemic stroke cases and found 36%

with definite an acquired The VIPS pediatric AIS an active defined by active 2.2 [95% CI, including 61 6.9% (23/335) stroke tested the main incidental in

- In an analysis to 2014 903 (28%) cause of patent cardiac ovale, 177 stroke aerv ($n=92$) or supported separate of ischemic quent in 32%;
- Without disease will hood.²⁴¹ In Doppler mentation of children velocities prevalence thalassemia in label phase 2 that even children with cranial risk (treatment cranial pared with A double-that for low-income countries, low-dose hydroxyurea is non-inferior to moderate

Complications

- A cohort study ischemic that 91% of 32% developed

seizures, and 28% experienced learning difficulties at school.²⁴⁵ In a meta-analysis of school-aged children with intraventricular hemorrhage, there was 61% increased risk of hemiplegia (95% CI, 39.2%–82.9%), and 24.2-point lower IQ (95% CI, 17.7–30.7 points lower).²⁴⁶

- Among 355 children with stroke followed up prospectively as part of a multicenter study with a median follow-up of 2 years, the 1 month and 12% (95% CI, 8.5%–15%) at 1 year.²⁴⁷ The sole predictor of recurrence was the presence of an arteriopathy, which increased the risk of recurrence 5-fold compared with previously healthy children with no risk identified after an appropriate stroke assessment (HR, 5.0 [95% CI, 1.8–14]).
- A retrospective study of 83 children first diagnosed with ischemic and hemorrhagic stroke at the Pediatric Department, Chiang Mai University Hospital between January 1, 2009, and December 31, 2018 followed up 51 patients with ischemic (56%) and 32 with hemorrhagic (35.2%) stroke, with a median age at onset of 6.9 years for ischemic and 5.3 years for hemorrhagic stroke.²⁴⁸ The mortality rate was higher in hemorrhagic compared with ischemic stroke (16.6 [95% CI, 8.9–30.8] versus 1.1 [95% CI, 0.3–4.6] per 100 PY). Thirty children (36.1%) developed epilepsy during the follow-up (median duration, 26 months). Recurrent stroke occurred in 1 child with ischemic and 1 child with hemorrhagic stroke.

that the proportion of all strokes in adults <55 years of age increased from 12.9% in 1993 to 1994 to 18.6% in 2005 ($P<0.0001$), which was true in both Black Americans and White Americans.²⁵¹ In the 20 to 54 years of age group, among Black individuals, incidence of stroke increased from 83 per 100 000 PY (95% CI, 64–101) in 1993 to 1994 to 128 per 100 000 PY

Neurological deficits were seen in 70% of childhood ischemic strokes during the follow-up.

Cost

- In a study of 111 pediatric stroke cases admitted to a single American children's hospital, the median 1-year direct cost of a childhood stroke (inpatient and outpatient) was ≈\$50 000, with a maximum approaching \$1 000 000. More severe neurological impairment after a childhood stroke correlated with higher direct costs of a stroke at 1 year and poorer quality of life in all domains.²⁴⁹
- A prospective study at 4 centers in the United States and Canada found that the median 1-year out-of-pocket cost incurred by the family of a child with a stroke was \$4354 (maximum, \$38 666), which exceeded the median American household cash savings of \$3650 at the time of the study and represented 6.8% of the family's annual income.²⁵⁰

Stroke in Young Adults and in Midlife

- Approximately 10% to 20% of strokes occur in

to 1994 to 48 per 100 000 PY (95% CI, 42–53) in 2005. A systematic review of studies reporting stroke incidence in high-income countries comparing younger (usually <45, <55, or <60 years of age) with older age during at least 2 time periods found that among 50 studies in 20 countries, temporal trends in stroke incidence are diverging by age, with less favorable trends at younger versus older ages (pooled relative temporal rate ratio, 1.57 [95% CI, 1.42–1.74]; see the Secular Trends section).⁶

- In the GCNKSS, among young adults 20 to 44 years of age, stroke incidence per 10 000 PY was 17 in 1993 to 1994 and rose to 28 in 2015 ($P<0.05$).¹³⁹ In midlife, among adults 45 to 64 years of age, stroke incidence was 165 in 1993 to 1994 and 171 in 2015 with no significant change over time. From 1985 to 2017, 4451 first-time ischemic strokes were captured in the population-based Dijon Stroke Registry; of these, 469 (10.5%) were in adults 18 to 55 years of age.²⁵² In young adults 18 to 45 years of age, incidence per 100 000 PY was 5.4 (95% CI, 4.3–6.9) before 2003 and rose to 12.8 (95% CI, 10.7–15.1) after 2003. In midlife adults 45 to 55 years of age, incidence per 100 000 PY was 47 (95% CI, 37–61) before 2003 and rose to 82 (95% CI, 67–100) after 2003.
- Stroke incidence may differ by sex among younger adults. In 1 retrospective cohort of young adults with first-time strokes in a US nationwide claims data-base, there were more young females than males with strokes in the 25 to 34 (male/female IRR, 0.70 [95% CI, 0.57–0.86]) and 35 to 44 years of age groups (IRR, 0.87 [95% CI, 0.78–0.98]) from 2001 until 2014.²⁵³ Similarly, a population-based study of residents in Ontario, Canada, found more females than males with first-time strokes or TIAs among those 18 to 29 years of age (female HR, 1.26 [95% CI, 1.10–1.45]), with no sex difference among those 30 to 39 years of age (female HR, 1.00 [95% CI, 0.94–1.06]) and fewer females than males among those 40 to 49 years of age (female HR, 0.84 [95% CI, 0.82–0.87]).⁴

adults <55 years of age, generally referred to as

Risk Factors

young adult and midlife. The GCNKSS, a retrospective population-based epidemiology study, found

- A pooled analysis of consecutive patients with ischemic stroke 18 to 50 years of age looked at

differences in prevalence of of ischemic stroke between racial groups, geographic with different income levels.²⁵⁴ patients from 32 cohorts in 29 included. Hypertension and prevalent in Black individuals (diabetes, 20.7%) and Asian (hypertension 46.1%, diabetes, 20.9%). middle-income countries were

vascular risk factors, and more often died within 3 months compared with those from high-income countries (OR, 2.49 [95% CI, 1.42–4.36]).

- The distribution of risk factors according to the IPSS classification in patients with cryptogenic and noncryptogenic stroke according to the TOAST and ASCOD classification was assessed among 1322 patients 18 to 49 years of age with first-ever, imaging-confirmed ischemic stroke between 2013 and 2021 (median age, 44.2 years; 52.7% males).²⁵⁵ Of these, 333 (25.2%) had a cryptogenic stroke according to the TOAST classification. Additional classification with the ASCOD criteria reduced the number of patients with cryptogenic stroke to 260 (19.7%). When risk factors according to the IPSS were considered, the number of patients with no potential cause or risk factor for stroke reduced to 10 (0.8%).
- A prospective multicenter study of strokes in Korea, the CRCS-K-NIH, analyzed 7095 patients with AIS 18 to 50 years of age from 2008 to 2019.²⁵⁶ Over 12 years, smoking decreased from 68.2% to 54.7% in males ($P<0.001$) and remained similar from 10.7% to 13.2% in females ($P=0.32$); obesity (BMI ≥ 30 kg/m²) more than doubled from 5.2% to 13.1% in males ($P<0.001$) and increased from 5.4% to 9.2% in

stroke, or ICH.²⁵⁸ Those after a mean follow-up (years). young patients with being unemployed (females 2.9]; males OR, 3.2 [95% CI, outcomes assessed by the tal activities of daily living predictors of poor functional >2. instrumental activities of female sex (OR, 2.7 [95% CI,

females ($P=0.053$). However, there was no change over time in hypertension, diabetes, and hyperlipidemia. Although second-ary preventions improved over time, including dual antiplatelets for minor strokes (26.7% to 47.0%; $P<0.001$), DOACs for AF (0% to 56.2%; $P<0.001$), and statins for large-vessel atherosclerosis (76.1% to 95.3%; $P<0.001$), the 1-year stroke recurrence rate increased (4.1% to 5.5%; $P=0.04$).

Long-Term Outcomes

- In a Dutch population-based study of 15 527 patients 18 to 49 years of age with stroke, the 15-year mortality in 30-day ischemic stroke survivors was 5.1 times (95% CI, 4.7–5.4) that of the general population.²⁵⁷ The standardized mortality rate for 30-day survivors of ICH was 8.4 times (95% CI, 7.4–9.3) that of the general population.
- A hospital-based study followed up 694 patients 18 to 50 years of age with first-ever TIA, ischemic

line NIHSS score (OR, 1.1 [95% CI, 1.1–1.2]).²⁵⁹ In the Young ESUS longitudinal cohort study conducted in 41 stroke research centers in 13 countries, a total of 535 consecutive patients ≤50 years of age (mean±SD age, 40.4±7.3 years; 297 [56%] male) with a diagnosis of embolic stroke of undetermined source were enrolled.²⁶⁰ The recurrent ischemic stroke and death rate was 2.19 per 100 patient-years, and the ischemic stroke recurrence rate was 1.9 per 100 patient-years.

Organization of Stroke Care

- The RACECAT trial assessed 1401 patients with suspected acute large-vessel occlusion stroke in Catalonia, Spain, between March 2017 and June 2020.²⁶¹ The investigators compared transportation to an EVT-capable center (n=688) with transportation to the closest local stroke center (n=713) and assessed disability at 90 days. Patients directly transported to EVT-capable centers had lower odds of thrombolysis (229/482 [47.5%] versus 282/467 [60.4%]; OR, 0.59 [95% CI, 0.45–0.76]) and higher odds of EVT (235/482 [48.8%] versus 184/467 [39.4%]; OR, 1.46 [95% CI, 1.13–1.89]). There was no significant difference in 90-day neurological outcomes. Among patients with ICH (n=302), direct transfer to an EVT-capable center resulted in worse functional outcome at 90 days (OR, 0.63 [95% CI, 0.41–0.96]).²⁶²
- MSUs are ambulances equipped with a CT scanner and personnel able to treat acute stroke in the prehospital setting.²⁶⁴ An observational, prospective multicenter trial in the US (BEST-MSU) assessed outcomes from MSU or standard of care within 4.5 hours after onset of acute stroke symptoms.²⁶⁵ Using on a 1-week-on/1-week-off study design, the trial found that n=617 received care by MSU and n=430 by EMS. Utility-weighted mRS scores at 90 days were better in those treated with the MSU (0.73) compared with EMS (0.67; OR, 2.12 [95% CI, 1.54–2.93]). A prospective nonrandomized study in Germany enrolled patients with suspected stroke (B_PROUD).²⁶⁶ Simultaneous dispatch of MSU with conventional ambulance (n=749) compared with conventional ambulance alone (n=794) showed that

patients with MSU dispatched had lower median mRS score at 3 months (1; interquartile range, 0–3) compared with those with conventional ambulance dispatched (2; interquartile range, 0–3; OR for worse mRS score, 0.71 [95% CI, 0.58–0.86]).

- A retrospective study of US patients ≥ 65 years of age in the GWTG-Stroke linked to a Medicare database looked at the effect of $n=38\,913$ treated with thrombolysis and $n=3946$ treated with both thrombolysis and EVT, each 15-minute delay in door-to-needle time for thrombolysis was associated with higher odds of never discharged home (aOR, 1.12 [95% CI, 1.06–1.19]), less time spent at home (aOR, 0.93 [95% CI, 0.89–0.98]), and higher all-cause mortality (aHR, 1.07 [95% CI, 1.02–1.11]). In the secondary analysis, thrombolysis and EVT were compared with EVT only. Shorter door-to-needle time for thrombolysis (≤ 60 , 45, and 30 minutes) achieved better functional outcome (mRS score 0–2) at discharge (22.3%, 23.4%, and 25.0%, respectively) compared with EVT only (16.4% $P<0.001$ for each).
- An observational study in the United Kingdom characterized factors leading to longer ambulance on-scene times for suspected patients with stroke. Among $N=2307$ patients, 3 potentially modifiable factors were identified as

(2018–2021) in the Transition of Care Stroke Disparities Study who were discharged home or to rehabilitation and had an mRS score of 0 to 3.²⁶⁹

Using a summary metric of adequate transition of care behavior,

investigators found that 1 in 3 patients did not attain 30-day adequate transition of care behaviors.

COMPASS, a large cluster randomized trial, identified contributors to extended on-scene times: performing additional advanced neurological assessment added 10% (34 minutes versus 31 minutes; $P<0.001$), intravenous cannulation added 13% (35 minutes versus 31 minutes; $P<0.001$), and ECGs added 22% (35 minutes versus 28 minutes; $P<0.001$). In a multinational survey of neurointerventionalists to quantify time savings that could be achieved in optimizing workflows for EVT, prenotification of the neurointerventional team (≈ 19 minutes), optimizing the spatial setup (≈ 18 minutes), streamlining workflow in the ED (≈ 17 minutes), all-time available anesthesiologist (≈ 18 minutes), and prepared thrombectomy equipment and kits (≈ 13 minutes) were identified as time-saving steps.²⁶⁸

- A wide array of artificial intelligence clinical decision support systems have been developed for the diagnosis and recognition of early ischemic stroke. A systematic review and meta-analysis of artificial intelligence-driven ASPECTS software for the

telephone visit within 2 days and a clinical visit between 7 and 14 days of discharge, which incorporated education and caregiver support. Hospitals had difficulty maintaining staffing; only 35% of patients completed in-person clinic visits, and 59% had outcomes data, which did not show significant benefit (functional status based on Stroke Impact Scale-16 at 90 days; 80.6 ± 21.1 in treatment group versus 79.9 ± 21.4 in usual care; $P=0.61$).

Hospital Discharges and Ambulatory Care Visits

- In 2021, there were 889 399 inpatient discharges from short-stay hospitals with stroke as the principal diagnosis (HCUP, unpublished NHLBI tabulation).
- In 2021, there were 806 960 ED visits with stroke as the principal diagnosis (HCUP,²⁷¹ unpublished NHLBI tabulation). In 2019, physician office visits for a first-listed diagnosis of stroke totaled 2 782 000 (NAMCS,²⁷² unpublished NHLBI tabulation).
- An analysis of the NIS 2011 to 2012 for AIS found that after risk adjustment, all underrepresented racial and ethnic groups except Native American people had a significantly higher likelihood of length of stay ≥ 4 days than White people.²⁷³

Operations and Procedures

- In the HCUP 2013 to 2016 Nationwide Readmissions Database ($n=925\,363$ AIS admissions before the endovascular era [January 2013–January 2015] and $n=857\,347$ during the endovascular era [February 2015–December 2016]), the proportion of patients receiving intra-venous thrombolysis increased from 7.8% to 8.4%, and the proportion receiving endovascular therapy doubled from 1.3% to 2.6%.²⁷⁴ Length of stay declined from 6.8 to 5.7 days in the endovascular era, but total charges were higher (\$56 691 versus \$53 878).
 detection of early stroke changes in noncontrast CT, including 11 studies with $N=1976$ patients, found good reliability of automatic predictions compared with reference standard (intraclass correlation coefficient, 0.72 [95% CI, 0.61–0.80]).
 • Adequate transition of care behaviors was

- A systemic review comparing complications of intra-venous tenecteplase with alteplase for the treatment of AIS examined results from 26 studies.²⁷⁵ The RR of symptomatic ICH in tenecteplase- versus alteplase-treated patients was 0.89 (95% CI, 0.65–1.23), assessed in 550 participants with

- AURORA, a pooled patient-domized clinical trials, vessel occlusions of the >6 and up to 24 hours from Among N=505 patients. EVT and 239 controls. EVT ability at 90 days (aOR, 2.54 No significant difference in EVT and controls was days (16.5% versus 19.3%) or (5.3% versus 3.3%).
- A systematic review examined the effect of EVT in patients with occlusions of the basilar artery by 4 randomized clinical trials (BEST, BASICS, BAOCHE, and ATTENTION).²⁷⁷ A total of 988 patients were enrolled (556 in EVT and 432 in medical therapy). Patients undergoing EVT were more likely to achieve favorable outcomes (mRS score 0–3: RR, 1.54 [95% CI, 1.16–2.04]) and functional independence (mRS score 0–2: RR, (487 in general anesthesia, anesthesia). General lization during EVT from [95% CI, 1.26–2.42]) and the achieving functional recovery versus 44.6%; OR, 1.43 [95% CI, 1.08–3.08]) at 90 days. However, patients undergoing EVT had higher risk of symptomatic ICH (RR, 7.48 [95% CI, 2.27–24.61]). A systematic review examined the effects of EVT in anterior circulation strokes with large core infarcts (ASPECTS 3–5) by 3 randomized clinical

Cost

- In 2020 to 2021 (average 1.83 [95% CI, 1.08–3.08]) at 90 days. However, patients undergoing EVT had higher risk of symptomatic ICH (RR, 7.48 [95% CI, 2.27–24.61]). A systematic review examined the effects of EVT in anterior circulation strokes with large core infarcts (ASPECTS 3–5) by 3 randomized clinical

lished NHLBI tabulation):

– The estimated direct medical cost of ischemic stroke/TIA was \$25.0 billion. This includes hospital outpatient or office-based health care professional visits, hospital inpatient stays, ED visits, prescribed medicines, and home health care.

Separate estimates of the direct medical cost of hemorrhagic and unspecified stroke are not available. The indirect cost of stroke (all types) mortality was \$24.0 billion.

- The mean expense per patient for direct care for any type of service (including hospital inpatient stays, outpatient and office-based visits, ED visits, prescribed medicines, and home health care) in the United States was estimated at \$7034 for ischemic stroke/TIA (unpublished NHLBI tabulation using trials (RESCUE Japan-LIMIT, ANGEL-ASPECT, and SELECT-2).²⁷⁸ A total of 1101 patients were included (510 in EVT, and 501 in medical management). The RR for the primary outcome of mRS score of 0 to 2 favored EVT (RR, 2.53 [95% CI, 1.84–3.47]). Symptomatic ICH occurred more frequently in the EVT arm but did not reach significance (RR, 1.84 [95% CI, 0.94–3.60]).
- In an individual patient-level meta-analysis of 7 cohort studies, a 10-point increase in mean SBP levels during the first 24 hours after EVT was associated with a lower functional improvement (aOR, 0.88 [95% CI, 0.84–0.93]), mRS score ≤ 2 (aOR, 0.87 [95% CI, 0.82–0.93]), and higher all-cause mortality (aOR, 1.15 [95% CI, 1.06–1.23]) at 3 months.²⁷⁹ However, a recent RCT of 821 patients in China who underwent successful EVT comparing intensive BP control (target <120 mm Hg) with less intensive BP control (target, 140–180 mm Hg) was stopped prematurely.

- Among Medicare beneficiaries >65 years of age in the US nationwide GWTG-Stroke Registry linked to Medicare claims data (2011–2014), in those with minor stroke (NIHSS score ≤ 5) or high-risk TIA (n=62 518 patients from 1471 hospitals), the mean Medicare payment for the index hospitalization was \$7951, and the cumulative all-cause inpatient Medicare spending per patient (with or without any subsequent admission) was \$1451 at 30 days and \$8105 at 1 year.²⁸³
- In an analysis of trends in physician reimbursement from 2000 to 2019, after adjustment for inflation, the average reimbursement for stroke (*ICD-10* I60–I63) procedures decreased by an average of 0.43%/y (11.2% from 2000–2019).²⁸⁴ The adjusted reimbursement rate for telestroke codes decreased by 12.1% from 2010 to 2019, and from 2005 to 2019, the reimbursement for alteplase rose by 163.98% (average of +7.3%/y) because of safety concerns. Patients in the more intensive BP control arm had a higher incidence of poor functional outcome and early neurological

- Between 2015 and 2035, total direct medical stroke-related costs are projected to more than double, from \$36.7 billion to \$94.3 billion, with deterioration.²⁸⁰
- A systematic review examined the efficacy of general anesthesia versus nongeneral anesthesia techniques such as conscious sedation or local anesthesia alone among patients undergoing EVT for large-vessel occlusion strokes.²⁸¹ Seven RCTs were included that enrolled a total of 980 patients

much of the projected increase in costs arising from those ≥ 80 years of age.²⁸⁵

- The total cost of stroke in 2035 (in 2015 dollars) is projected to be \$81.1 billion for NH White people, \$32.2 billion for NH Black people, and \$16.0 billion for Hispanic people.²⁸⁵

Global Burden of Stroke

Prevalence

(See Tables 15-4 through 15-7 and Charts 15-8 through 15-11)

Based on 204 countries and territories in 2021²⁸⁶:

- Globally, there were 93.82 (95% UI, 89.03–99.34) million prevalent cases of all stroke subtypes. The age-standardized prevalence rate decreased by 1.34% (95% UI, –3.77% to 1.03%) from 2010 to 2021 (Table 15-4).
- Among regions, age-standardized stroke prevalence rates were highest for sub-Saharan Africa and East, Southeast, and Central Asia. Rates were the lowest for Australasia (Chart 15-8).
- The global prevalence of ischemic stroke was 69.94 (95% UI, 64.79–75.01) million cases. There was an increase of 1.07% (95% UI, –1.96% to 4.11%) in the age-standardized prevalence rate from 2010 to 2021 (Table 15-5).
- Among regions, age-standardized prevalence of ischemic stroke was highest for southern sub-Saharan Africa, followed by western sub-Saharan Africa and East and Central Asia (Chart 15-9).
- The prevalence of ICH among regions was highest for western sub-Saharan Africa, Southeast Asia, Oceania, and high-income Asia Pacific (Chart 15-10).
- The global prevalence of SAH was 7.85 (95% UI, 7.16–8.58) million cases. There was a decrease
- Globally, the number of total deaths attributable to ischemic stroke was 3.59 (95% UI, 3.21–3.89) million. The age-standardized mortality rate decreased by 15.76% (95% UI, –20.47% to –11.09%) from 2010 (Table 15-5).
- Age-standardized mortality attributable to ischemic stroke among regions was highest for Eastern Europe, followed by North Africa and the Middle East and Central Asia. Mortality was lowest for Australasia (Chart 15-13).
- Globally, the number of total deaths attributable to ICH was 3.31 (95% UI, 3.02–3.59) million. The age-standardized mortality rate decreased by 19.35% (95% UI, –25.63% to –12.77%) from 2010 (Table 15-6).
- Among regions, ICH mortality was highest for Oceania, followed by Southeast and East Asia and central and eastern sub-Saharan Africa. (Chart 15-14).
- Globally, the number of total deaths attributable to SAH was 2.65 (95% UI, 2.36–2.94) million. The age-standardized mortality rate decreased by 4.08% (95% UI, –5.91% to –1.95%) in the age-standardized prevalence rate from 2010 to 2021 (Table 15-7).
- Age-standardized prevalence of SAH among regions was highest for high-income Asia Pacific and Andean Latin America (Chart 15-11).

COVID-19 and Stroke

- A systematic review assessed the risk of ischemic stroke in COVID-19 survivors after SARS-CoV-2 infection.²⁸⁷ The analysis included 8 studies with 23 559 428 patients (mean age 56; 54.3% males), 1 595 984 of whom had COVID-19. Over the follow-up period, incident ischemic stroke occurred in 4.40 (95% CI, 4.36–4.43) of 1000 patients with a previous COVID-19 infection compared with 3.25 (95% CI, 3.21–3.29) of 1000 noninfected patients. Patients who were recovered from COVID-19 presented a higher risk of ischemic stroke (HR, 2.06

[95% CI, 1.75–2.41]; $P<0.0001$; $I^2=63.7\%$)

compared with people who did not have COVID-19. Patients with COVID-19 hospitalized at the time of the infection had a subsequent higher risk of stroke during the follow-up compared with those not

Mortality

(See Tables 15-4 through 15-7 and Charts 15-12 through 15-15)

Based on 204 countries and territories in 2021²⁸⁶:

- The number of total deaths attributable to

was 7.25 (95% UI, 6.57–7.81) million, and the age-standardized mortality rate decreased by 17.45% (95% UI, –22.96% to –12.12%) since 2010 (Table 15-4).

- Age-standardized mortality attributable to stroke among regions was highest for Oceania and Southeast Asia. Rates were lowest for Australasia and Western Europe (Chart 15-12).

- A systematic review was conducted to identify the influence of the COVID-19 pandemic on the presentation and treatment of stroke globally in populations ≥ 65 years of age.²⁸⁸ In 38 articles included, 84% of studies reported decreased admissions rates during the COVID-19 pandemic and higher severity of stroke on average among those admitted. Implementation of COVID-19 protocols resulted in

increased treatment times in increased in-hospital mortality. The prevalence of stroke (intracerebral hemorrhagic) and primary thrombolysis (intravenous or thrombolysis) did not change during the COVID-19 pandemic.

- A retrospective multicenter cohort study of the safety and outcomes of thrombolysis in consecutive patients tested for COVID-19.²⁸⁹ Of the

853 (5.6%) were diagnosed with COVID-19; 5848 (38.7%) received intravenous thrombolysis only, and 9280 (61.3%) endovascular treatment (with or without intravenous thrombolysis).

neurological disorders during the vaccination phase of the

- In an interim analysis of safety from the Vaccine Safety Datalink, vaccine-eligible members were followed from December 14, 2020, to December 26, 2021.²⁹² A total of 11 845 111 vaccinees (57% BNT162b2; 6 699 315 second doses) were included in the analysis to 6.2 million individuals.

Patients with COVID-19 had a higher rate of symptomatic ICH.

females). The incidence of selected serious out-comes was not significantly higher 1 to 21 days after vaccination compared with 22 to 42 days after vaccination, including incidence of ischemic stroke (1612 versus 1781; RR, 0.97 [95% CI,

(aOR, 1.53 [95% CI, 1.16–2.01]), symptomatic SAH (OR, 1.80 [95% CI, 1.20–2.69]), and symptomatic ICH and symptomatic SAH combined (OR, 1.56 [95% CI, 1.23–1.99]) and had an unfavorable shift in the distribution of mRS score at 3 months (OR, 1.42 [95% CI, 1.26–1.60]).

- An international multicenter retrospective cohort study of consecutive patients with AIS tested for

0.87–1.08]).

SARS-CoV-2 receiving intravenous thrombolysis and endovascular treatment between 2020 and 2021 evaluated the safety and outcomes of revascularization treatments in patients with AIS with asymptomatic or symptomatic COVID-19 com-

- A recent review looked at stroke and cerebro-vascular disease as a complication of the SARS-CoV-2 infection and outlined the main clinical and radiological characteristics of cerebrovascular complications of vaccinations, with a focus on vaccine-induced immune thrombotic thrombocytopenia.²⁹³ The review found that the risk of stroke and other outcomes of interest (thrombocytopenia, VTE, arterial thrombosis, cerebral venous sinus thrombosis, and MI) after a SARS-CoV-2 infection was significantly higher than after vaccination with either the Oxford-AstraZeneca or the Pfizer

pared with COVID-19–negative controls.²⁹⁰ Among 15 124 patients from 105 centers, 849 (5.6%) had COVID-19, of whom 395 (46%) were asymptomatic and 454 (54%) were symptomatic. Compared with controls, patients with asymptomatic COVID-19 and symptomatic COVID-19 had higher symptomatic ICH rates (COVID-19 controls, 5%; asymptomatic COVID-19, 7.6%; symptomatic COVID-19, 9.4%), with an aOR of 1.43 (95% CI, 1.03–1.99) and 1.63 (95% CI, 1.14–2.32), respectively.

- The Neuro-COVID Italy study, a multicenter, observational cohort study recruited consecutive hospitalized patients presenting new neurological disorders associated with COVID-19 (neuro-COVID-19).²⁹¹ Among 52 759 hospitalized patients with COVID-19, 1865 presented with 2881 neuro-COVID-19 cases. The incidence of

vaccine.

neuro-COVID-19 declined over time in a comparison of the first 3 pandemic waves (8.4%, 5.0%, 3.3%, respectively; $P=0.027$). The most frequent neurological disorders were acute encephalopathy (25.2%), hyposmia-hypo-geusia (20.2%), AIS (18.4%), and cognitive impairment (13.7%). During a median of 6.7 months of follow-up, a good functional outcome was achieved by 64.6% of patients with neuro-COVID-19, and disabling symptoms were common only in stroke survivors (47.6%). Incidence of COVID-associated

- A retrospective review of patients with a discharge diagnosis of AIS from the GWTG data-base from 2 Comprehensive Stroke Centers in New York was performed from January 1, 2019, to July 1, 2020, comparing the pre-COVID-19 (January/February), peak COVID-19 (March/ April), and post-COVID-19 time periods. Stroke volumes were found to be significantly lower during the peak COVID-19 period in 2020 compared with 2019 (absolute decline, 49.5%; $P<0.001$). Patients were more likely to present after 24 hours from last known well during the 2020 peak COVID-19 period ($P=0.03$), but there was not a significant difference in the rate of treatment with either tPA or mechanical thrombectomy during the peak COVID-19 period. Relative treatment rates increased during the 2020 post-COVID-19 period to 11.4% ($P=0.01$).²⁹⁴
- A cohort study using the French national database of hospital admissions extracted data on all hospitalizations in France with at least 1 stroke diagnosis between January 1, 2019, and June 30, 2020.²⁹⁵ Stroke hospitalizations dropped from March 10, 2020 (slope gradient, -11.70) and began to rise again from March 22 (slope gradient, 2.090) to May 7, representing a total decrease of 18.42%. The

percentage change was -15.63%, -25.19%, and -18.62% for ischemic strokes, TIAs, and hemorrhagic strokes, respectively. Overall stroke hospitalizations in France experienced a decline during the first lockdown period, which could not be explained by a sudden change in stroke incidence and thus is likely to be a direct or indirect result of the COVID-19 pandemic.

- A cohort study of patients with COVID-19 3, 2020, and August 28, 2020, with and without AIS and a subcohort of hospitalized patients with COVID-19 demonstrating a neurological symptom with and without AIS was conducted. A total of 1827 patients were included (AIS, n=44; no AIS, n=1783). Among all hospitalized patients with

with a history of stroke who were <60 years of age (derivation AUC, 0.83; validation AUC, 0.81). In an ischemic stroke control cohort without COVID-19 (n=168), patients with AIS were significantly older and less likely to have had a prior stroke.²⁹⁶

- A systematic review looked at the clinical features and etiological characteristics of patients with COVID-19, history of stroke and platelet count >200×1000/μL at hospital presentation were independent predictors of AIS (derivation AUC, 0.89; validation AUC, 0.82), regardless of COVID-19 severity. In the subcohort of patients with a neurological symptom (n=827), the

tile range, 55–75 years); 75% were male; stroke occurred after a median of 6 days from COVID-19 infection diagnosis; and patients had a median NIHSS score of 19. Cryptogenic strokes were more frequent (51.8%) followed by cardioembolic strokes (26.5%). A significant association was observed between the etiological classification and the interval between the COVID-19 diagnosis and the cerebrovascular event ($P_{\text{trend}}=0.039$). The clinical severity of stroke was significantly associated with the severity grade of COVID-19 infection risk of AIS was significantly higher among patients ($P_{\text{trend}}=0.03$).²⁹⁷

Table 15-1. Stroke in the United States

Population group	Prevalence, 2017–2020, ≥20 y of age	New and recurrent attacks, 1999, all ages	Mortality, 2022, all ages*	Age-adjusted mortality rates per 100 000 (95% CI),*
Both sexes	9 400 000 (3.3% [95% CI, 2.8%–3.8%])	795 000	165 393	39.5 (39.3– 39.7)
Males	4 000 000 (2.9%)	370 000 (46.5%)†	71 819 (43.4%)†	40.5 (40.2–40.8)
Females	5 400 000 (3.6%)	425 000 (53.5%)†	93 574 (56.6%)†	38.2 (38.0–38.5)
NH White males	2.7%	325 000‡	51 042	38.6 (38.2–38.9)
NH White females	3.6%	365 000‡	68 887	37.5 (37.2–37.8)
NH Black males	4.8%	45 000‡	10 293	63.5 (62.2–64.8)
NH Black females	5.4%	60 000‡	12 363	52.2 (51.3–53.2)
Hispanic males	2.5%	...	6673	37.6 (36.7–38.6)
Hispanic females	2.5%	...	7551	33.0 (32.2–33.7)
NH Asian males	1.8%	...	2852§	31.6 (30.4–32.7)§
NH Asian females	1.5%	...	3630§	29.0 (28.1–30.0)§
NH American Indian or	...	...	747	30.3 (28.1–32.5)
NH Native Hawaiian or Other	...	...	298	52.7 (46.6–58.9)

CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading.

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.²⁹⁸

COVID-19 indicates coronavirus disease 2019; ellipses (...), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Mortality for Hispanic people, American Indian or Alaska Native people, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native decedents, Asian and Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total stroke incidence or mortality that applies to males versus females.

‡Estimates include Hispanic and NH people. Estimates for White people include other non-Black races.

§Includes Chinese, Filipino, Japanese, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.²⁹⁹ Percentages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population. Incidence: Greater Cincinnati/Northern Kentucky Stroke Study and National Institutes of Neurological Disorders and Stroke data for 1999 provided on July 9, 2008. US estimates compiled by NHLBI. See also Kissela et al.³⁰⁰ Data include children. Mortality (for underlying cause of stroke): Unpublished NHLBI tabulation using National Vital Statistics System²⁰³ and CDC WONDER.²⁰² These data represent underlying cause of death only.

Table 15-2. Hemorrhagic Stroke in Relation to BP Categories in Korea Among 947 378 Adults 20 to 64 Years of Age Who Had Stable BP Levels During 10 Years of Observation, 2009 to 2018 (335 Cases of ICH and 566 Cases of SAH)

Korean National Health	SBP/DBP categories, mm Hg		
	<110/<80	110–119/<80	120–129/<80
ICH			
Males			
Incidence rate per 100 000 person-years	4.9	2.9	3.8
HR (95% CI)	1.00 (reference)	0.68 (0.43–1.08)	0.95 (0.52–1.74)
Females			
Incidence rate per 100 000 person-years	2.7	2.4	3.4
HR (95% CI)	1.00 (reference)	0.91 (0.59–1.40)	1.24 (0.56–2.76)

BP indicates blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; ICH, intracerebral hemorrhage; P-Y, person-years; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

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Table 15-3. SAH in Relation to BP Categories in the United Kingdom Among 500 598 Adults 40 to 69 Years of Age Over a Mean of 4.5 Years of Follow-Up, 2006 to 2017 (539 Cases of SAH)

UK Biobank	SBP categories, mm Hg					
	<120	120–129	130–139	140–159	160–179	>180
HR (95% CI)	1.00 (reference)	1.41 (1.02–1.95)	1.74 (1.28–2.38)	1.60 (1.18–2.16)	1.99 (1.39–2.84)	1.81 (1.02–3.21)
DBP categories, mm Hg						
	<80	80–84	85–89	90–99	100–109	>100
HR (95% CI)	1.00 (reference)	1.26 (1.00–1.58)	1.07 (0.83–1.39)	1.31 (1.03–1.66)	1.61 (1.09–2.40)	3.23 (1.66–6.31)
Meta-analysis with UK Biobank	SBP categories, mm Hg					
	<120	120–130	130–140	140–160	160–180	>180
Males						
HR (95% CI)	1.00 (reference)	1.37 (1.00–1.90)	1.64 (1.00–2.69)	1.64 (0.93–2.91)	1.91 (1.01–3.59)	2.41 (0.63–9.12)
Females						
HR (95% CI)	1.00 (reference)	1.42 (1.09–1.84)	1.93 (1.49–2.50)	2.16 (1.40–3.32)	3.35 (1.77–6.34)	7.47 (1.53–36.52)

BP indicates blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

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Table 15-4. Global Mortality and Prevalence of Total Stroke by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	7.25 (6.57 to 7.81)	93.82 (89.03 to 99.34)	3.78 (3.43 to 4.15)	47.81 (45.34 to 50.57)	3.48 (3.07 to 3.81)	46.01 (43.54 to 48.77)
Percent change (%) in total	44.09 (32.29 to 56.03)	86.09 (83.00 to 89.35)	57.69 (40.28 to 76.50)	93.20 (90.01 to 96.68)	31.75 (20.05 to 45.24)	79.23 (75.92 to 82.59)
Percent change (%) in total	14.30 (6.47 to 21.79)	28.39 (25.08 to 31.49)	15.88 (5.03 to 27.70)	27.56 (24.17 to 30.77)	12.62 (4.39 to 21.84)	29.26 (25.96 to 32.50)
Rate per 100 000, age standardized	87.45 (78.92 to 94.14)	1099.31 (1044.17 to 1162.11)	103.07 (93.06 to 112.85)	1184.35 (1124.19 to 1252.12)	74.54 (65.81 to 81.55)	1027.71 (974.35 to 1088.08)
Percent change (%) in rate, age	-39.40 (-43.96 to -34.65)	-8.48 (-9.67 to -7.33)	-34.32 (-41.22 to -27.04)	-6.69 (-8.08 to -5.37)	-44.16 (-48.91 to -38.75)	-10.82 (-12.10 to -9.49)
Percent change (%) in rate, age	-17.45 (-22.96 to -12.12)	-1.34 (-3.77 to 1.03)	-16.47 (-24.10 to -8.33)	-2.54 (-5.02 to -0.15)	-18.62 (-24.49 to -12.00)	-0.33 (-2.76 to 2.03)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²⁸⁶

Table 15-5. Global Mortality and Prevalence of Ischemic Stroke by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	3.59 (3.21 to 3.89)	69.94 (64.79 to 75.01)	1.78 (1.61 to 1.96)	35.24 (32.61 to 37.81)	1.81 (1.57 to 2.00)	34.70 (32.10 to 37.27)
Percent change (%) in total	55.00 (43.20 to 66.76)	101.76 (97.30 to 105.84)	76.56 (56.08 to 99.55)	109.68 (104.98 to 114.08)	38.41 (27.12 to 50.27)	94.30 (90.22 to 98.95)
Percent change (%) in total	19.02 (12.15 to 25.83)	33.38 (29.23 to 37.48)	22.87 (12.41 to 34.82)	32.42 (28.25 to 36.59)	15.47 (8.48 to 22.87)	34.36 (30.09 to 38.57)
Rate per 100 000, age	44.18 (39.29 to 47.81)	819.47 (760.26 to 878.71)	51.16 (46.21 to 56.22)	881.94 (818.60 to 944.54)	38.54 (33.46 to 42.53)	769.40 (712.98 to 825.99)
Percent change (%) in rate, age standardized,	-39.60 (-43.79 to -35.32)	-3.53 (-5.12 to -2.06)	-33.13 (-40.35 to -25.01)	-2.55 (-4.35 to -0.75)	-44.85 (-48.86 to -40.36)	-5.28 (-6.91 to -3.53)
Percent change (%) in rate, age	-15.76 (-20.47 to -11.09)	1.07 (-1.96 to 4.11)	-13.71 (-20.71 to -5.76)	-0.62 (-3.68 to 2.54)	-17.82 (-22.68 to -12.52)	2.46 (-0.82 to 5.48)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²⁸⁶

Table 15-6. Global Mortality and Prevalence of ICH, by Sex, 2021

	Both sexes		Male	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	3.31 (3.02 to 3.59)	16.60 (15.16 to 18.18)	1.82 (1.63 to 2.05)	9.35 (8.49 to 10.24)
Percent change (%) in total	41.29 (27.35 to 56.22)	48.59 (43.95 to 52.76)	51.19 (31.05 to 75.70)	57.95 (52.65 to 62.71)
Percent change (%) in total	9.93 (1.28 to 19.05)	13.85 (10.57 to 16.89)	10.46 (-1.76 to 23.96)	14.15 (10.55 to 17.61)
Rate per 100 000, age	39.09 (35.65 to 42.45)	194.51 (177.99 to 212.53)	47.43 (42.33 to 53.18)	225.08 (204.86 to 245.59)
Percent change (%) in rate, age	-36.58 (-42.54 to -29.83)	-22.27 (-23.92 to -20.71)	-32.65 (-41.50 to -21.74)	-17.97 (-19.91 to -16.20)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; ICH, intracerebral hemorrhage; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²⁸⁶

Table 15-7. Global Mortality and Prevalence of SAH, by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	0.35 (0.31 to 0.40)	7.85 (7.16 to 8.58)	0.17 (0.14 to 0.22)	3.54 (3.22 to 3.89)	0.18 (0.16 to 0.21)	4.31 (3.95 to 4.69)
Percent change (%) in total	-5.89 (-22.78 to 25.51)	60.21 (56.86 to 63.39)	-3.98 (-25.98 to 57.27)	61.68 (57.93 to 65.11)	-7.67 (-25.96 to 26.54)	59.01 (55.62 to 62.07)
Percent change (%) in	10.84 (1.56 to 22.37)	20.68 (18.39 to 23.46)	8.57 (-2.94 to 23.87)	20.77 (18.27 to 23.67)	13.13 (1.57 to 27.47)	20.61 (18.35 to 23.38)
Rate per 100 000, age standardized	4.18 (3.66 to 4.76)	92.17 (84.08 to 100.60)	4.48 (3.64 to 5.56)	85.52 (77.67 to 93.74)	3.91 (3.41 to 4.55)	97.88 (89.66 to 106.58)
Percent change (%) in rate, age	-56.12 (-64.27 to -40.74)	-16.13 (-17.70 to -14.76)	-55.15 (-65.76 to -23.58)	-14.16 (-15.73 to -12.76)	-57.16 (-65.47 to -41.07)	-17.64 (-19.20 to -16.20)
Percent change (%) in rate, age	-16.83 (-23.82 to -8.26)	-4.08 (-5.91 to -1.95)	-17.90 (-26.66 to -6.46)	-3.16 (-5.11 to -0.96)	-15.76 (-24.53 to -5.13)	-4.80 (-6.63 to -2.78)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; SAH, subarachnoid hemorrhage; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²⁸⁶

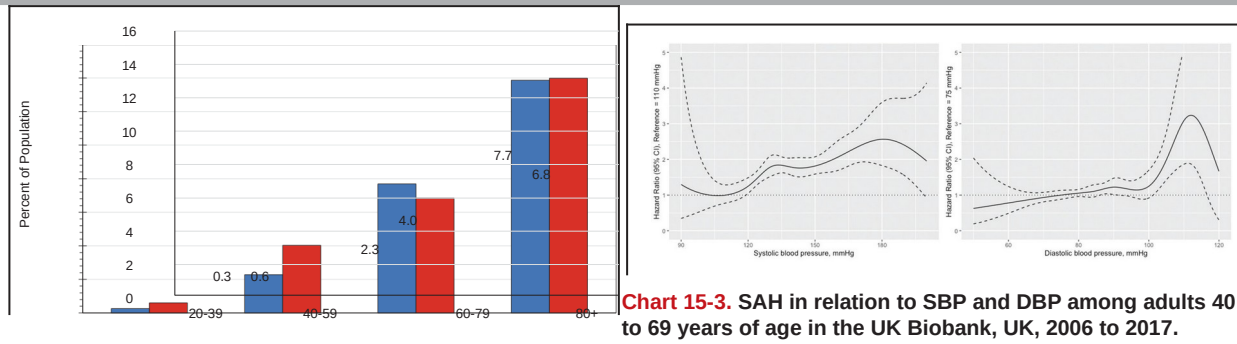
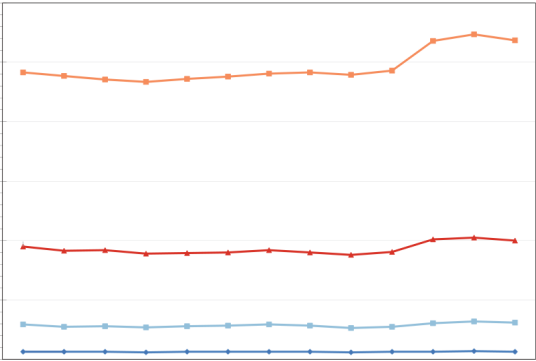


Chart 15-1. Prevalence of stroke, by age and sex, United States (NHANES, 2017–2020).

NHANES indicates National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.²⁹⁹



DBP. Solid line represents the HR; dotted line represents the 95% CI.
Reference for SBP was 110 mm Hg and for DBP was 75 mm Hg.
DBP indicates diastolic blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HR, hazard ratio; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.
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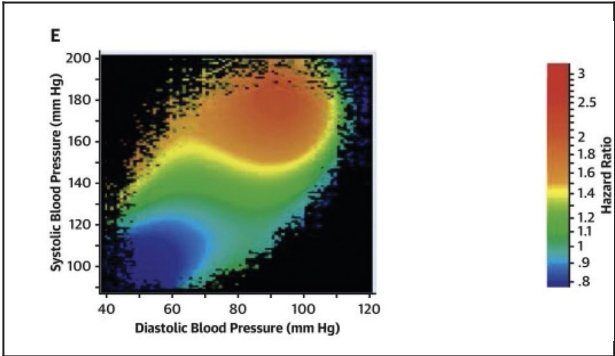


Chart 15-2. Heat map of stroke risk at all combinations of SBP and DBP observed in ALLHAT.

ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; DBP, diastolic blood

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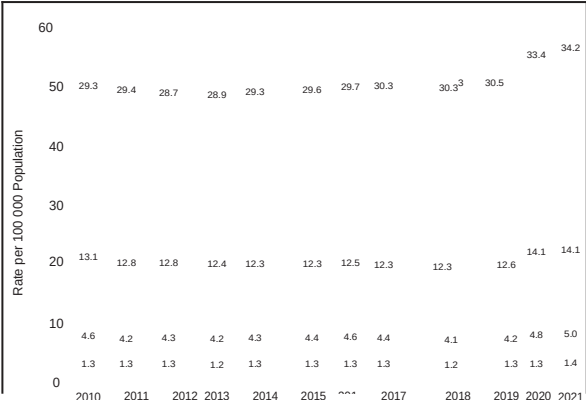


Chart 15-4. Crude stroke mortality rates among young US adults (25–64 years of age), 2010 to 2022.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.²⁰²

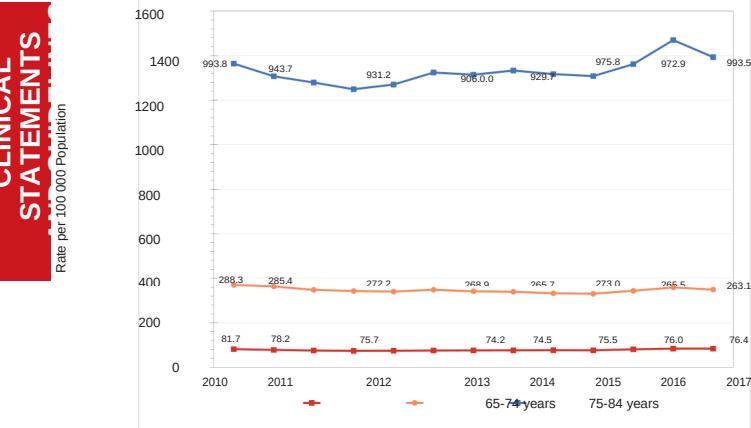


Chart 15-5. Crude stroke mortality rates among older US adults (≥65 years of age), 2010 to 2022.

Source: Unpublished National Heart, Lung, and Blood Institute
tabulation using Centers for Disease Control and Prevention
Wide-
Ranging Online Data for Epidemiological Research.²⁰²

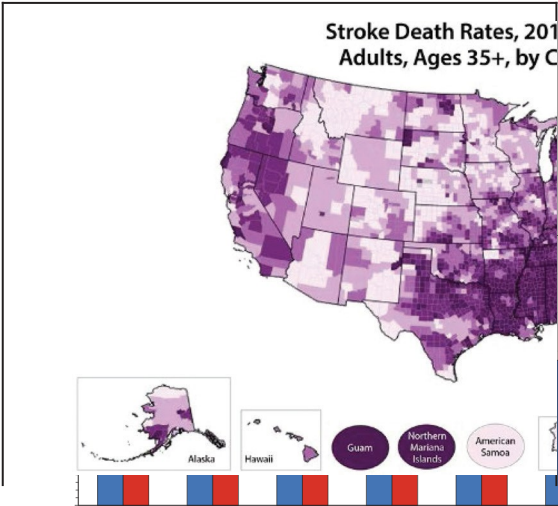


Chart 15-6. Stroke death rates, 2018 through 2020, among adults ≥35 years of age, by US county.

Rates are spatially smoothed to enhance the stability of rates in counties with small populations. ICD-10 codes for stroke: I60 through I69. CDC indicates Centers for Disease Control and Prevention; and ICD-10, International Classification of Diseases, 10th

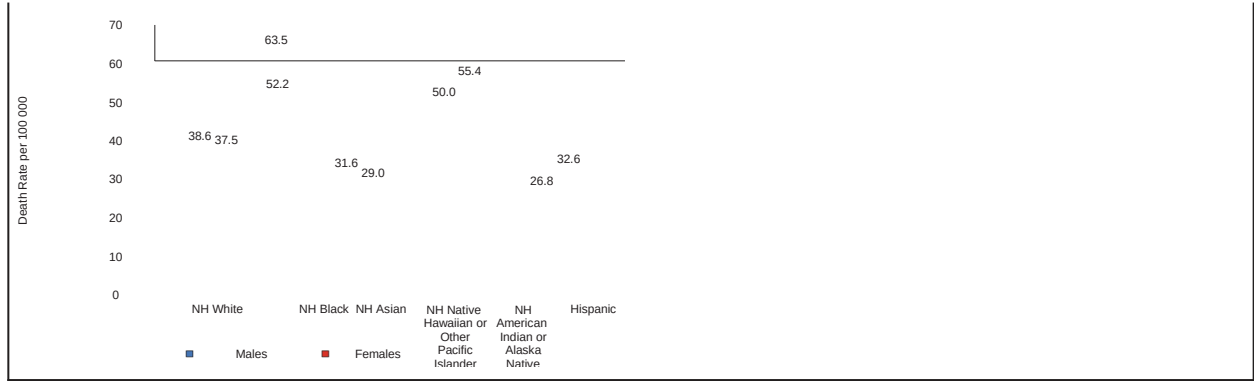


Chart 15-7. Age-adjusted death rates for stroke, by sex and race and ethnicity, United States, 2022.

Death rates for the American Indian or Alaska Native and Asian or Pacific Islander populations are known to be underestimated. Stroke includes *ICD-10* codes I60 through I69 (cerebrovascular disease). *ICD-10* indicates *International Classification of Diseases, 10th Revision*; and NH, non-Hispanic. Source: Unpublished National Heart, Lung, and Blood Institute

tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.²⁰²

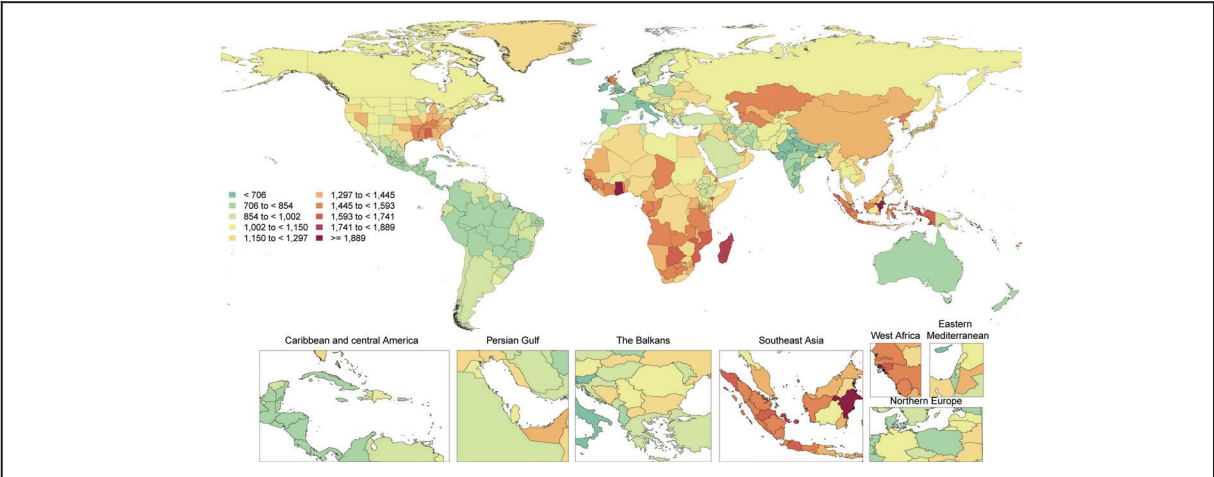


Chart 15-8. Age-standardized global prevalence rates of total stroke (all subtypes) per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

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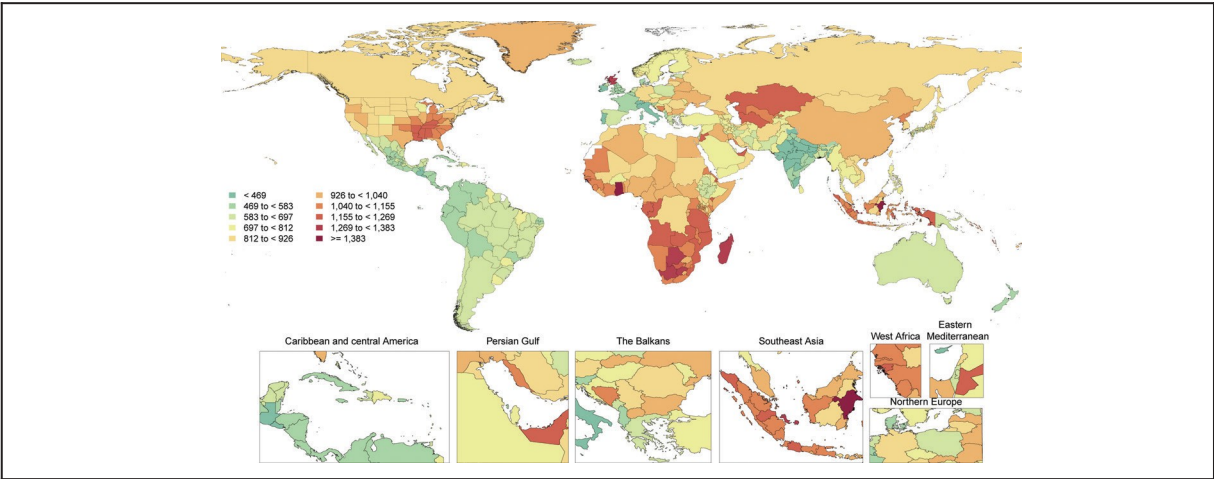


Chart 15-9. Age-standardized global prevalence rates of ischemic stroke per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

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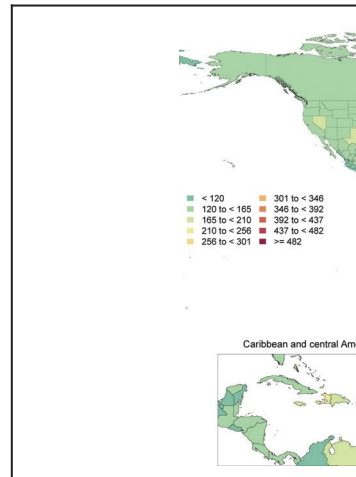


Chart 15-10. Age-standardized global prevalence rates of ICH per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and ICH, intracerebral hemorrhage.

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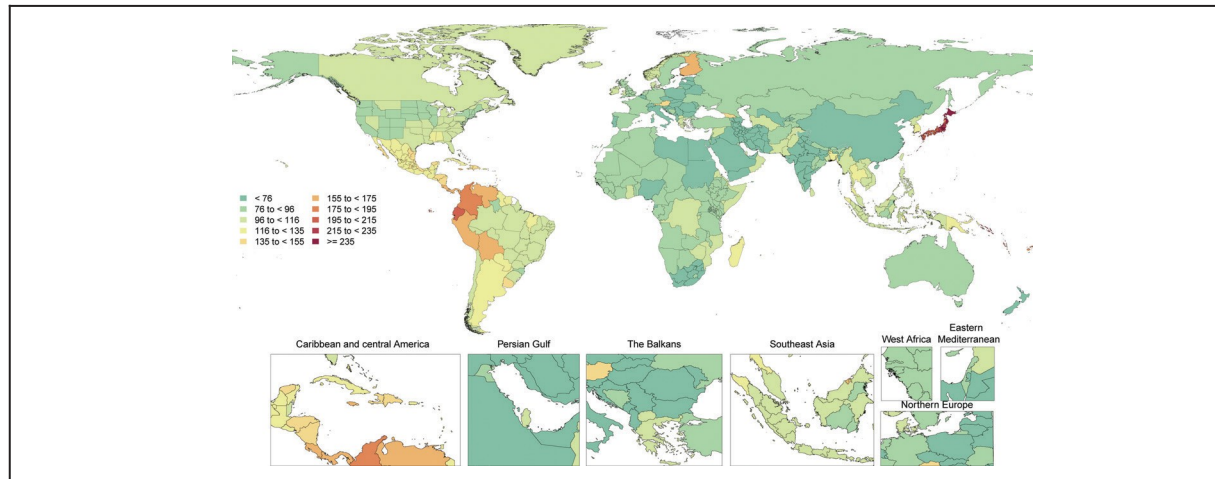


Chart 15-11. Age-standardized global prevalence rates of SAH per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and SAH, subarachnoid hemorrhage.

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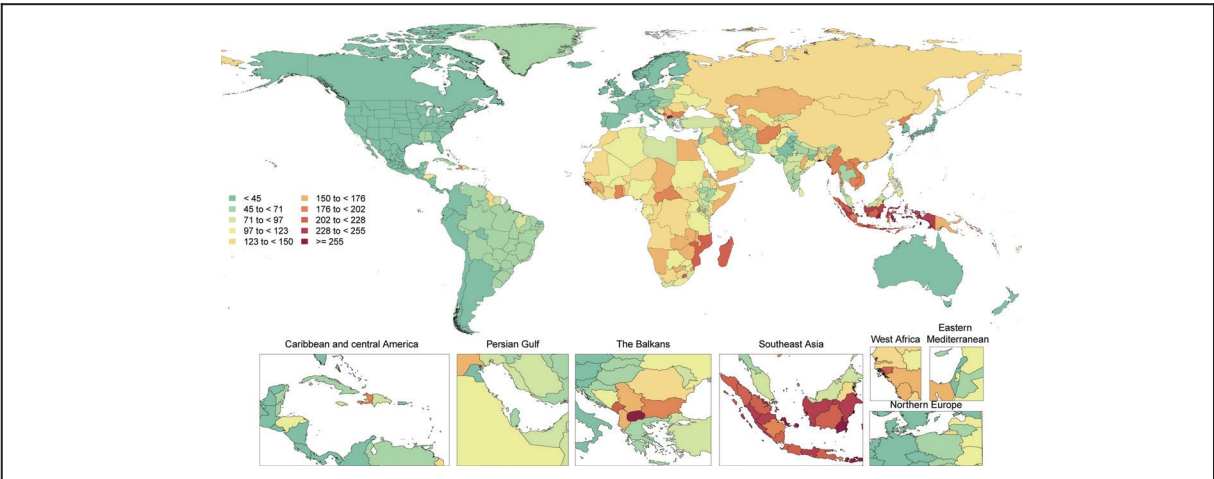


Chart 15-12. Age-standardized global mortality rates of total stroke (all subtypes) per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

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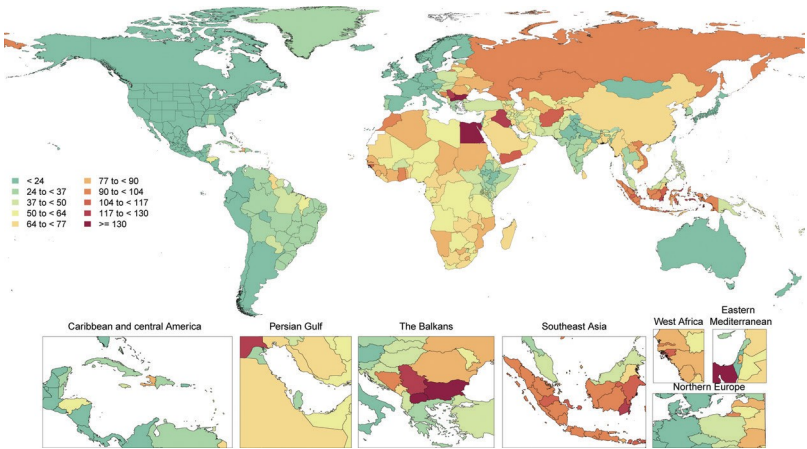


Chart 15-13. Age-standardized global mortality rates of ischemic stroke per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

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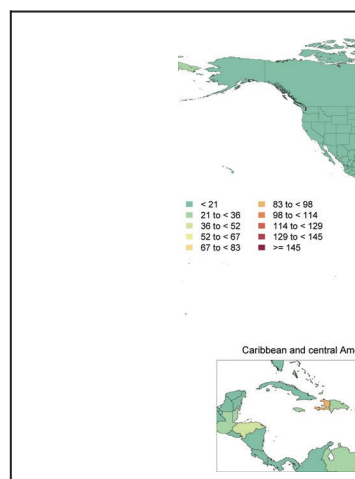


Chart 15-14. Age-standardized global mortality rates of ICH per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and ICH; intracerebral hemorrhage.

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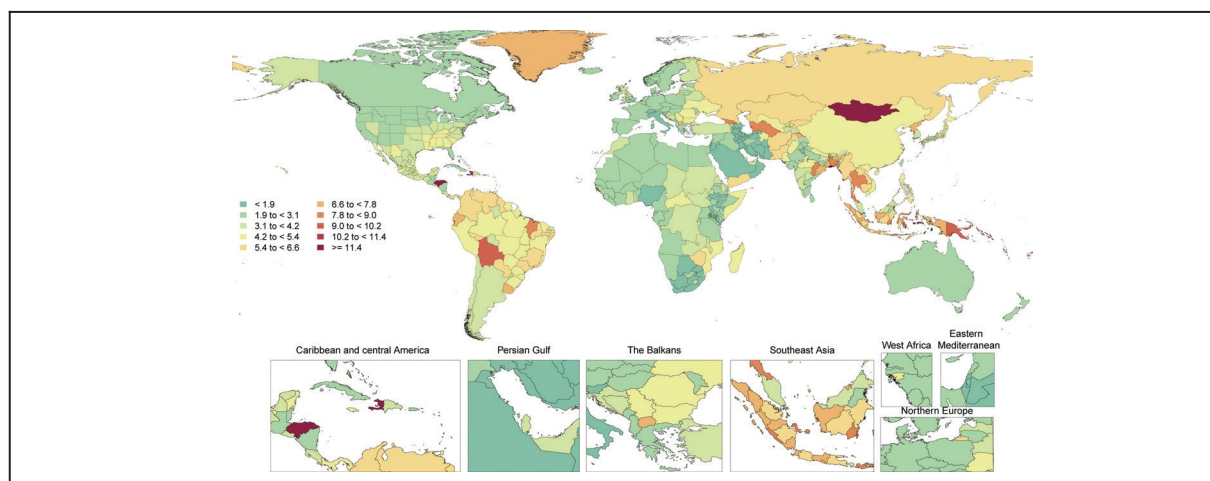


Chart 15-15. Age-standardized global mortality rates of SAH per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and SAH, subarachnoid hemorrhage.

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REFERENCES

- Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS prevalence & trends data. Accessed March 7, 2024.
- Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, Lackland DT, Lichtman JH, Mohl S, Sacco RL, et al; on behalf of the American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association [published correction appears in *Stroke*. 2015;46:e179]. *Stroke*. 2013;44:2361–2375. doi: 10.1161/STR.0b013e31829734f2
- GBD Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20:795–820. doi: 10.1016/S1474-4422(21)00252-0
- Vyas MV, Silver FL, Austin PC, Yu AYY, Pequeno P, Fang J, Laupacis A, Kapral MK. Stroke incidence by sex across the lifespan. *Stroke*. 2021;52:447–451. doi: 10.1161/STROKEAHA.120.032898
- Li L, Scott CA, Rothwell PM. Association of younger vs older ages with changes in incidence of stroke and other vascular events, 2002–2018. *JAMA*. 2022;328:563–574. doi: 10.1001/jama.2022.12759
- Scott CA, Li L, Rothwell PM. Diverging temporal trends in stroke incidence in younger vs older people: a systematic review and meta-analysis. *JAMA Neurol*. 2022;79:1036–1048. doi: 10.1001/jamaneurol.2022.1520
- Koton S, Sang Y, Schneider ALC, Rosamond WD, Gottesman RF, Coresh J. Trends in stroke incidence rates in older US adults: an update from the Atherosclerosis Risk in Communities (ARIC) cohort study. *JAMA Neurol*. 2019;77:109–1131. doi: 10.1001/jamaneurol.2019.3258
- Skajaa N, Adelborg K, Horvath-Puho E, Rothman KJ, Henderson VW, Casper Thygesen L, Sorensen HT. Nationwide trends in incidence and mortality of stroke among younger and older adults in Denmark. *Neurology*. 2021;96:e1711–e1723. doi: 10.1212/WNL.00000000000011636
- Shah 9. Zheng L, Xie Y, Zheng J, Guo R, Wang Y, Sun Y. Associations between ideal blood pressure based on different BMI categories and stroke incidence. *J Hypertens*. 2010;1097/10.1159/000519327
- Gavish B, Burszty M, Thijs L, Wei DM, J, Hansen TW, Asayama K, Ohkubo T, et al; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome Investigators. Predictive power of 24-h ambulatory pulse pressure and its components for 10.1093/eurheartj/ehy036 pants recruited from 13 populations. *J*
- Wang Y, Jiang G, Zhang J, Wang J, You W, Zhu J. Blood glucose level affects prognosis of patients who received intravenous thrombolysis
- Itoga NK, Tawfik DS, Montez-Rath ME, Chang TI. Contributions of systolic and diastolic blood pressures to cardiovascular outcomes in the ALLHAT study. *J Am Coll Cardiol*. 2021;78:1671–1678. doi: 10.1016/j.jacc.2021.08.035
- Clarke R, Wright N, Walters R, Gan W, Guo Y, Millwood IY, Yang L, Chen Y, Lewington S, Lv J, et al; China Kadoorie Biobank Collaborative Group. Genetically predicted differences in systolic blood pressure and risk of cardiovascular and noncardiovascular diseases: a mendelian randomization study in Chinese adults. *Hypertension*. 2023;80:566–576. doi: 10.1161/HYPERTENSIONAHA.122.20120
- Georgakis MK, Gill D, Malik R, Protogerou AD, Webb AJS, Dichgans M. Genetically predicted blood pressure across the lifespan: differential effects of mean and pulse pressure on stroke risk. *Hypertension*. 2020;76:953–961. doi: 10.1161/HYPERTENSIONAHA.120.15136
- Shim HS, Park JM, Lee YJ, Kim YD, Kim T, Ban SP, Bang JS, Kwon OK, Oh CW, Lee SU. Optimal target blood pressure for the primary prevention of hemorrhagic stroke: a nationwide observational study. *Front Neurol*. 2023;14:1268542. doi: 10.3389/fneur.2023.1268542
- Ewbank F, Gaastra B, Hall S, Galea I, Bulters D. Risk of subarachnoid haemorrhage reduces with blood pressure values below hypertensive thresholds. *Eur J Neurol*. 2024;31:e16105. doi: 10.1111/ene.16105
- Zhong X-L, Dong Y, Xu W, Huang Y-Y, Wang H-F, Zhang T-S, Sun L, Tan L, Dong Q, Yu J-T. Role of blood pressure management in stroke prevention: a systematic review and network meta-analysis of 93 randomized controlled trials. *J Stroke*. 2021;23:1–11. doi: 10.5853/jos.2020.02698
- Reboldi G, Angeli F, Gentile G, Verdecchia P. Benefits of more intensive versus less intensive blood pressure control: updated trial sequential analysis. *Eur J Intern Med*. 2022;101:49–55. doi: 10.1016/j.ejim.2022.03.032
- Malhotra K, Ahmed N, Filippatou A, Katsanos AH, Goyal N, Tsioufis K, Manios E, Pikiidou M, Schellinger PD, Alexandrov AW, et al. Association of elevated blood pressure levels with outcomes in acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. *J Stroke*. 2019;21:78–90. doi: 10.5853/jos.2018.02369
- Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet*. 2014;383:1973–1980. doi: 10.1016/S0140-6736(14)60040-4
- Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ*. 2016;355:i5953. doi: 10.1136/bmj.i5953
- Fang H, Zhou Y, YJ T, Du H, YX S, LY Z. Effects of intensive glucose lowering in treatment of type 2 diabetes mellitus on cardiovascular outcomes: a meta-analysis of data from 58,160 patients in 13 randomized controlled trials. *Int J Cardiol*. 2016;218:50–58.
- Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, Fansler A, Van de Bruinhorst K, Janis S, Durkalski-Mauldin VL; Neurological Emergencies Treatment Trials Network and the SHINE Trial Investigators. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. *JAMA*. 2019;322:326–335. doi: 10.1001/jama.2019.9346
- Li J, Ji C, Zhang W, Lan L, Ge W. Effect of new glucose-lowering drugs on stroke in patients with type 2 diabetes: a systematic review and meta-analysis. *J Diabetes Complications*. 2023;37:108362. doi: 10.1016/j.jdiacomp.2022.108362
- Bellastella G, Maiorino MI, Longo M, Scappaticcio L, Chiodini P, Esposito K, Giugliano D. Glucagon-like peptide-1 receptor agonists and prevention of stroke systematic review of cardiovascular outcome trials with meta-analysis. *Stroke*. 2020;51:666–669. doi: 10.1161/STROKEAHA.119.027557
- McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZL, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6:148–158. doi: 10.1001/jamacardio.2020.4511
- Zhang L, Li X, Wolfe CDA, O'Connell MDL, Wang Y. Diabetes as an independent risk factor for stroke recurrence in ischemic stroke patients: an updated meta-analysis.
- Echouffo-Tcheugui JB, Xu H, Matsouaka RA, Xian Y, Schwamm LH, Smith EE, Bhatt DL, Hernandez AF, Heidenreich PA, Fonarow GC. Diabetes and long-term outcomes of ischaemic stroke: findings from Get With The Guidelines-Stroke. *Eur Heart J*. 2018;39:2376–2386.
- Wang Y, Jiang G, Zhang J, Wang J, You W, Zhu J. Blood glucose level affects prognosis of patients who received intravenous thrombolysis

- after acute ischemic stroke? A meta-2023;14:1120779. doi: 10.1161/STROKEAHA.120.029048
36. Rataiczak-Tretel B, Lambert AT, Al-Ani R, Bekkeseth HMO, Bierkeli V, Eldoen G, et al. Underlying causes of cryptogenic stroke: Atrial Fibrillation and Stroke (NOR-FIB) comprehensive clinical evaluation. *BMC* 2023;10:1186/s12883-023-03155-0
 37. Bernstein RA, Kamel H, Granger CB, CA, Ziegler PD, Franco NC, Schwamm LH: Effect of Long-term continuous cardiac ablation of atrial fibrillation in patients with small-vessel disease: the STROKE-AF 2021;325:2169–2177. doi: 10.1001/jama.2021.6470
 38. Schwamm LH, Kamel H, Granger CB, Piccini JP, Katz JM, Sethi PP, Sidorov EV, Kasner SE, Silverman SB, Merriam TT, et al; STROKE AF Investigators. Predictors of atrial fibrillation in patients with stroke attributed to large- or small-vessel disease: a prespecified secondary analysis of the STROKE AF randomized clinical trial. *JAMA Neurol* 2023;80:99–103. doi: 10.1001/jamaneurol.2022.4038
 39. Oyama K, Giugliano RP, Berg DD, Ruff CT, Jarolim P, Tang M, Murphy SA, Lanz HJ, Grosso MA, Antman EM, et al. Serial assessment of biomarkers and the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. *Eur Heart J* 2021;42:1698–1706. doi: 10.1093/eurheartj/ehab141
 40. Singleton MJ, Yuan Y, Dawood FZ, Howard G, Judd SE, Zakai NA, Howard VJ, Herrington DM, Soliman EZ, Cushman M. Multiple fibrillation, and other cardiac 10.1161/STROKEAHA.120.029048
 52. Sun L, Clarke R, Bennett D, Guo Y, IY, Bian Z, Chen Y, et al: China Causal associations of blood lipids cerebral hemorrhage in Chinese 10.1038/s41591-019-0366-x
 53. Amarenco P, Kim JS, Labreuche J, Cha JK, Ducrocq G, Giroud M, et al: comparison of two LDL cholesterol *Med*. 2020;382:9–19. doi: 10.1161/JAHA.120.020157
 54. Judae C, Rutledge S, Costello M, A, Ferguson J, Gorev S, Nolan A blood biomarkers and stroke risk in atrial fibrillation: the REGARDS study. *J Am Heart Assoc* 2021;10:e020157. doi: 10.1161/JAHA.120.020157
 41. Mentel A, Quinn TJ, Cameron AC, Lees KR, Abdul-Rahim AH. The impact of atrial fibrillation type on the risks of thromboembolic recurrence, mortality and major haemorrhage in patients with previous stroke: a sys-

- apy, low-density lipoprotein level and risk of intracerebral hemorrhage: 10.1016/j.jstrokecerebrovasdis.2019.02.018
55. Masson W, Lobo M, Siniawski D, Masson G, Lavallo-Cobo A, Molinero a meta-analysis. *J Stroke Cerebrovasc Dis.* 2021;30:105655. doi: 10.1016/j.jstrokecerebrovasdis.2021.105655
56. Qie R, Liu L, Zhang D, Han M, Wang B, Zhao Y, Liu D, Guo C, Li Q, Zhou Q, cholest- terol and stroke: a systematic review and meta-analysis of prospective co- 10.5888/pcd18.200278
57. Hindy G, Engstrom G, Larsson SC, Traylor M, Markus HS, Melander Network (SiGN). Role of blood lipids in the development of ischemic stroke and its subtypes: 2018;49:820–827. doi: 10.1161/STROKEAHA.117.019653
58. Georgakis MK, Malik R, Anderson CD, Parhofer KG, Hopewell JC, Dichgans disease: role of high-density lipoprotein cholesterol. *Brain.* 2020;143:597–610. doi: 10.1093/brain/awz413
- tematic review and meta-analysis of observational studies. *Eur Stroke J.* 2020;5:155–168. doi: 10.1177/2396987319896674
42. Lin MH, Kamel H, Singer DE, Wu YL, Lee M, Ovbiagele B. Perioperative/ postoperative atrial fibrillation and risk of subsequent stroke and/or mortality. *Stroke.* 2019;50:1364–1371. doi: 10.1161/STROKEAHA.118.023921
43. Alturki A, Marafi M, Proietti R, Cardinale D, Blackwell R, Dorian P, Bessissow A, Vieira L, Greiss I, Essebag V, et al. Major adverse cardio- vascular events associated with postoperative atrial fibrillation after non- cardiac surgery: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol.* 2020;13:e007437. doi: 10.1161/CIRCEP.119.007437
44. Nauffal V, Trinquart L, Osho A, Sundt TM, Lubitz SA, Ellinor PT. Non- vitamin K antagonist oral anticoagulant vs warfarin for post cardiac surgery atrial fibrillation. *Ann Thorac Surg.* 2021;112:1392–1401. doi: 10.1016/j.athoracsur.2020.12.031
45. Grymonprez M, Simoons C, Steurbaut S, De Backer TL, Lahousse L. Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: a systematic review and meta-analysis. *Europace.* 2022;24:887–898. doi: 10.1093/europace/euab303
46. Lee KJ, Kim BJ, Han MK, Kim JT, Choi KH, Shin DI, Yeo MJ, Cha JK, Kim DH, Nah HW, et al; CRCS-K (Clinical Research Collaboration for Stroke in Korea) Investigators. Effect of heart rate on stroke recurrence and mortality in acute ischemic stroke with atrial fibrillation. *Stroke.* 2020;51:162–169. doi: 10.1161/STROKEAHA.119.026847
- a meta-analysis. *J Stroke Cerebrovasc Dis.* 2019;28:1703–1709. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.018
- G. LDL-C levels below 55 mg/dl and risk of hemorrhagic stroke: 10.1016/j.jstrokecerebrovasdis.2021.105655
- et al. Dose-response association between high-density lipoprotein hort studies. *Prev Chronic Dis.* 2021;18:E45. doi: 10.1016/j.jstrokecerebrovasdis.2021.105655
- O, Orho-Melander M; Stroke Genetics a mendelian randomization study. *Stroke.* 2021;52:100–107. doi: 10.1161/STROKEAHA.120.038413
47. Benz AP, Hohnloser SH, Eikelboom JW, Carnicelli AP, Giugliano RP, Granger CB, Harrington J, Hijazi Z, Morrow DA, Patel MR, et al. Outcomes of patients with atrial fibrillation and ischemic stroke while on oral anticoagulation. *Eur Heart J.* 2023;44:1807–1814. doi: 10.1093/eurheartj/ehad200
48. Lyth J, Svennberg E, Bernfort L, Aronsson M, Frykman V, Al-Khalili F, Friberg L, Rosenqvist M, Engdahl J, Levin L. Cost-effectiveness of population screening for atrial fibrillation: the STROKESTOP study. *Eur Heart J.* 2023;44:196–204. doi: 10.1093/eurheartj/ehac547
49. Al-Kawaz M, Omran SS, Parikh NS, Elkind MSV, Soliman EZ, Kamel H. Comparative risks of ischemic stroke in atrial flutter versus atrial fibrillation. *J Stroke Cerebrovasc Dis.* 2018;27:839–844. doi: 10.1016/j.jstrokecerebrovasdis.2017.10.025
50. Meng L, Tsiaousis G, He J, Tse G, Antoniadis AP, Korantzopoulos P, Letsas KP, Baranchuk A, Qi W, Zhang Z, et al. Excessive supraventricular ectopic activity and adverse cardiovascular outcomes: a systematic review and meta-analysis. *Curr Atheroscler Rep.* 2020;22:14. doi: 10.1007/s11883-020-0832-4
51. Bodin A, Bisson A, Gaborit C, Herbert J, Clementy N, Babuty D, Lip GYH,

59. Yuan S, Huang X, Ma W, Yang R, Xu F, Han D, Huang T, Peng M, Xu A, Lyu J. Associations of HDL-C/LDL-C with myocardial infarction, all-cause mortality, haemorrhagic stroke and ischaemic stroke: a longitudinal study based on 384 093 participants from the UK Biobank. *Stroke Vasc Neurol*. 2023;8:119–126. doi: 10.1136/svn-2022-001668

60. Lee H, Park JB, Hwang IC, Yoon YE, Park HE, Choi SY, Kim YJ, Cho GY, Han K, Kim HK. Association of four lipid components with mortality, myocardial infarction, and stroke in statin-naïve young adults: a nationwide cohort study. *Eur J Prev Cardiol*. 2020;27:870–881. doi: 10.1177/2047487319898571

61. Rist PM, Buring JE, Ridker PM, Kase CS, Kurth T, Rexrode KM. Lipid levels and the risk of hemorrhagic stroke among women. *Neurology*. 2019;92:e2286–e2294. doi: 10.1212/WNL.0000000000007454

62. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr., Juliano RA, Jiao L, Granowitz C, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22. doi: 10.1056/NEJMoa1812792

63. Yang XH, Zhang BL, Cheng Y, Fu SK, Jin HM. Association of remnant cholesterol with risk of cardiovascular disease events, stroke, and mortality: a systematic review and meta-analysis. *Atherosclerosis*. 2023;371:21–31. doi: 10.1016/j.atherosclerosis.2023.03.012

64. Wang Y, Zha F, Han Y, Cai Y, Chen M, Yang C, Cai X, Hu H, Cao C, Luo J. Nonlinear connection between remnant cholesterol and stroke risk: evidence from the China Health and Retirement Longitudinal Study. *Lipids Health Dis*. 2023;22:181. doi: 10.1186/s12944-023-01943-8

65. Navarese EP, Vine D, Proctor S, Grzelakowska K, Berti S, Kubica J, Raggi P. Independent causal effect of remnant cholesterol on atherosclerotic cardiovascular outcomes: a mendelian randomization study. *Arterioscler Thromb Vasc Biol*. 2023;43:e373–e380. doi: 10.1161/ATVBAHA.123.319297

66. Chauhan G, Adams HHH, Satizabal CL, Bis JC, Teumer A, Sargurupremraj M, Hofer E, Trompet S, Hilal S, Smith AV, et al; Stroke Genetics Network (SiGN), International Stroke Genetics Consortium (ISGC), METASTROKE, Alzheimer's Disease Genetics Consortium (ADGC), and the Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population-based setting. *Neurology*. 2019;92:e486–e503. doi: 10.1212/WNL.0000000000006851

67. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovic D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ*. 2018;360:j5855. doi: 10.1136/bmj.j5855

Fauchier L. Ischemic stroke in patients with sinus node disease, atrial

68. Awad K, Mohammed M, Martin SS, Banach M. Association between electronic nicotine delivery systems use and risk of stroke: a meta-analysis of 1,024,401 participants. *Arch Med Sci*. 2023;19:1538–1540. doi: 10.5114/aoms/171473
69. Anadani M, Turan TN, Yaghi S, Spiotta AM, Gory B, Sharma R, Sheth KN, de Havenon A. Change in smoking behavior and outcome after ischemic stroke: post-hoc analysis of the SPS3 trial. *Stroke*. 2023;54:921–927. doi: 10.1161/STROKEAHA.121.038202
70. Fischer F, Kraemer A. Meta-analysis of the association between second-hand smoke exposure and ischaemic heart diseases, COPD and stroke. *BMC Public Health*. 2015;15:1202. doi: 10.1186/s12889-015-2489-4
71. Lin MP, Ovbiadele B, Markovic D, Towfighi A. Association of second-hand smoke exposure and risk for subarachnoid hemorrhage. *Stroke*. 2016;47:1975–1981. doi: 10.1161/STROKEAHA.116.012957
72. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Sex, smoking, and risk for subarachnoid hemorrhage. *Stroke*. 2016;47:1975–1981. doi: 10.1161/STROKEAHA.116.012957
73. Etminan N, Chang HS, Hackenberg K, de Rooij NK, Vergouwen MDI, Rinkel GJE, Algra A. Worldwide incidence of aneurysmal subarachnoid hemorrhage according to region, time period, blood pressure, and smoking prevalence in the population: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76:588–597. doi: 10.1001/jamaneurol.2019.0006
74. Parikh NS, Salehi Omran S, Kamel H, Elkind MSV, Willey JZ. Smoking cessation pharmacotherapy for patients with stroke and TIA: systematic review. *J Clin Neurosci*. 2020;78:236–241. doi: 10.1016/j.jocn.2020.04.026
75. Wu AD, Lindson N, Hartmann-Boyce J, Wahedi A, Hajizadeh A, Theodoulou A, Thomas ET, Lee C, Aveyard P. Smoking cessation for secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2019;76:588–597. doi: 10.1001/jamaneurol.2019.0006
76. Parikh NS, Navi BB, Merkler AE, Kamel H. Electronic cigarette use and smoking cessation attempts among stroke survivors in the US. *JAMA Neurol*. 2021;78:759–760. doi: 10.1001/jamaneurol.2021.0636
77. Vidyasagaran AL, Siddiqi K, Kanaan M. Use of smokeless tobacco and risk of cardiovascular disease: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23:1970–1981. doi: 10.1177/2047487316654026
78. Jeffers AM, Glantz S, Byers AL, Keyhani S. Association of cannabis use with cardiovascular outcomes among US adults. *J Am Heart Assoc*. 2024;13:e030178. doi: 10.1161/JAHA.123.030178
79. Qi W, Ma J, Guan T, Zhao D, Abu-Hanna A, Schut M, Chao B, Wang L, Liu Y. Risk factors for incident stroke and its subtypes in China: a prospective study. *J Am Heart Assoc*. 2020;9:e016352. doi: 10.1161/JAHA.120.016352
80. Hooker SP, Diaz KM, Blair SN, Colabianchi N, Hutto B, McDonnell MN, Vena JE, Howard VJ. Association of accelerometer-measured sedentary time and physical activity with risk of stroke among US adults. *JAMA Netw Open*. 2022;5:e2215385. doi: 10.1001/jamanetworkopen.2022.15385
88. Prestgaard E, Mariampillai J, Engeseth K, Erikssen J, Bodegard J, Liestol K, Gjesdal K, Kjeldsen S, Grundvold I, Berge E. Change in cardiorespiratory fitness and risk of stroke and death: long-term follow-up of healthy middle-aged men. *Stroke*. 2019;50:155–161. doi: 10.1161/STROKEAHA.118.021798
89. Ehrman JK, Keteyian SJ, Johansen MC, Blaha MJ, Al-Mallah MH, Brawner CA. Improved cardiorespiratory fitness is associated with lower incident ischemic stroke risk: Henry Ford FIT project. *J Stroke Cerebrovasc Dis*. 2023;32:107240. doi: 10.1002/14651858.CD014936.pub2

- Giugliano RP, Fox KAA, Hijazi Z, Lopes RD, et al. Direct oral anticoagulants versus warfarin across the spectrum of kidney function: patient-level network meta-analyses from COMBINE AF. *Circulation*. 2023;147:1748–1757. doi: 10.1161/CIRCULATIONAHA.122.062752
92. Miwa K, Koga M, Nakai M, Yoshimura S, Sasahara Y, Koge J, Sonoda K, Ishigami A, Iwanaga Y, Miyamoto Y, et al; Japan Stroke Data Bank Investigators. Etiology and outcome of ischemic stroke in patients with renal impairment including chronic kidney disease: Japan Stroke Data Bank. *Neurology*. 2022;98:e1738–e1747. doi: 10.1212/WNL.0000000000200153
93. Reinecke H, Engelbertz C, Bauersachs R, Breithardt G, Echterhoff HH, Gerss J, Haeusler KG, Hewing B, Hoyer J, Juergensmeyer S, et al. A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 study. *Circulation*. 2023;147:296–309. doi: 10.1161/CIRCULATIONAHA.122.062779
94. El Hussein N, Fonarow GC, Smith EE, Ju C, Schwamm LH, Hernandez AF, Schulte PJ, Xian Y, Goldstein LB. Renal dysfunction is associated with poststroke discharge disposition and in-hospital mortality: findings from Get With The Guidelines–Stroke. *Stroke*. 2017;48:327–334. doi: 10.1161/STROKEAHA.116.014601
95. Arnon Y, Hoshen M, Berliner-Sendrey A, Reges O, Balicer R, Leibowitz M, Avgil Tsadok M, Haim M. Risk of stroke, bleeding, and death in patients with nonvalvular atrial fibrillation and chronic kidney disease. *Cardiology*. 2020;145:178–186. doi: 10.1159/000504877
96. Toth-Manikowski SM, Yang W, Appel L, Chen J, Deo R, Frydrych A, Krousel-Wood M, Rahman M, Rosas SE, Sha D, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Sex differences in cardiovascular outcomes in CKD: findings from the CRIC study. *Am J Kidney Dis*. 2021;78:200–209.e1. doi: 10.1053/j.ajkd.2021.01.020
97. Ruban A, Daya N, Schneider ALC, Gottesman R, Selvin E, Coresh J, Lazo M, Koton S. Liver enzymes and risk of stroke: the Atherosclerosis Risk in Communities (ARIC) study. *J Stroke*. 2020;22:357–368. doi: 10.1161/STROKEAHA.120.045000
81. Ghozy S, Zayan AH, El-Qushayri AE, Parker KE, Varney J, Kallmes KM, Morsy S, Abbas AS, Diestro JDB, Dmytriw AA, et al. Physical activity level and stroke risk in US population: a matched case-control study of 102,578 individuals. *Ann Clin Transl Neurol*. 2022;9:264–275. doi: 10.5853/jos.2020.00290

98. Bisaccia G, Ricci F, Khanji MY, Sorella A, Melchiorre E, Iannetti G, Galanti K, Mantini C, Pizzi AD, Tana C, et al. Cardiovascular morbidity and mortality related to non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Curr Probl Cardiol.* 2023;48:101643. doi: 10.1002/acn3.51511
82. Hung SH, Ebaid D, Kramer S, Werden E, Baxter H, Campbell BC, Brodtmann A. Pre-stroke physical activity and admission stroke severity: a systematic review. *Int J Stroke.* 2021;16:1009–1018. doi: 10.1177/1747493021995271
83. Susts J, Reinholdsson M, Sunnerhagen KS, Abzhandadze T. Physical activity before stroke is associated with dependency in basic activities of daily living 3 months after stroke. *Front Neurol.* 2023;14:1094232. doi: 10.3389/fneur.2023.1094232
84. Buvarp D, Viktorisson A, Axelsson F, Lehto E, Lindgren L, Lundstrom E, Sunnerhagen KS. Physical activity trajectories and functional re-

10.1016/j.cpcardiol.2023.101643

99. Baloch ZQ, Haider SJ, Siddiqui HF, Shaikh FN, Shah BUD, Ansari MM, Qintar M. Utility of cerebral embolic protection devices in transcatheter procedures: a systematic review and meta-analysis. *Curr Probl Cardiol.* 2023;48:101675. doi: 10.1016/j.cpcardiol.2023.101675
100. Ghoreishi M, Sundt TM, Cameron DE, Holmes SD, Roselli EE, Pasrija C, Gammie JS, Patel HJ, Bavaria JE, Svensson LG, et al. Factors associated with acute stroke after type A aortic dissection repair: an analysis of the Society of Thoracic Surgeons National Adult Cardiac Surgery Database. *J Thorac Cardiovasc Surg.* 2020;159:2143–2154.e3. doi: 10.1016/j.jtcvs.2019.06.016
85. Tikkanen E, Gustafsson S, Ingelsson E. Associations of fitness, physical activity, strength, and genetic risk with cardiovascular disease: longitudinal

101. Yu Y, Wang J, Duan B, Wang P. Thoracic endovascular aortic repair ver-sus open surgery for Stanford type B aortic dissection: a meta-analysis and systematic review. *Heart Surg Forum*. 2023;26:E303–E310. doi: 10.1161/CIRCULATIONAHA.117.032432
86. Sui X, Howard VJ, McDonnell MN, Ernstsens L, Flaherty ML, Hooker SP, Lavie CJ. Racial differences in the association between nonexercise es-

102. Kogan EV, Sciria CT, Liu CF, Wong SC, Bergman G, Ip JE, Thomas G, Markowitz SM, Lerman BB, Kim LK, et al. Early stroke and mor-tality after percutaneous left atrial appendage occlusion in patients with atrial fibrillation. *Stroke*. 2023;54:947–954. doi:

2018;93:884–894. doi: 10.1016/j.mayocp.2018.05.002

87. Liu Y, Zhu J, Guo Z, Yu J, Zhang X, Ge H, Zhu Y. Estimated

cardiorespi-ratory fitness and incident risk of cardiovascular disease in China. *BMC Public Health*. 2023;23:2338. doi: 10.1186/s12889-023-16864-5

- cardiac
doi:
104. Park DW, Ahn JM, SW, Park GM, et al. drug-eluting stents coronary disease: 2020:141:1437–1437.
105. Ariomandi Rad A, Subbiah Ponniah al. Left ventricular surgery: a 27. doi:
106. Hielholt TJ, of CHA2 DS2 - in hip fracture 10.1111/ins.16452
107. Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, McClure JA, Lindsay MP. The incidence of pregnancy-related stroke: a systematic review and meta-analysis. *Int J Stroke*. 2017;12:687–697. doi: 10.1177/1747493017723271
108. Jacobson LT, Hade EM, Collins TC, Margolis KL, Waring ME, Van Horn LV, Silver B, Sattari M, Bird CE, Kimminau K, et al. Breastfeeding history and risk of stroke among parous postmenopausal women in the Women's Health Initiative. *J Am Heart Assoc*. 2018;7:e008739. doi: 10.1161/JAHA.118.008739
109. Poorthuis MH, Algra AM, Algra A, Kappelle LJ, Klijn CJ. Female- and male-specific risk factors for stroke: a systematic review and meta-analysis. *JAMA Neurol*. 2017;74:75–81. doi: 10.1001/jamaneurol.2016.3482
110. Liang C, Chung HF, Dobson AJ, Mishra GD. Infertility, miscarriage, stillbirth, and the risk of stroke among women: a systematic review and meta-analysis. *Stroke*. 2022;53:328–337. doi: 10.1161/STROKEAHA.121.036271
111. de Havenon A, Delic A, Stulberg E, Sheibani N, Stoddard G, Hanson H, Theilen L. Association of preeclampsia with incident stroke in later life among women in the Framingham Heart Study. *JAMA Netw Open*. 2021;4:e215077. doi: 10.1001/jamanetworkopen.2021.5077
112. Kisanuki K, Muraki I, Yamagishi K, Kokubo Y, Saito I, Yatsuya H, Sawada N, Iso H, Tsugane S; JPHC Study Group. Weight change during
121. Lu H, Wu PF, Li RZ, Zhang W, Huang GX. Sleep duration and stroke: a mendelian randomization study. *Front Neurol*. 2020;11:976. doi: 10.3389/fneur.2020.00976
122. Ma Y, Wang M, Chen X, Ruan W, Yao J, Lian X. Daytime sleepiness and risk of stroke: a mendelian randomization analysis. *Clin Neurol Neurosurg*. 2021;208:106857. doi: 10.1016/j.clineuro.2021.106857
123. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Ananav S, et al: INTERSTROKE Investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388:761–775. doi: 10.1016/S0140-6736(16)30506-2
124. Jackson CA, Sudlow CLM, Mishra GD. Psychological distress and risk of myocardial infarction and stroke in the 45 and Up Study. *Circ Cardiovasc Qual Outcomes*. 2017;10:1161/CIRCOUTCOMES.117.004500
125. Li H, He P, Zhang Y, Lin T, Liu C, Xie D, Liang M, Wang G, Nie J, Song middle age and risk of stroke and coronary heart disease: the Japan Public Health Center-based Prospective Study. *Atherosclerosis*. 2021;322:67–73. doi: 10.1016/j.atherosclerosis.2021.02.017
113. Okoth K, Wang J, Zemedikun D, Thomas GN, Nirantharakumar K, Adderley NJ. Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: a retrospective matched cohort study. *BJOG*. 2021;128:1598–1609. doi: 10.1111/1471-0528.16692
114. Lin YW, Wang JY, Lin MH, Lin M-H. Stroke risk associated with NSAIDs uses in women with dysmenorrhea: a population-based cohort study. *PLoS One*. 2021;16:e0259047. doi: 10.1371/journal.pone.0259047
115. Chang WC, Wang JH, Ding DC. Conjugated equine estrogen used in post-menopausal women associated with a higher risk of stroke than estradiol. *Sci Rep*. 2021;11:10801. doi: 10.1038/s41598-021-90357-6
116. Chow FC, Wilson MR, Wu K, Ellis RJ, Bosch RJ, Linas BP. Stroke incidence is highest in women and non-Hispanic blacks living with HIV in the AIDS Clinical Trials Group Longitudinal Linked

Y, et al. Self-perceived psychological stress and risk of first stroke in treated hypertensive patients. *Psychosom Med*. 2022;84:237–243. doi: 10.1097/PSY.0000000000001030

126. Nanavati HD, Arevalo A, Memon AA, Lin C. Associations between post-traumatic stress and stroke: a systematic review and meta-analysis. *J Trauma Stress*. 2023;36:259–271. doi: 10.1002/jts.22925

127. Cai W, Ma W, Mueller C, Stewart R, Ji J, Shen WD. Association between late-life depression or depressive symptoms and stroke morbidity in elders: a systematic review and meta-analysis of cohort studies. *Acta Psychiatr Scand*. 2023;148:405–415. doi: 10.1111/acps.13613

128. Murphy RP, Reddin C, Rosengren A, Judge C, Hankey GJ, Ferguson J, Alvarez-Iglesias A, Oveisgharan S, Wasay M, McDermott C, et al; for the INTERSTROKE Investigators. Depressive symptoms and risk of acute stroke: INTERSTROKE case-control study. *Neurology*. 2023;100:e1787–e1798. doi: 10.1212/WNL.000000000000207093

129. Cummings DM, Lutes LD, Wilson JL, Carraway M, Safford MM, Cherrington A, Long DL, Carson AP, Yuan Y, Howard VJ, et al. Persistence of depressive symptoms and risk of incident cardiovascular disease with and without diabetes: results from the REGARDS study. *J Gen Intern Med*. 2022;37:4080–4087. doi: 10.1007/s11606-022-07449-w

130. Ford CD, Gray MS, Crowther MR, Wadley VG, Austin AL, Crowe MG, Pulley L, Unverzagt F, Kleindorfer DO, Kissela BM, et al. Depressive symptoms and risk of stroke in a national cohort of Blacks and Whites from REGARDS. *Neurol Clin Pract*. 2021;11:e454–e461. doi: 10.1212/cpj.0000000000000983

131. On BI, Vidal X, Berger U, Sabate M, Ballarin E, Maisterra O, San-Jose A, Ibanez L. Antidepressant use and stroke or mortality risk in the elderly. *Eur J Neurol*. 2022;29:469–477. doi: 10.1111/ene.15137

132. Hu J, Zheng X, Shi G, Guo L. Associations of multiple chronic disease and depressive symptoms with incident stroke among Chinese middle-aged and elderly adults: a nationwide population-based cohort study. *BMC Geriatr*. 2022;22:660. doi: 10.1186/s12877-022-03329-4

133. Hakulinen C, Pulkki-Råback L, Virtanen M, Jokela M, Kivimäki M, Elovainio M. Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women. *Heart*. 2018;104:1536–1542. doi: 10.1136/heartjnl-2017-312663

134. Sun YA, Kalpakavadi S, Prior S, Thrift AG, Waddingham S, Phan H, Gall Randomized Trials cohort. *AIDS*. 2018;32:1125–1135. doi: SL.

10.1097/QAD.0000000000001799

117. Chow FC, Regan S, Zanni MV, Looby SE, Bushnell CD, Meigs JB, Grinspoon SK, Feske SK, Triant VA. Elevated ischemic stroke risk among women living with HIV infection. *AIDS*. 2018;32:59–67. doi: 10.1097/QAD.0000000000001650

118. Austin K, Seebo S, Ibiebele I, Ford J, Morris J, Torvaldsen S. Pregnancy outcomes for women with a history of stroke: a population-based re-cord linkage study. *Aust N Z J Obstet Gynaecol*. 2021;61:239–243. doi:

- a systematic review and meta-analysis. *Health Qual Life Outcomes*. 2023;21:115. doi: 10.1186/s12955-023-02194-y
135. Zierath R, Claggett B, Hall ME, Correa A, Barber S, Gao Y, Talegawkar S, Ezekwe EI, Tucker K, Diez-Roux AV, et al. Measures of food inadequacy and cardiovascular disease risk in Black individuals in the US from the Jackson Heart Study. *JAMA Network Open*. 2023;6:e2252055. doi: 10.1001/jamanetworkopen.2022.52055
136. Stamm B, Royan R, Trifan G, Alvarado-Dyer R, Velez FGS, Taylor W, Pinna P, Reish NJ, Vargas A, Goldenberg FD, et al. Household income
119. Song Y, Dong Q, Chang Z, Song C, Cui K, Wu S, Gao G, Fu R, Gao Y, Dou K. The impact of sleep quality and its change on the long-term risk of stroke in middle-aged and elderly people: findings from the English Longitudinal Study of Ageing. *Sleep Med*. 2023;107:281–288. doi:

- is associated with functional outcomes in a multi-institutional cohort of patients with ischemic stroke and COVID-19. *J Stroke Cerebrovasc Dis.* 2023;32:107059. doi: 10.1016/j.jstrokecerebrovasdis.2023.107059
137. Heron M. Deaths: leading causes for 2019. *Natl Vital Stat Rep.* 2021;70:1–114.
- 10.1016/j.sleep.2023.04.032
120. Li W, Kondracki A, Gautam P, Rahman A, Kiplagat S, Liu H, Sun W. The association between sleep duration, napping, and stroke stratified by self-health status among Chinese people over 65 years old from the China Health and Retirement Longitudinal Study. *Sleep Breath.* 2021;25:1239–1246. doi: 10.1007/s11325-020-02214-x

138. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. The lifetime risk of stroke: estimates from the Framingham study. *Stroke*. 2006;37:345–350. doi: 10.1161/01.STR.0000199613.38911.b2 139. Madsen TE, Khoury JC, Leppert M, Alwell K, Moomaw CJ, Sucharew H, Woo D, Ferioli S, Martini S, Adeoye O, et al. Temporal trends in stroke incidence

over time by sex and age in the GCNKSS. *Stroke*. 2020;51:1070–1076. doi: 10.1161/STROKEAHA.120.028910

140. Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, Hunkeler E, Lash TL, Millman A, Quinn VP, et al. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Ann Intern Med*. 2018;169:205–213. doi: 10.7326/M17-2785

141. van Zilverden LM, Wienies CM, van Diemen JJK, Thiis A, den Heijer M. Cardiovascular disease in transgender people: a systematic review and meta-analysis. *Eur J Endocrinol*. 2024;190:S13–S24. doi: 10.1093/ejendo/lvad170

142. Park B, Budzynska K, Almasri N, Islam S, Alyas F, Carolan RL, Abraham BE, Castro-Camero PA, Shreve ME, Rees DA, et al. Tight versus standard blood pressure control on the incidence of myocardial infarction and stroke: an observational retrospective cohort study in the general ambulatory setting. *BMC Fam Pract*. 2020;21:91. doi: 10.1186/s12875-020-01163-4

143. Cagna-Castillo D, Salcedo-Carrillo AL, Carrillo-Larco RM, Bernabé-Ortiz A. Prevalence and incidence of stroke in Latin America and the Caribbean: a systematic review and meta-analysis. *Sci Rep*. 2023;13:6809. doi: 10.1038/s41598-023-33182-3

144. Gardener H, Sacco RL, Rundek T, Battistella V, Cheung YK, Elkind MSV. Race and ethnic disparities in stroke incidence in the

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.

- term risk of recurrent vascular events and mortality in young stroke patients: insights from a multicenter study. *Eur J Neurol.* 2023;30:2675–2683. doi: 10.1111/ene.15850
161. Zhang F, Liu L, Zhang C, Ji S, Mei Z, Li T. Association of metabolic syndrome and its components with risk of stroke recurrence and mortality: a meta-analysis. *Neurology.* 2021;97:e695–e705. doi: 10.1212/WNL.00000000000012415
162. Goeggel Simonetti B, Rafay MF, Chung M, Lo WD, Beslow LA, Billinghamurst Northern Manhattan Study. *Stroke.* 2020;51:1064–1069. doi: 10.1161/STROKEAHA.119.028806
145. Herman AL, Sheth KN, Williams OA, Johnston KC, Prabhakaran S, de Havenon A. Self-reported race as a social determinant of stroke risk in observational versus clinical trial datasets. *J Stroke Cerebrovasc Dis.* 2022;31:106219. doi: 10.1016/j.jstrokecerebrovasdis.2021.106219
146. Hong C, Pencina MJ, Wojdyla DM, Hall JL, Judd SE, Cary M, Engelhardt MM, Berchuck S, Xian Y, D'Agostino R Sr, et al. Predictive accuracy of

Comparative study of posterior and anterior circulation stroke in child-hood: results from the International Pediatric Stroke Study. *Neurology*. 2020;94:e337–e344. doi: 10.1212/WNL.0000000000008837

163. Del Brutto VJ, Diener HC, Easton JD, Granger CB, Cronin L, Kleindorf E, et al. Predictors of recurrent stroke after embolic stroke of undetermined source in the stroke risk prediction models across Black and White race, sex, and age groups. *JAMA*. 2023;329:306–317. doi: 10.1001/jama.2022.24683
147. Forman R, Okumu R, Mageid R, Baker A, Neu D, Parker R, Peyravi R, Schindler JL, Sansing LH, Sheth KN, et al. Association of neighborhood-level socioeconomic factors with delay to hospital arrival in patients with acute stroke. *Neurology*. 2024;102:e207764. doi: 10.1212/wnl.00000000000207764
148. Jimenez MC, Manson JE, Cook NR, Kawachi I, Wassertheil-Smoller S, Haring B, Nassir R, Rhee JJ, Sealy-Jefferson S, Rexrode KM. Racial variation in stroke risk among women by stroke risk factors. *Stroke*. 2019;50:797–804. doi: 10.1161/STROKEAHA.117.017759
149. Muller CJ, Alonso A, Forster J, Vock DM, Zhang Y, Gottesman RF, Grauer C, Brueckmann M, Toyoda K, Schellinger PD, et al. Predictors RE-SPECT ESUS trial. *J Am Heart Assoc*. 2022;11:e023545. doi: 10.1161/JAHA.121.023545

164. Xu J, Zhang X, Jin A, Pan Y, Li Z, Meng X, Wang Y. Trends and risk factors associated with stroke recurrence in China, 2007-2018. *JAMA Network Open*. 2022;5:e2216341. doi: 10.1001/jamanetworkopen.2022.16341
165. Albright KC, Huang L, Blackburn J, Howard G, Mullen M, Bittner V, Muntner P, Howard V. Racial differences in recurrent ischemic stroke risk and recurrent stroke case fatality. *Neurology*. 2018;91:e1741–e1750. doi: 10.1212/WNL.0000000000006467
166. Kauw F, Takx RAP, De Jong HWAM, Velthuis BK, Kappelle LJ, Dankbaar JW. Clinical and imaging predictors of recurrent ischemic stroke: a systematic review and meta-analysis. *Cerebrovasc Dis*. 2018;45:279–287. doi: 10.1159/000490422
- Rosamond W, Longstreth WT Jr., MacLehose RF. Stroke Incidence and Survival in American Indians, Blacks, and Whites: the Strong Heart Study and Atherosclerosis Risk in Communities Study. *J Am Heart Assoc*. 2019;8:e010229. doi: 10.1161/JAHA.118.010229
150. Wallace AN, Gibson DP, Asif KS, Sahlein DH, Warach SJ, Malisch T, Lamonte MP. Racial disparity in mechanical thrombectomy utilization: multicenter registry results from 2016 to 2020. *J Am Heart Assoc*. 2022;11:e021865. doi: 10.1161/jaha.121.021865
151. Lioutas VA, Ivan CS, Himali JJ, Aparicio HJ, Leveille T, Romero JR, Beiser AS, Seshadri S. Incidence of transient ischemic attack and association with long-term risk of stroke. *JAMA*. 2021;325:373–381. doi: 10.1001/jama.2020.25071
152. Shahjouei S, Sadighi A, Chaudhary D, Li J, Abedi V, Holland N, Phipps M,

167. Georgakis MK, Duering M, Wardlaw JM, Dichgans M. WMH and long-term outcomes in ischemic stroke: a systematic review and meta-analysis. *Neurology*. 2019;92:e1298–e1308. doi: 10.1212/WNL.0000000000007142
168. Yafasova A, Fosbol EL, Johnsen SP, Kruuse C, Petersen JK, Alhakak A, Vinding NE, Torp-Pedersen C, Gislason GH, Kober L, et al. Time to thrombolysis and long-term outcomes in patients with acute ischemic stroke: a nationwide study. *Stroke*. 2021;52:1724–1732. doi: 10.1161/strokeaha.120.032837
169. Pan Y, Li Z, Li J, Jin A, Lin J, Jing J, Li H, Meng X, Wang Y, Wang Y. Residual risk and its risk factors for ischemic stroke with adherence to guideline-based secondary stroke prevention. *J Stroke*. 2021;23:51–60. doi: 10.5853/jos.2020.03391
- Zand R. A 5-decade analysis of incidence trends of ischemic stroke after transient ischemic attack: a systematic review and meta-analysis. *JAMA Neurol*. 2021;78:77–87. doi: 10.1001/jamaneurol.2020.3627
153. Hurford R, Li L, Lovett N, Kubiak M, Kuker W, Rothwell PM; Oxford Vascular Study. Prognostic value of "tissue-based" definitions of TIA and minor stroke: population-based study. *Neurology*. 2019;92:e2455–e2461. doi: 10.1212/WNL.0000000000007531
154. Joundi RA, Yu AYY, Smith EE, Zerna C, Penn AM, Balshaw RF, Votova K, Bibok MB, Penn M, Saly V, et al. Association between duration of transient neurological events and diffusion-weighted brain lesions. *J Am Heart Assoc*. 2023;12:e027861. doi: 10.1161/jaha.122.027861
155. Cucchiara B, Elm J, Easton JD, Coutts SB, Willey JZ, Biros MH, Ross MA, Johnston SC. Disability after minor stroke and transient

170. Liu T, Jiang Y, Hu J, Li Z, Guo Y, Li X, Xiao J, Yuan L, He G, Zeng W, et al. Association of ambient PM1 with hospital admission and recurrence of stroke in China. *Sci Total Environ*. 2022;828:154131. doi: 10.1016/j.scitotenv.2022.154131
171. Ueki K, Matsuo R, Kuwashiro T, Irie F, Wakisaka Y, Ago T, Kamouchi M, Kitazono T; Fukuoka Stroke Registry Investigators. Decreased estimated glomerular filtration rate and proteinuria and long-term outcomes after ischemic stroke: a longitudinal observational cohort study. *Stroke*. 2023;54:1268–1277. doi: 10.1161/STROKEAHA.122.040958
172. Bao Q, Zhang J, Wu X, Zhao K, Guo Y, Yang M, Du X. Clinical significance of plasma D-dimer and fibrinogen in outcomes after stroke: a systematic review and meta-analysis. *Cerebrovasc Dis*. 2023;52:318–343. doi: 10.1159/000526476
- 10.1161/STROKEAHA.119.027465
156. Sherlock L, Lee SF, Katsanos AH, Cukierman-Yaffe T, Canavan M, Joundi R, Sharma M, Shoamanesh A, Brayne C, Gerstein HC, et al. Cognitive performance following stroke, transient ischaemic attack, myocardial infarction, and hospitalisation: an individual participant data meta-analysis of six randomised controlled trials. *Lancet Healthy Longev*. 2023;4:e665–e674.

173. McCabe JJ, Walsh C, Gorey S, Harris K, Hervella P, Iglesias-Rey R, Jern C, Li L, Miyamoto N, Montaner J, et al. C-reactive protein, interleukin-6, and vascular recurrence after stroke: an individual participant data meta-analysis. *Stroke*. 2023;54:1289–1299. doi: 10.1161/STROKEAHA.122.040529
174. Li M, Wang H, Gao Y. Serum uric acid levels and recurrence rate of ischemic stroke: a meta-analysis. *Horm Metab Res*. 2023;55:493–497. doi: 10.1016/S2666-7568(23)00207-6
- doi: 10.1055/a-2091-1951

175. Andersen KK, Olsen TS. Social inequality term cause-specific mortality after stroke. *J* 2019;28:1529–1536. doi:
176. Sato T, Sakai K, Nakada R, Shiraishi T, Terasawa Y, Umehara T, Omoto S, et al. Ethnic stroke and weekly variation of stroke 2021;30:105873. doi:
177. Gafarova AV, Gromova EA, Panov DO. Social support and stroke risk: an aged 25–64 years in Russia/Siberia (the Program). *Neurol Neurosushiatrv* 10.14412/2074-2711-2019-1-12-20
178. Bevan S, Traylor M, Adih-Samii P, Malik R M, Rothwell PM, Sudlow C, Dichgans M, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genome-wide associations. *Stroke*. 2012;43:3161–3167. doi: 10.1161/STROKEAHA.112.665760
179. Markus HS, Bevan S. Mechanisms and treatment of ischaemic stroke: insights from genetic associations. *Nat Rev Neurol*. 2014;10:723–730. doi: 10.1038/nrneurol.2014.196
180. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, et al; AFGen Consortium. Multi-ancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*. 2018;50:524–537. doi: 10.1038/s41588-018-0058-3
181. Mishra A, Malik R, Hachiya T, Jurgenson T, Namba S, Posner DC, Kamanu FK, Koido M, Le Grand Q, Shi M, et al; COMPASS Consortium. Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature*. 2022;611:115–123. doi: 10.1038/s41586-022-05165-3
182. Akinyemi RO, Tiwari HK, Srinivasasainagendra V, Akpa O, Sarfo FS, Akpalu A, Wahab K, Obiako R, Komolafe M, Owolabi L, et al; for the SIREN Team. Novel functional insights into ischemic stroke biology provided by the first genome-wide association study of stroke in indigenous Africans. *Genome Med*. 2024;16:25. doi: 10.1186/s13073-023-01273-5
183. Devan WJ, Falcone GJ, Anderson CD, Jagiella JM, Schmidt H, Hansen BM, Jimenez-Conde J, Giralt-Steinhauer E, Cuadrado-Godia E, Soriano C, et al; International Stroke Genetics Consortium. Heritability estimates identify a substantial genetic contribution to risk and outcome of intracerebral hemorrhage. *Stroke*. 2013;44:1578–1583. doi: 10.1161/STROKEAHA.111.000089
184. Carpenter AM, Singh IP, Gandhi CD, Prestigiacomo CJ. Genetic risk factors for spontaneous intracerebral haemorrhage. *Nat Rev Neurol*. 2016;12:40–49. doi: 10.1038/nrneurol.2015.226
185. Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, Anderson CD, Brouwers HB, Valant V, Battey TW, et al; International Stroke Genetics Consortium. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J* Low-frequency and common genetic METASTROKE collaboration. 10.1212/WNL.0000000000002528
191. Xu H, Nauven K, Gavnor BJ, Lind H, Stine OC, Ryan KA, Lynch M, et al; TOPMed Stroke Working Group. stroke cases from the SiGN 1410.3390/aenes14010061
192. Aldridge CM, Braun R, Keene KL, Hsu polymorphisms associated with motor aphasia stroke: GWAS study. 10.1212/WNL.00000000000207716
193. Aldridge CM, Braun R, Johse K, de *Hum Genet*. 2014;94:511–521. doi: 10.1016/j.ajhg.2014.02.012
186. Bakker MK, van der Spek RAA, van Rheenen W, Morel S, Bourcier R, Hostettler IC, Alg VS, van Eijk KR, Koido M, Akiyama M, et al; HUNT All-In Stroke. Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors. *Nat Genet*. 2020;52:1303–1313. doi: 10.1038/s41588-020-00725-7
187. Traylor M, Malik R, Nalls MA, Cotlarciuc I, Radmanesh F, Thorleifsson G, Hanscombe KB, Langeveld C, Saleheen D, Rost NS, et al; METASTROKE, UK Young Lacunar DNA Study, NINDS Stroke Genetics Network, Neurology Working Group of the CHARGE Consortium. Genetic variation at 16q24.2 is associated with small vessel stroke. *Ann Neurol*. 2017;81:383–394. doi: 10.1002/ana.24840
188. Traylor M, Persyn E, Tomppo L, Klasson S, Abedi V, Bakker MK, Torres N, Li L, Bell S, Rutten-Jacobs L, et al; Helsinki Stroke, Study Dutch Parelsnoer Institute–Cerebrovascular Accident (CVA) Study Group. Genetic basis of lacunar stroke: a pooled analysis of individual patient data and genome-wide association studies. *Lancet Neurol*. 2021;20:351–361. doi: 10.1016/S1474-4422(21)00031-4
189. Jaworek T, Xu H, Gaynor BJ, Cole JW, Rannikmae K, Stanne TM, Tomppo L, Abedi V, Amouyel P, Armstrong ND, et al; Cervical Artery Dissections Ischemic Stroke Patients (CADSIP) Consortium; INVENT Consortium; Early Onset Stroke Genetics Consortium of the International Stroke Genetics Consortium (ISGC). Contribution of common genetic variants to risk of early onset ischemic stroke. *Neurology*. 2022;99:e1738–e1754. doi: 10.1212/WNL.00000000000201006
190. Malik R, Traylor M, Pulit SL, Bevan S, Hopewell JC, Holliday EG, Zhao W, Abrantes P, Amouyel P, Attia JR, et al; ISGC Analysis Group.

- Lindgren AG, Keene KL, Hsu FC, Worrall BB. Genome-wide association studies of 3 distinct recovery phenotypes in mild ischemic stroke. *Neurology*. 2024;102:e208011. doi: 10.1212/WNL.0000000000208011
194. Georgakis MK, Gill D, Rannikmae K, Traylor M, Anderson CD, Lee JM, Kamatani Y, Hopewell JC, Worrall BB, Bernhagen J, et al. Genetically determined levels of circulating cytokines and risk of stroke. *Circulation*. 2019;139:256–268. doi: 10.1161/CIRCULATIONAHA.118.035905
195. Gill D, Georgakis MK, Laffan M, Sabater-Lleal M, Malik R, Tzoulaki I, Veltkamp R, Dehghan A. Genetically determined FXI (Factor XI) levels and risk of stroke. *Stroke*. 2018;49:2761–2763. doi: 10.1161/STROKEAHA.118.022792
196. de Vries PS, Sabater-Lleal M, Huffman JE, Marten J, Song C, Pankratz N, Bartz TM, de Haan HG, Delgado GE, Eicher JD, et al; INVENT Consortium. A genome-wide association study identifies new loci for factor VII and implicates factor VII in ischemic stroke etiology. *Blood*. 2019;133:967–977. doi: 10.1182/blood-2018-05-849240
197. Cai H, Cai B, Liu Z, Wu W, Chen D, Fang L, Chen L, Sun W, Liang J, Zhang H. Genetic correlations and causal inferences in ischemic stroke. *J Neurol*. 2020;267:1980–1990. doi: 10.1007/s00415-020-09786-4
198. Patel A, Fang J, Gillespie C, Odom E, King SC, Luncheon C, Ayala C. Awareness of stroke signs and symptoms and calling 9-1-1 among US adults: National Health Interview Survey, 2009 and 2014. *Prev Chronic Dis*. 2019;16:E78. doi: 10.5888/pcd16.180564
199. Visaria A, Dharamdasani T, Gaur S, Ghoshal B, Singh V, Mathur S, Varghese C, Demissie K. Effectiveness of a cultural stroke prevention program in the United States: South Asian Health Awareness About Stroke (SAHAS). *J Immigr Minor Health*. 2021;23:747–754. doi: 10.1007/s10903-020-01071-w
200. Menkin JA, McCreath HE, Song SY, Carrillo CA, Reyes CE, Trejo L, Choi SE, Willis P, Jimenez E, Ma S, et al. “Worth the walk”: culturally tailored stroke risk factor reduction intervention in community senior centers. *J Am Heart Assoc*. 2019;8:e011088. doi: 10.1161/JAHA.118.011088
201. Brissette V, Rioux B, Choi T, Poppe AY. Impact of bilingual face, arm, speech, time (FAST) public awareness campaigns on emergency medical services (EMS) activation in a large Canadian metropolitan area. *CJEM*. 2023;25:403–410. doi: 10.1007/s43678-023-00482-6
202. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.
203. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
204. Howard G, Evans GW, Pearce K, Howard VJ, Bell RA, Mayer EJ, Burke GL. Is the Stroke Belt disappearing? An analysis of racial, temporal, and age effects. *Stroke*. 1995;26:1153–1158. doi: 10.1161/01.str.26.7.1153
205. Hay CC, Graham JE, Pappadis MR, Sander AM, Hong I, Reistetter TA. The impact of one’s sex and social living situation on rehabilitation outcomes after a stroke. *Am J Phys Med Rehabil*. 2020;99:48–55. doi: 10.1097/PHM.0000000000001276
206. Sennfalt S, Pihlsgard M, Petersson J, Norrving B, Ullberg T. Long-term outcome after ischemic stroke in relation to comorbidity: an observational study from the Swedish Stroke Register (Riksstroke). *Eur Stroke J*. 2020;5:36–46. doi: 10.1177/2396987319883154
207. Dai S, Lemaire C, Piscicelli C, Pérennou D. Lateropulsion prevalence after stroke: a systematic review and meta-analysis. *Neurology*. 2022;98:e1574–e1584. doi: 10.1212/WNL.0000000000200010
208. Duong P, Sauve-Schenk K, Egan MY, Meyer MJ, Morrison T. Operational definitions and estimates of return to work poststroke: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2019;100:1140–1152. doi: 10.1016/j.apmr.2018.09.121

209. Badve MS, Zhou Z, van de Beek D, Anderson CS, Hackett ML. Frequency of post-stroke pneumonia: systematic review and meta-analysis of observational studies. *Int J Stroke*. 2019;14:125–136. doi: 10.1177/1747493018806196
210. Holmes RJ, McManus KJ, Koulouglioti C, Hale B. Risk factors for poststroke shoulder pain: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2020;29:104787. doi: 10.1016/j.jstrokecerebrovasdis.2020.104787
211. Banda KJ, Chu H, Kang hemorrhagic stroke: results from the kaiser XL, Liu D, Pien L-C, Jen H-J, Hsiao S-TS, Chou K-R. Prevalence pediatric stroke study. *Pediatrics*. 2009;123:823–828. doi: 10.1542/peds.2008-0874
- of dysphagia and risk of pneumonia and mortality in acute stroke patients: a meta-analysis. *BMC Geriatr*. 2022;22:420. doi: 10.1186/s12877-022-02960-5
212. Faura J, Bustamante A, Reverte S, Garcia-Berrocso T, Millan M, et al. Blood biomarker panels for the early prediction of stroke-associated complications. *J Am Heart Assoc*. 2021;10:e018946. doi: 10.1161/JAHA.120.018946
213. Seiler A, Camilo M, Korostovtseva L, Haynes AG, Brill AK, Horvath T, Egger M, Bassetti CL. Prevalence of sleep-disordered breathing after stroke and TIA: a meta-analysis. *Neurology*. 2019;92:e648–e654. doi: 10.1212/WNL.0000000000006904
- and outcomes of arterial ischemic stroke in children: the Canadian Pediatric Ischemic Stroke Registry. *Pediatr Neurol*. 2017;69:58–70. doi: 10.1016/j.pediatrneurol.2017.01.016
228. Armstrong-Wells J, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Prevalence and predictors of perinatal of stroke in children: ethnic and gender disparities. *Neurology*. 2003;61:189–194. doi: 10.1212/WNL.0000000000006904
214. Lisabeth LD, Sánchez BN, Chervin RD, Morgenstern LB, Zahuranec DB, Tower SD, Brown DL. High prevalence of post-stroke sleep disordered breathing in Mexican Americans. *Sleep Med*. 2017;33:97–102. doi: 10.1016/j.sleep.2016.01.010
215. Liu X, Lam DC, Chan KPF, Chan HY, Ip MS, Lau KK. Prevalence and determinants of sleep apnea in patients with stroke: a me-

- spective population-based study. *Lancet Neurol.* 2014;13:35–43. doi: 10.1016/S1474-4422(13)70290-4
231. Earley CJ, Kittner SJ, Feeser BR, Gardner J, Epstein A, Wozniak MA, Wityk R, Stern BJ, Price TR, Macko RF, et al. Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study. *Neurology.* 1998;51:169–176. doi: 10.1212/wnl.51.1.169
232. Ferriero DM, Fullerton HJ, Bernard TJ, Billingham L, Daniels SR, DeBaun MR, deVeber G, Ichord RN, Jordan LC, Massicotte P, et al; on behalf of the American Heart Association Stroke Council and Council on Cardiovascular and Stroke Nursing. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. *Stroke.* 2019;50:e51–e96. doi: 10.1161/STR.0000000000000183
233. Xia Q, Yang Z, Xie Y, Zhu Y, Yang Z, Hei M, Ding Y, Kong W, Kang L, Yang S, et al. The incidence and characteristics of perinatal stroke in Beijing: a multicenter study. *Front Public Health.* 2022;10:783153. doi: 10.3389/fpubh.2022.783153
216. Mayman NA, Tuhim S, Jette N, Dhamoon MS, Stein LK. Sex differences in post-stroke depression in the elderly. *J Stroke Cerebrovasc Dis.* 2021;30:106129. doi: 10.1016/j.jstrokecerebrovasdis.2021.106129
217. Avadhani R, Thompson RE, Carhuapoma L, Yenokyan G, McBee N, Lane K, Ostapovich N, Stadnik A, Awad IA, Hanley DF, et al. Post-stroke depression in patients with large spontaneous intracerebral hemorrhage. *J Stroke Cerebrovasc Dis.* 2021;30:106082. doi: 10.1016/j.jstrokecerebrovasdis.2021.106082
218. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: a systematic review and meta-analysis. *Ageing Res Rev.* 2019;50:102–109. doi: 10.1016/j.arr.2019.01.013
219. Almeida OP, Hankey GJ, Ford AH, Etherton-Beer C, Flicker L, Hackett ML; AFFINITY Trial Investigators. Measures associated with early, late, and persistent clinically significant symptoms of depression 1 year after stroke in the AFFINITY trial. *Neurology.* 2022;98:e1021–e1030. doi: 10.1212/WNL.00000000000020058
220. Chye A, Hackett ML, Hankey GJ, Lundström E, Almeida OP, Gommans J, Dennis M, Jan S, Mead GE, Ford AH, et al. Repeated measures of modified Rankin Scale scores to assess functional recovery from stroke: AFFINITY study findings. *J Am Heart Assoc.* 2022;11:e025425. doi: 10.1161/jaha.121.025425
221. Balucani C, Levine SR, Sanossian N, Starkman S, Liebeskind D, Gornbein JA, Shkirkova K, Stratton S, Eckstein M, Hamilton S, et al. Neurologic improvement in acute cerebral ischemia: frequency, magnitude, predictors, and clinical outcomes. *Neurology.* 2023;100:e1038–e1047. doi: 10.1212/WNL.000000000000201656
222. Dong Y, Ding M, Cui M, Fang M, Gong L, Xu Z, Zhang Y, Wang X, Xu X, Liu X, et al. Development and validation of a clinical model (DREAM-LDL) for post-stroke cognitive impairment at 6 months. *Aging (Albany NY).* 2021;13:21628–21641. doi: 10.18632/aging.203507
223. Khan M, Heiser H, Bernicchi N, Packard L, Parker JL, Edwardson MA, Silver B, Elisevich KV, Henninger N. Leukoaraiosis predicts short-term cognitive but not motor recovery in ischemic stroke patients during rehabilitation. *J Stroke Cerebrovasc Dis.* 2019;28:1597–1603. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.037
224. Ohlmeier L, Nannoni S, Pallucca C, Brown RB, Loubiere L, Markus HS; DNA Lacunar 2 Investigators. Prevalence of, and risk factors for, cognitive impairment in lacunar stroke. *Int J Stroke.* 2023;18:62–69. doi: 10.1177/17474930211064965
225. Fox C. Pediatric ischemic stroke. *Continuum (Minneapolis).* 2023;29:566–583. doi: 10.1212/CON.0000000000001239
226. Gao L, Lim M, Nguyen D, Bowe S, MacKay MT, Stojanovski B, Moodie M. The incidence of pediatric ischemic stroke: a systematic review and meta-analysis. *Int J Stroke.* 2023;18:765–772. doi: 10.1177/17474930231155336
227. deVeber GA, Kirton A, Booth FA, Yager JY, Wirrell EC, Wood E, Shevell M, Surmava AM, McCusker P, Massicotte MP, et al. Epidemiology

234. Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, Ferriero DM, Fullerton HJ, Barkovich AJ, Wu YW. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA*. 2005;293:723–729. doi: 10.1001/jama.293.6.723
235. Roy B, Webb A, Walker K, Morgan C, Badawi N, Nunez C, Eslick G, Kent AL, Hunt RW, Mackay MT, et al. Prevalence & risk factors for perinatal stroke: a population-based study. *Child Neurol Open*. 2023;10:2329048X231217691. doi: 10.1177/2329048X231217691
236. Sporns PB, Fullerton HJ, Lee S, Kirton A, Wildgruber M. Current treatment for childhood arterial ischaemic stroke. *Lancet Child Adolesc Health*. 2021;5:825–836. doi: 10.1016/S2352-4642(21)00167-X
237. Wintermark M, Hills NK, deVeber GA, Barkovich AJ, Elkind MS, Sear K, Zhu G, Leiva-Salinas C, Hou Q, Dowling MM, et al; VIPS Investigators. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the Vascular Effects of Infection in Pediatric Stroke study. *Stroke*. 2014;45:3597–3605. doi: 10.1161/STROKEAHA.114.007404
238. Elkind MS, Hills NK, Glaser CA, Lo WD, Amlie-Lefond C, Dlamini N, Kneen R, Hod EA, Wintermark M, deVeber GA, et al; VIPS Investigators. Herpesvirus infections and childhood arterial ischemic stroke: results of the VIPS study. *Circulation*. 2016;133:732–741. doi: 10.1161/CIRCULATIONAHA.115.018595
239. Beslow LA, Agner SC, Santoro JD, Ram D, Wilson JL, Harrar D, Appavu B, Fraser SM, Rossor T, Torres MD, et al; International Pediatric Stroke Study Group. International prevalence and mechanisms of SARS-CoV-2 in childhood arterial ischemic stroke during the COVID-19 pandemic. *Stroke*. 2022;53:2497–2503. doi: 10.1161/STROKEAHA.121.038250
240. Chung MG, Williams KP, Wilson JL, Beslow LA, Dowling MM, Friedman NR, Hassanein SMA, Ichord R, Jordan LC, Mackay MT, et al; International Pediatric Stroke Study Investigators. Arterial ischemic stroke secondary to cardiac disease in neonates and children. *Pediatr Neurol*. 2019;100:35–41. doi: 10.1016/j.pediatrneurol.2019.06.008
241. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*. 1998;91:288–294.
242. DeBaun MR, Jordan LC, King AA, Schatz J, Vichinsky E, Fox CK, McKinstry RC, Telfer P, Kraut MA, Daraz L, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv*. 2020;4:1554–1588. doi: 10.1182/bloodadvances.2019001142
243. Ambrose EE, Latham TS, Songoro P, Charles M, Lane AC, Stuber SE, Makubi AN, Ware RE, Smart LR. Hydroxyurea with dose escalation for primary stroke risk reduction in children with sickle cell anaemia in Tanzania (SPHERE): an open-label, phase 2 trial. *Lancet Haematol*. 2023;10:e261–e271. doi: 10.1016/S2352-3026(22)00405-7

- 10.1016/j.arcped.2023.07.007
247. Fullerton HJ, Wintermark M, Hills NK, Dowling MM, Tan M, Rafay MF, Elkind MS, Barkovich AJ, deVeber GA; VIPS Investigators. Risk of recurrent arterial ischemic stroke in childhood: a prospective international study. *Stroke*. 2016;47:53–59. doi: 10.1161/STROKEAHA.115.011173
248. Pangprasertkul S, Borisoot W, Buawangpong N, Sirikul W, Wiwattanadittakul N, Katanyuwong K, Sanguansermisri C. Comparison of arterial ischemic and hemorrhagic pediatric stroke in etiology, risk factors, clinical manifestations, and prognosis. *Pediatr Emerg Care*. 2022;38:e1569–e1573. doi: 10.1097/PEC.0000000000002614
249. Hamilton W, Huang H, Seiber E, Lo W. Cost and outcome in pediatric ischemic stroke. *J Child Neurol*. 2015;30:1483–1488. doi: 10.1177/0883073815570673
250. Plumb P, Seiber E, Dowling MM, Lee J, Bernard TJ, deVeber G, Ichord RN, Bastian R, Lo WD. Out-of-pocket costs for childhood stroke: a systematic review. *Arch*
244. Abdullahi SU, Sunusi S, Abba MS, Sani S, Gambo A, Musa B, Covert Greene BV. for secondary stroke prevention in children Nigera: a randomized controlled trial. 10.1182/blood.2022016620
245. Chabrier S, Pevric E, Drutel L, Deron J, L. Lefranc J, Thebault G, Drav G, et al: nouveau-né (AVCnn: [Neonatal Stroke]) come at 7 years of age after neonatal 2016:172:156–161.e3. doi: 246. Giraud A, Stenhens CM, Fluss J. Long-term developmental condition emic stroke: a systematic review. *Arch*
261. Pérez de la Ossa N, Abilleira S, Jovin Cardona P, Cocho D, Purrov F. Effect of direct transportation to stroke center on neurological vessel occlusion stroke in nonurban cal trial. *JAMA*. 2022;327:1782–1794.
262. Ramos-Pachon A, Rodriguez-Luna D, Bustamante A, Martinez-Sanchez M, C. Camms-Renom P, et al: RACECAT ino the closest stroke center in secondary analysis of the RACECAT 2023:80:1028–1036. doi: 263. Deleted in proof stroke: the impact of chronic illness on parents' pocketbooks. *Pediatr Neurol*. 2015;52:73–76. doi: 10.1016/j.pediatrneurol.2014.09.010
251. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, De Los Rios La Rosa F, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79:1781–1787. doi: 10.1212/WNL.0b013e318270401d
252. Bejot Y, Duloquin G, Thomas Q, Mohr S, Garnier L, Graber M, Giroud M. Temporal trends in the incidence of ischemic stroke in young adults: Dijon Stroke Registry. *Neuroepidemiology*. 2021;55:239–244. doi:

264. Navi BB, Audebert HJ, Alexandrov AW, Cadilhac DA, Grotta JC; PRESTO (Prehospital Stroke Treatment Organization) Writing Group. Mobile stroke units: evidence, gaps, and next steps. *Stroke*. 2022;53:2103–2113. doi: 10.1161/STROKEAHA.121.037376
265. Grotta JC, Yamal JM, Parker SA, Rajan SS, Gonzales NR, Jones WJ, Alexandrov AW, Navi BB, Nour M, Spokorny I, et al. Prospective, multicenter, controlled trial of mobile stroke units. *N Engl J Med*. 2021;385:971–981. doi: 10.1056/NEJMoa2103879
266. Ebinger M, Siegerink B, Kunz A, Wendt M, Weber JE, Schwabauer E, Geisler F, Freitag E, Lange J, Behrens J, et al; Berlin_PRehospital Or Usual Delivery in stroke care (B_PROUD) study group. Association between dispatch of mobile stroke units and functional outcomes among patients with acute ischemic stroke in Berlin. *JAMA*. 2021;325:454–466. doi: 10.1001/jama.2020.26345
267. Man S, Solomon N, Mac Grory B, Alhanti B, Uchino K, Saver JL, Smith EE, Xian Y, Bhatt DL, Schwamm LH, et al. Shorter door-to-needle times are associated with better outcomes after intravenous thrombolytic therapy and endovascular thrombectomy for acute ischemic stroke. *Circulation*. 2023;148:20–34. doi: 10.1161/CIRCULATIONAHA.123.064053
268. Ospel JM, Almekhlafi MA, Menon BK, Kashani N, Chapot R, Fiehler J, Hassan AE, Yavagal D, Majoie C, Jayaraman MV, et al. Workflow patterns and potential for optimization in endovascular stroke treatment across the world: results from a multinational survey. *J Neurointerv Surg*. 2020;12:1194–1198. doi: 10.1136/neurintsurg-2020-015902
269. Dong C, Gardener H, Rundek T, Marulanda E, Gutierrez CM, Campo-Bustillo ology, and outcome of ischemic stroke in young adults: a worldwide meta-analysis: the GOAL initiative. *Neurology*. 2022;98:e573–e588. doi: 10.1212/WNL.0000000000013195
253. Leppert MH, Ho PM, Burke J, Madsen TE, Kleindorfer D, Sillau S, Daugherty S, Bradley CJ, Poisson SN. Young women had more strokes than young men in a large, United States claims sample. *Stroke*. 2020;51:3352–3355. doi: 10.1161/STROKEAHA.120.030803
254. Jacob MA, Ekker MS, Allach Y, Cai M, Aarnio K, Arauz A, Arnold M, Bae HJ, Bando L, Barboza MA, et al. Global differences in risk factors, etiology, and outcome of ischemic stroke in young adults: a worldwide meta-analysis: the GOAL initiative. *Neurology*. 2022;98:e573–e588. doi: 10.1212/WNL.0000000000013195
255. Ekker MS, Verhoeven JI, Schellekens MMI, Boot EM, van Alebeek ME, Brouwers P, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, et al.

I, Gordon Perue G, Johnson KH, Sacco RL, Romano JG; Transitions of Care Stroke Disparities Study (TCSD-S) Investigators. Factors and behaviors re-lated to successful transition of care after hospitalization for ischemic stroke.

Stroke. 2023;54:468–475. doi: 10.1161/STROKEAHA.122.040891 270. Duncan PW, Bushnell CD, Jones SB, Psioda MA, Gesell SB, D'Agostino RB Jr, Sissine ME, Coleman SW, Johnson AM, Barton-Percival BF, et al; COMPASS Site Investigators and Teams. Randomized pragmatic trial of stroke transitional care: the COMPASS Study. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006285. doi: 10.1161/CIRCOUTCOMES.119.006285

271. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024.

Risk factors and causes of ischemic stroke in 1322 young adults. *Stroke*. 2023;54:439–447. doi: 10.1161/strokeaha.122.040524

256. Kim J, Kim JY, Kang J, Kim BJ, Han MK, Lee JY, Park TH, Lee KJ, Kim JT, Choi KH, et al. Improvement in delivery of ischemic stroke treatments but stagnation of clinical outcomes in young adults in South Korea. *Stroke*. 2023;54:3002–3011. doi: 10.1161/STROKEAHA.123.044619

257. Ekker MS, Verhoeven JI, Vaartjes I, Jolink WMT, Klijn CJM, de Leeuw FE. Association of stroke among adults aged 18 to 49 years

272. Centers for Disease Control and Prevention and National Center for data files. Accessed May 1, 2024.

273. Kumar N, Khera R, Pandey A, Garg N. Racial differences in out-comes after acute ischemic stroke hospitalization in the United States. *J Stroke Cerebrov Dis*. 2016;25:19 doi:10.1001/jama.2019.6560

Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use

10.1001/jama.2019.6560

258. Maaijwee NA, Rutten-Jacobs LC, Arntz RM, Schaapsmeeders P, Schoonderwaldt HC, van Dijk EJ, de Leeuw FE. Long-term increased risk of unemployment after young stroke: a long-term follow-up study. *Neurology*. 2014;83:1132–1138. doi: 10.1212/WNL.0000000000000817

259. Synhaeve NE, Arntz RM, van Alebeek ME, van Pamelen J, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, de Kort PL, van Dijk EJ, de Leeuw FE. Women have a poorer very long-term functional outcome after stroke among adults aged 18-50 years: the FUTURE study. *J Neurol*. 2016;263:1099–1105. doi: 10.1007/s00415-016-8042-2

260. Perera KS, de Sa Boasquevisque D, Rao-Melacini P, Taylor A, Cheng A, Hankey GJ, Lee S, Fabregas JM, Ameriso SF, Field TS, et al; Young ESUS Investigators. Evaluating rates of recurrent ischemic stroke among young adults with embolic stroke of undetermined source: the Young ESUS longitudinal cohort study. *JAMA Neurol*. 2022;79:450–458. doi: 10.1001/jamaneurol.2022.0048

10.1016/j.jstrokecerebrovasdis.2016.03.049

274. Stein L, Tuhim S, Fifi J, Mocco J, Dhamoon M. National trends in endovascular therapy for acute ischemic stroke: utilization and outcomes. *J Neurointerv Surg.* 2020;12:356–362. doi: 10.1136/neurintsurg-2019-015019

275. Rose D, Cavalier A, Kam W, Cantrell S, Lusk J, Schrag M, Yaghi S, Stretz C, de Havenon A, Saldanha IJ, et al. Complications of intravenous tenecteplase versus alteplase for the treatment of acute ischemic stroke: a systematic review and meta-analysis. *Stroke.* 2023;54:1192–1204. doi: 10.1161/STROKEAHA.122.042335

276. Jovin TG, Nogueira RG, Lansberg MG, Demchuk AM, Martins SO, Mocco J, Ribo M, Jadhav AP, Ortega-Gutierrez S, Hill MD, et al. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. *Lancet.* 2022;399:249–258. doi: 10.1016/S0140-6736(21)01341-6

277. Adusumilli G, Kobeissi H, Ghozy S, Hardy N, Kallmes KM, Hutchison K, Kallmes DF, Brinjikji W, Albers GW, Heit JJ. Endovascular thrombectomy

- after acute ischemic stroke of the basilar artery: a meta-analysis of four randomized controlled trials. *J Neurointerv Surg*. 2023;15:e446–e451. doi: 10.1136/jnis-2022-019776
278. Panigrahi B, Thakur Hameer S, Bhatia R, Halder P, Sharma A, Srivastava MVP. Effect of endovascular therapy in large anterior circulation ischaemic strokes: a systematic review and meta-analysis of randomised controlled trials. *Eur Stroke J*. 2023;8:932–941. doi: 10.1177/23969873231196381
279. Katsanos AH, Malhotra K, Ahmed N, Seitidis G, Mistry EA, Mavridis D, Kim JT, Veroniki AA, Maier I, Matusevicius M, et al. Blood pressure after endovascular thrombectomy and outcomes in patients with acute ischemic stroke: an individual patient data meta-analysis. *Neurology*. 2022;98:e291–e301. doi: 10.1212/WNL.0000000000013049
280. Yang P, Song L, Zhang Y, Zhang X, Chen X, Li Y, Sun L, Wan Y, Billot L, Li Q, et al; ENCHANTED2/MT Investigators. Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): a multicentre, open-label, blinded-end-point, randomised controlled trial. *Lancet*. 2022;400:1585–1596. doi: 10.1016/S0140-6736(22)01882-7
- esthesia compared with non-GA in endovascular thrombectomy for ischemic stroke: a systematic review and meta-analysis of randomized controlled trials. *Neurology*. 2023;100:e1655–e1663. doi: 10.1212/WNL.0000000000207066
- treatment in patients with acute ischemic stroke and COVID-19: the Global COVID-19 Stroke Registry. *Neurology*. 2023;100:e739–e750. doi: 10.1212/WNL.0000000000201537
290. Strambo D, Marto JP, Ntaios G, Nguyen TN, Michel P; Global COVID-19 Stroke Registry. Effect of asymptomatic and symptomatic COVID-19 on acute ischemic stroke revascularization outcomes. *Stroke*. 2024;55:78–88. doi: 10.1161/STROKEAHA.123.043899
291. Beretta S, Cristillo V, Camera G, Morotti Colleoni C, Pellitteri G, Viti B, Bianchi E, Gipponi S, Grimoldi M, Valente M, et al; for Neuro-COVID Italy. Incidence and long-term functional outcome of neurologic disorders in hospitalized patients with COVID-19 infected with pre-omicron variants. *Neurology*. 2023;101:e892–e903. doi: 10.1212/WNL.0000000000207534
292. Klein NP, Lewis N, Goddard K, Fireman B, Zerbo O. COVID-19 vaccination. *Circ Res*. 2022;130:1. doi: 10.1161/CIRCRESAHA.122.319954
282. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2024.

294. White TG, Martinez G, Wang J, Gribko M, Boltyenkov A, Arora R, Katz JM, Woo HH, Sanelli PC. Impact of the COVID-19 pandemic on acute ischemic stroke presentation, treatment, and outcomes. *Stroke Res Treat*. 2021;2021:8653396. doi: 10.1155/2021/8653396
295. Risser C, Tran Ba Loc P, Binder-Foucard F, Fabacher T, Lefèvre H, Sauvage C, Sauleau EA, Wolff V. COVID-19 impact on stroke admissions during France's first epidemic peak: an exhaustive, nationwide, observational risk TIA: a GWTG-Stroke study. *J Stroke Cerebrovasc Dis*. 2020;29:105399. doi: 10.1016/j.jstrokecerebrovasdis.2020.105399
283. Kaufman BG, Shah S, Hellkamp AS, Lytle BL, Fonarow GC, Schwamm LH, Lesen E, Hedberg J, Tank A, Fita E, et al. Disease burden following non-cardioembolic minor ischemic stroke or high-

- study. *Cerebrovasc Dis*. 2022;51:663–669. doi: 10.1159/000523685
296. Peng TJ, Jasne AS, Simonov M, Abdelhakim S, Kone G, Cheng YK, Rethana M, Tarasaria K, Herman AL, Baker AD, et al. Prior stroke and age predict acute ischemic stroke among hospitalized COVID-19 patients: a derivation and validation study. *Front Neurol*. 2021;12:741044. doi: 10.3389/fneur.2021.741044
284. Pines AR, Hagline J, Demaerschalk BM. Changes in Medicare physician reimbursement for stroke procedures from 2000 to 2019. *Neurosurg Open*. 2021;2:okab003. doi: 10.1093/neuopn/okab003
285. RTI International. Projections of cardiovascular disease prevalence and costs: 2015–2035. Technical report (report prepared for the American Heart Association). RTI International; November 2016. RTI project No. 021480.003.001.001.
286. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed July 1, 2024.

297. Vidale S. Risk factors, and clinical and etiological characteristics of ischemic strokes in COVID-19-infected patients: a systematic review of literature. *Cerebrovasc Dis*. 2021;50:371–374. doi: 10.1159/000514267
 298. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, Fryar CD, Gu S, Hales CM, Hughes JP, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Rep*. 2021;158. doi: 10.15620/cdc:106273
 299. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2024.
287. Zuin M, Mazzitelli M, Rigatelli G, Bilato C, Cattelan AM. Risk of ischemic stroke in patients recovered from COVID-19 infection: a systematic review and meta-analysis. *Eur Stroke J*. 2023;8:915–922. doi: 10.1177/23969873231190432
288. Van Dusen RA, Abernethy K, Chaudhary N, Paudyal V, Kurmi O. Association of the COVID-19 pandemic on stroke admissions and treatment globally: a systematic review. *BMJ Open*. 2023;13:e062734. doi:

300. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP, et al. Epidemiology of ischemic stroke in patients with diabetes: the Greater Cincinnati/ Northern Kentucky Stroke Study. *Diabetes Care*. 2005;28:355–359.
doi: 10.2337/diacare.28.2.355
289. Marto JP, Strambo D, Ntaios G, Nguyen TN, Herzig R, Czlonkowska A, Demeestere J, Mansour OY, Salerno A, Wegener S, et al; Global COVID-19 Stroke Registry. Safety and outcome of revascularization
301. Centers for Disease Control and Prevention. Stroke death rates. Accessed June 28, 2024.

16. BRAIN HEALTH

ICD-9 290, 291.2, 291.8, 294, 331; F00–F03, G30–G31 See Tables and Charts 16-1 through 16-3

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Definition

Brain health has traditionally been defined in terms of the absence of disease or the presence of a healthy state,¹ but it is an evolving concept with calls to include mental health and social well-being.² Brain health has been defined as “the state of brain functioning...allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders.”³ This definition includes the capacity to perform all the diverse tasks for which the brain is responsible, including movement, perception, learning and memory, communication, problem solving, judgment, decision-making, and emotion. Stroke and clinical cerebrovascular disease more broadly are important precursors and risk factors for cognitive decline and dementia; their presence indicates an absence of brain health. Conversely, evidence of systemic and cerebral vascular health has been associated with healthy aging and retained cognitive function.

Although this chapter provides prevalence and incidence estimates for dementia overall (unspecified) and separately for AD and vascular dementia, most dementia pathology is mixed, with contributions of both AD and vascular dementia. Postmortem neuropathology studies suggest that ≈1 in 4 people who receive a clinical diagnosis of AD has non-AD pathology as a primary explanation for

Last, there is also no evidence pathological AD diagnosis or pathology have been tantamount of understanding both brain health. The list of ICD chapter matches the list of the GBD Study, which of dementia.⁷ AD/ADRD refers dementias, including vascular impairment and dementia, frontotemporal degeneration, Lewy body dementia, and dementias of multiple causes.⁸

their dementia.⁴ Notably, neither cognitive performance nor demographic variables appear to have any bearing on which patients diagnosed with MCI will develop postmortem pathology consistent with AD. In addition, vascular dementia prevalence and incidence are likely underestimated because (1) most dementia cases have multiple pathologies at autopsy, including signs of ischemia, and (2) vascular disease is common.^{5,6}

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Prevalence

Dementia

- A systematic analysis of data from the GBD Study
alient neurological disorder in the United States
people.⁹ Among 3496 participants in the HRS ≥65
dementia, and 804 (22% [95% CI, 20%–24%])
neurological disorders, AD/ADRD was the leading
per 100 000 population per year [95% UI, 38–39]),
 - According to administrative claims data of US
of age in 2014, AD/ADRD prevalence was 11.5%
pared with males (8.6%); prevalence was higher
ties, but these numbers were not age adjusted.¹¹
with age (65–74 years of age, 3.6%; 75–84 years
prevalence of AD/ADRD was 13.8% in Black indi-
NH White individuals, 9.1% in American Indian and
Pacific Islander individuals.
 - Of the 46.8 million people estimated to be living with dementia globally in 2015, 58% of them were living in low- or
middle-income countries.¹² However, the predicted annual total cost of dementia per patient in 2015 was highest in
higher-income countries: \$10 467 for upper-middle–income countries com-pared with \$3865 for low-middle–income
countries and \$939 for low-income countries.¹³ However, a systematic review estimated that low-income coun-tries
had the highest total cost as a percentage of their GDP (0.46%) followed by upper-middle–income countries
(0.43%) and then low-middle–income countries (0.35%), dedicated to dementia care.¹⁴
- showed that AD/ADRD was the fourth most prev-
in 2017, affecting 2.9 (95% UI, 2.6–3.2) million
years of age, 393 (10% [95% CI, 9%–11%]) had
were classified as having MCI in 2016.¹⁰ Among
cause of mortality in the United States (38 deaths
greater than that for stroke.⁹
- Medicare fee-for-service beneficiaries ≥65 years
with a higher prevalence in females (12.2%) com-
in females among all reported races and ethnici-
In terms of age, AD/ADRD prevalence increased
of age, 13.6%; and ≥85 years of age, 34.6%). The
viduals, 12.2% in Hispanic individuals, 10.3% in
Alaska Native individuals, and 8.4% in Asian and

-
- Young-onset dementia, defined as symptoms before 65 years of age, was estimated in a meta-analysis to have prevalence globally of 1.1 per 100 000 at 30 to 34 years of age, 1.0 per 100 000 at 35 to 39 years of age, 3.8 per 100 000 at 40 to 44 years of age, 6.3 per 100 000 at 45 to 49 years of age, 10.0 per 100 000 at 50 to 54 years of age, 19.2 per 100 000 at 55 to 59 years of age, and 77.4 per 100 000 at 60 to income countries.¹⁵
 - The age-adjusted prevalence of subjective cognitive decline among adults ≥ 45 years of age in the United States, as assessed by BRFSS data between 2015 and 2020, was higher among data.⁹ The US age-standardized incidence rate of AD/ADRD was 85 cases per 100 000 people (95% UI, 78–93).
 - In a retrospective analysis of the HRS (N=3435), for up to 3 years after dementia onset, using the TICS to define dementia onset, Black individuals were less likely to receive a diagnosis of ADRD (unadjusted HR Hispanic adults (11.4%) and American Indian or Alaska Native adults (16.7%) compared with NH White adults (9.3%) but similar in NH Black adults (10.1%) and lower among NH Asian or Pacific Islander adults

adjusted for demographics, income, and level of

- In a nationally representative cohort study of receiving care in the Veterans Healthcare System differences in the incidence of dementia by race dementia was higher among underrepresented (5.0%).¹⁶

Alzheimer Disease

- In 2024, ≈6.9 million adults ≥65 years of age in the United States were living with AD. In other words, 10.9% of the US population, or ≈1 in 9 people, was living with AD.¹⁷ Prevalence estimates for AD are estimated to be lower if the definition necessitates both clinical

education (HR, 0.79 [95% CI, 0.66–0.96]).²¹

US veterans (N=1 869 090; ≥55 years of age between 1999 and 2019), there were significant and ethnicity.²² The age-adjusted incidence of

racial and ethnic groups compared with White

symptoms and AD biomarkers (≈4.8 million adults ≥65 years of age).

- Prevalence estimates vary with age. According to data from CHAP, the 2020 US census-adjusted prevalence per 100 people is 5.3% (95% CI, 4.9%–5.7%) for 65 to 74 years of age, 13.8% (95% CI, 13.1%–14.5%) for 75 to 84 years of age, and 34.6% (95% CI, 33.3%–35.8%) for those >85

racial and ethnic groups (14.2 per 1000 PY [95% CI, 13.3–15.1] in American Indian or Alaska Native participants, 12.4 [95% CI, 11.7–13.1] in Asian participants, 19.4 [95% CI, 19.2–19.6] in Black participants, and 20.7 [95% CI, 20.1–21.3] in Hispanic participants compared with 11.5 [95% CI, 11.4–11.6] in White participants).

- Among those ≥ 90 years of age in the United States, the age-adjusted incidence rate of dementia was 100.5 cases per 1000 PY (95% CI, 92.8–108.3) with the highest rates among Black individuals (121.5 dementia cases per 1000 PY) and the low-est rates among Asian individuals (89.9 dementia cases per 1000 PY).²³

years of age.¹⁸

Vascular Dementia

- Vascular dementia accounts for $\approx 5\%$ to 10% of patients with dementia when both clinical and neuropathological criteria are used.¹⁷ The prevalence is estimated to be between 15% and 20% in Europe and North America and as high as 30% in some

Alzheimer Disease

Asian countries.¹⁹

- In a meta-analysis of studies from across the world (South America, Asia, Africa, Europe, and North America), the prevalence of vascular dementia was reported as higher in males than females (56 cases versus 32 cases per 10 000 people).²⁰

- Among 2794 individuals from CHAP, the annual incidence of clinically diagnosed AD was 3.6% (95% CI, 3.3%–3.9%).²⁴ Black individuals had a higher annual incidence of clinically diagnosed AD (4.1% [95% CI, 3.7%–4.6%]) than White individuals (2.6% [95% CI, 2.3%–3.0%]). The annual incidence of clinically diagnosed AD increased with age in both Black individuals and White individuals.
- In 2011 in the United States, the average incidence of AD per year was 0.4% in individuals 65 to 74 years of age, 3.2% in individuals 75 to 84 years of age, and 7.6% in individuals ≥85 years of age.²⁴

Vascular Dementia

Incidence

Dementia

- In a US cohort of >240 000 females diagnosed with

- In 2017, AD/ADRD had the fifth leading incidence rate of neurological disorders in the United States, after tension-type headache, migraine,

traumatic brain injury, and stroke, according to GBD Study

compared with White females (7.2 cases per 1000 PY) was higher in Black females (11.3 cases per 1000 PY; aHR versus White females, 1.51 [95% CI, 1.39–1.64]) and lower in Asian/Pacific Islander

females (5.58 cases per 1000
White females, 0.67 [95% CI,
• Data from the nationally
Mexico, 2012 and 2015
age- and sex-standardized
dementia among individuals
Mexico was 2.0 (95% CI, 1.3–2.7)

Lifetime Risk and Cumulative

Dementia

- In a population-based Japanese cohort of individuals ≥ 60 years of age, the lifetime risk of dementia was 54.8% (95% CI, 49.4%–60.1%); elderly females had a greater lifetime risk (64.8%

decrease [95% UI, 5.2%–
dardized prevalence
100 000 to 470.0 per 100 000
[95% UI, 5.1%–20.6%]);
increased from 35.0 per 100
100 000 (9.8% increase [95%
and DALY rates increased
to 418.8 per 100 000 (1.2%
1.9% decrease–4.2%

- Between 1990 and 2019, the
mated a significant increase
[95% CI, 57.4%–72.1%]) than
elderly males (40.8% [95% CI,

standardized mortality rates from dementia for males of 5.1% (95% CI, 0.4%–12.0%) and a nonsignificant increase for females of 3.0% (95% CI, –2.6% to 11.0%).³² The global all-age mortality rate from dementia increased 100.1% (95% CI, 33.0%–48.5%).²⁷

- Among participants in the Monzino 80-Plus population-based cohort study from Italy, the lifetime risk of dementia at 80 years of age was 55.9% (95% CI, 51.6%–59.8%) and was higher for females (63.0% [95% CI, 58.4%–67.3%]) than for males (42.9% [95% CI, 34.6%–51.0%]).²⁸

- According to nationwide individually linked cause-

89.1%–117.5%).

of-death and health register data in the Netherlands, the lifetime risk of dementia (estimated by the proportion of deaths in the presence of dementia) was ≈24.0%, higher for females (29.4%) than males

- A forecasting analysis based on the GBD Study 2019 projected stable global age-standardized prevalence (percentage change, 0.1% [−7.5% to 10.8%]) but an increase in the number of people living with dementia from 2019 to 2050, attributed largely to population growth and aging (57.4 [95% UI, 50.4–65.1] million cases in 2019 to 152.8 [95% UI, 130.8–175.9] million cases in 2050).³³ More females were estimated to be living with dementia in 2019 (RR, 1.69 [95% CI, 1.64–1.73]) and 2050 (RR, 1.67 [95% CI, 1.52–1.85]) compared with males. (18.3%).²⁹

Alzheimer Disease

- In a population-based Japanese cohort of individuals ≥60 years of age, the lifetime risk of AD was ≈2-fold higher for females (42.4% [95% CI, 35.1%–49.7%]) than for males (20.4% [95% CI, 6.6%–34.2%]).²⁷
- The 2023 AD lifetime risk estimates according to the FHS (reported in 2014) at 45 years of age were 1 in 5 females and 1 in 10 males (competing mortality-adjusted cumulative incidence in females, 19.5% [95% CI, 17.8%–21.2%]

and in males, 10.3% [95% CI, 8.9%–11.8%]).^{30,31}

Vascular Dementia

- In a population-based Japanese cohort of individuals ≥60 years of age, the estimated lifetime risk of vascular dementia was similar among females (16.3% [95% CI, 11.5%–21.1%]) and males (17.8% [95% CI, 12.9%–22.7%]).²⁷

- Data from the nationally representative HRS provide evidence that the prevalence of dementia among individuals ≥ 65 years of age declined significantly in the United States from 12.2% (95% CI, 11.7%–12.7%) in 2000 to 8.5% (95% CI, 7.9%–9.1%) in 2016.³⁴
- An analysis of Medicare data estimates that the AD/ADRD prevalence in the US population will increase to 3.3% and that AD/ADRD will affect 13.9 million Americans by 2060.¹¹
- In an analysis of 2 population-based cohort studies from Sweden, the incidence rate of dementia declined $\approx 30\%$ (HR, 0.70 [95% CI, 0.61–0.80]) from the late 1980s to the early 2010s in adults ≥ 75 years of age.³⁵ The decline in dementia incidence was present even after adjustment for education, psychosocial working conditions, lifestyle factors, and vascular disease (HR, 0.77 [95% CI, 0.65–0.90]).
- In a cohort study of Danish older adults ≥ 65 years of

Secular Trends

Dementia

age, from 2005 to 2018, the incidence of dementia declined by 22.5% in males and 34.2%

- According to an analysis of GBD Study data from 1990 to 2017, age-standardized incidence rates of AD/ADRD in the United States decreased from 97.2 per 100 000 to 85.2 per 100 000 (12.4%)

dence of dementia decreased by 18.1% in males and 23.5% in females. Individuals with high educational attainment (10% males, 14.7% females), high household wealth (12.1% males, 21.4% females),

no history of stroke (7.0% males, 15.6% females), and low medication use (21% males, 19.7% females) had a lower incidence of dementia than the general population but with a similar pattern of decline over time.

- An analysis of 7 population-based cohort studies in the United States and Europe demonstrated that for individuals >65 years of age, the incidence of all-cause dementia declined by 13% (95% CI, 7%–19%) per calendar decade from 1998 through 2015 with a more pronounced reduction in males (24% [95% CI, 14%–32%]) than in females (8% [95% CI, 0%–15%]).³⁷
- A meta-analysis of 53 cohorts from around the world demonstrated a decrease in dementia incidence across 3 older age groups (65–74, 75–84, and ≥85 years of age).³⁸ Each 10-year increase in birth year was associated with a reduction in the odds of incident dementia for individuals reaching each of the older age groups (OR, 0.20 [95% CI, 0.18–0.22] for individuals reaching 65 to 74 years of age; OR, 0.20 [95% CI, 0.19–0.21] for those 75 to 84 years of age; and OR, 0.72 [95% CI, 0.58–0.90] for individuals ≥85 years of age).
- In the HRS, a nationally representative study of adults ≥50 years of age in the United States, dementia prevalence estimates 2 years from 2000 to 2016 ranged between 1.4 and 1.8 times as high in NH Black individuals as in NH White individuals, standardized for age and sex. There was no evidence of a significant decrease in the racial difference over time (*P* ranging from 0.55–0.98 for tests of trend over time).
- In contrast to declining trends of dementia typically reported in high-income countries,

among those born from 1905–1914, 37% for 1915–1919, 30% for 1920–1924, and 22% for 1925–1930; *P*<0.001 across birth year categories, χ^2 test).

Alzheimer Disease

- In an analysis of 7 population-based cohorts in the United States and Europe from the Alzheimer Cohort Consortium, among individuals >65 years of age, the incidence of clinical AD declined by 16% (95% CI, 8%–24%) per calendar decade from 1998 through 2015.³⁷
- A meta-analysis of 35 cohorts from around the world demonstrated no significant decrease in the AD incidence rates across 3 older age groups (65–74 years, *P*=0.26; 75–84 years, *P*=0.90; and ≥85 years of age, *P*=0.54).³⁸ Although AD incidence rates were stable in Western countries, studies from non-Western countries demonstrated a significant increase in incidence rates for the age group of 65 to 74 years (OR, 2.78 [95% CI, 1.33–5.79]; *P*=0.04). No significant sex differences in AD incidence

Africa represents an understudied continent with a paucity of data available. Over a 9-year interval from 2009 to 2010 to 2018 to 2019, there was an increase in dementia prevalence from 6.4% to 8.9% among those >70 years of age in Tanzania.⁴⁰ It is estimated that 212 million individuals ≥60 years of age will be living in Africa by the year 2050, suggesting a rapidly aging

Vascular Dementia

- For FHS participants ≥ 60 years of age, the 5-year dementia declined over 4 epochs of time from 0.8 late 1970s and early 1980s to 0.4 per 100 individuals in the early 2010s ($P_{\text{trend}}=0.004$).⁴⁴

- According to a population-based cross-sectional Database, age-adjusted mortality for vascular dementia to 2016 (from 19.2 per 1 000 000 individuals in 2007 to 38.5 per 1 000 000 individuals in 2016).⁴³

age- and sex-adjusted incidence of vascular per 100 individuals (95% CI, 0.6–1.3) in the late 2000s and

study of US data from the WHO Mortality Database, age-adjusted mortality for vascular dementia increased by 2-fold from 2007 to 2016 (from 19.2 per 1 000 000 individuals in 2007 to 38.5 per 1 000 000 individuals in 2016).⁴³

population.⁴¹

- Among 1554 participants from 1997 to 2022

Risk Factors

(Religious Orders Study and the Rush Memory and Aging Project) with autopsy data, there were no differences in the age-standardized

prevalence of pathological AD diagnosis ($P=0.76$ across year of birth groups).⁴² However, there was a decrease

Vascular risk factors are increasingly recognized as the most important cluster of risk factors for brain health, particularly because of their high prevalence and potential for modification.

in the prevalence of neurodegenerative pathologies related to atherosclerosis/arteriosclerosis (eg, moderate to severe atherosclerosis was 54% *Blood Pressure*

- There is consistent and substantial evidence for the role of BP, including hypertension, as a risk

factor for cognitive decline analysis, midlife hypertension impairment in global cognition 1.19–2.03]; 4 studies) and 1.22 [95% CI, 1.06–1.41]; 2 dementia (RR, 1.20 [95% CI, and AD (RR, 1.19 [95% CI,

- Among 3201 middle-aged adults age) in the FHS (55% female) median of 17 years, every 1-

lative SBP was associated with a higher odds of developing late-life (≥ 65 years of age) all-cause dementia (OR, 1.50 [95% CI, 1.32–1.72]) and developing AD (OR, 1.45 [95% CI, 1.24–1.69]).⁴⁶

In the CHARLS cohort (N=4824; 62% females), hypertension at middle age (< 55 years of age) was associated with a faster decline in memory ($\beta = -1.12$ [95% CI, -1.41 to -0.83]), orientation

- In a meta-analysis of 3 studies lion females, HDP was not with higher risk for dementia HR, 1.08 [95% CI,
- In a meta-analysis of 8 studies 1000 and 8000 participants, nitive domain, arterial sectionally associated with measures of processing CI, 0.25–0.54], working ($\beta = -1.27$ [95% CI, -1.35 to -1.20]), and global cognition ($\beta = -1.61$ [95% CI, -1.74 to -1.48]) compared with no hypertension over 8 years of follow-up.⁴⁷ Longer duration of hypertension was associated with poorer memory ($\beta = -0.07$ [95% CI,

0.15–0.41]), short-term memory and learning (–0.27 [95% CI, –0.37 to –0.17]), and delayed recall (–0.20 [95% CI, –0.35 to –0.05]).⁵¹

• In studies of late-life hypertension, there is often no association or a protective association between hypertension and cognitive outcomes, particularly among the oldest old.^{49,52,53} Among 17 286 older adults (mean age, 74.5 years) in 7 pooled cohorts in Europe and the United States with 2799 incident dementia cases over a median of 7.3 years of follow-up, SBP at baseline had a U-shaped association with dementia risk, and the lowest dementia risk was observed at SBP of 185 mm Hg (95% CI, –0.11 to –0.03]).⁵⁴ The U-shaped relationship was more

- Among 2718 adults in CARDIA, longer duration of hypertension from early to middle adulthood was associated with significantly lower midlife scores on a measure of verbal memory (Rey Auditory Verbal Learning Test; 0.18 points lower [95% CI, 0.07–0.29 point lower]; $P=0.002$ per 5 additional years' duration) and with lower midlife scores, but not reaching statistical significance, on a measure of processing speed (digit symbol substitution test; 0.43 point lower [95% CI, 0.10 point higher–0.95 point lower]; $P=0.112$ per 5 additional years' duration) but not with a measure of executive function (Stroop test; 0.01 point lower [95% CI, 0.37 point higher–0.39 point lower]; $P=0.975$ per 5 additional years' duration).⁴⁸ Lower scores on verbal memory with longer hypertension duration were observed whether hypertension was controlled or uncontrolled.
- BP in early adulthood may also be associated with worse cognitive health. In a study that pooled

data from 4 observational cohorts of adults between 18 and 95 years of age at enrollment (N=15 001; 34% Black participants; 55% females), early adult vascular risk factors were associated with late-life cognitive decline.⁴⁹ Vascular risk factors were imputed across the life course in early adulthood, midlife, and late life for older adults. Early-adult elevated SBP was associated with an approximate doubling of mean 10-year decline in late life (4.44 points greater decline [95% CI, 0.99–7.88 points decline] on digit symbol substitution test over 10 years), even after adjustment for SBP exposure at midlife

- prominent in the oldest age groups, with lowest-risk SBP of 170 mm Hg (95% CI, 160–260) at 75 to 85 years of age and lowest-risk SBP of 162 mm Hg (95% CI, 153–240) at 85 to 95 years of age.
- Among 2688 males of Japanese ancestry in the Kuakini HHP (mean age, 77 years) followed up for a mean of 8.63 years with 104 incident vascular dementia and 513 incident AD cases, late-life hypertension was associated with incident vascular dementia (HR, 1.78 [95% CI, 1.05–2.99] for BP $\geq$ 140/90 mm Hg or self-reported antihypertensive use).⁵⁵ Late-life hypertension reduced the risk of AD among males with the *FOXO3* longevity genotype (HR, 0.73 [95% CI, 0.53–1.00]) but not among males without this genotype (HR, 1.09 [95% CI, 0.81–1.46]).
 - Older adults randomized to intensive BP control in SPRINT (a subset with MRI at baseline and follow-up; N=454) had greater declines in hippocampal volume over 4 years compared with those on standard treatment (β =–0.033 cm³ [95% CI, –0.062 to –0.003]; *P*=0.03).⁵⁶
 - Among 3319 older adults in the S.AGES cohort in France (mean age, 78 years; 57% females), BP variability may also be a marker of risk for poor brain health outcomes. Greater visit-to-visit SBP, DBP, and mean arterial BP variability, measured every 6 months over 3 years, was associated with worse global cognition (for each 1-SD increase of coefficient of variation: β =–0.12 [SE, 0.06], –0.20 [SE, 0.06], and –0.20 [SE, 0.06], respectively; *P*<0.05 for all) and risk of dementia (for each 1-SD increase of coefficient of

variation: HR, 1.23 [95% CI, 1.01–1.50], 1.28 [95% CI, 1.05–1.56], and 1.35 [95% CI, 1.12–1.63], respectively).⁵⁷ Among 12 298 adults in HRS and ELSA who were free of dementia at baseline, each 10% increment in coefficient of variation of visit-to-visit SBP variability was associated with 0.026–SD/y faster (95% CI, 0.016–0.036) global cognitive decline, and each 10% increment in DBP variability was associated with 0.022–SD/y faster (95% CI, 0.012–0.032) global cognitive decline. In the ASPREE trial, males in the highest SBP variability tertile compared with the lowest had higher incidence of dementia (HR, 1.68 [95% CI, 1.19–2.35]) but females in the highest tertile did not (HR, 1.01 [95% CI, 0.72–1.42]).⁵⁹ Among 820 older adults in the ACT study (mean age, 77 years), BP variability among those 90 years of age was

- The proportion of time spent in target SBP range may be associated with dementia risk. Among 8298 participants in the SPRINT MIND trial (mean age, 68 years; 35% female), greater time spent in the target SBP range (110–130 mm Hg for the intensive treatment group or 120–140 mm Hg for the standard treatment group) was associated with a lower risk of

Cardiac Dysfunction

Heart Failure

associated with higher life-time dementia risk (for each 1-SD increase in coefficient of variation: HR, 1.35 [95% CI, 1.02–1.79]).⁶⁰ BP variability was not associated with lifetime dementia risk at 60, 70, or 80 years of age.

- A diagnosis of HF is associated with cognitive decline. Among 4864 males and females in CHS initially free of HF and stroke, 496 participants who developed incident HF had greater adjusted declines over 5 years on the modified MMSE than those without HF (10.2 points [95% CI, 8.6–11.8] versus 5.8 points [95% CI, 5.3–6.2]).⁶⁶ The effect did not vary significantly by HFrEF versus HFpEF.
- Among 8493 older adults (mean age, 80.6 years) in the Chinese Longitudinal Healthy Longevity Survey, those whose SBP increased from 130 mm Hg at baseline to >150 mm Hg at follow-up had 48% higher odds (95% CI, 13%–93%) of incident cognitive impairment and those whose SBP decreased from 130 to 150 mm Hg at baseline to <130 mm Hg at follow-up had 28% higher odds (95% CI, 2%–61%) of incident cognitive impairment compared with those who maintained stable SBP from 130 to 150 mm Hg.⁶¹
 - In ARIC (N=4761; 21% Black participants; 59%

• In a meta-analysis of 4 longitudinal studies, the 1.80 (95% CI, 1.41–2.31).⁶⁷ • Among 6336 patients, the 1-year and 3-year cumulative incidences of ADRD after incident HF diagnosis were 7.6% (95% CI, 6.9%–8.3%) and 17.1% (95% CI, 16.2%–18.0%), respectively.⁶⁸ Patients with ADRD diagnosed after HF had a 3.7 times increased risk of death (95% CI, 3.34–4.10) compared with those who did not develop ADRD, even after adjustment for vascular risk factors, marital status, and education. • An individual patient meta-analysis of 19 378 participants from 5 cohort studies found that adjustment for cumulative mean SBP, suggesting that differences between Black individuals and White individuals in global cognition decline were no longer statistically significant after cumulative BP levels might contribute to racial disparities in cognitive decline.⁶³	adjusted for cumulative mean SBP, suggesting that Black individuals' higher cumulative BP levels might contribute to racial disparities in cognitive decline.⁶³ • An individual participant data meta-analysis of 34 519 older adults (mean age, 73 years) including 14 studies from COSMIC found a higher risk of dementia among participants with untreated hypertension compared with participants without hypertension (HR, 1.42 [95% CI, 1.15–1.76]) and compared with participants with treated hypertension (HR, 1.26 [95% CI, 1.03–1.54]).⁶⁴

- Among 3052 patients with HF in the FHS, the 1-year and 3-year cumulative incidences of AD/ADRD were 3.3% (95% CI, 2.6%–3.9%) and 13.8% (95% CI, 12.5%–15.1%).⁶⁹
 - In the ASPREE trial, 19 114 adults without CVD or dementia at baseline were followed up for 9 years to determine trajectories of cognitive change after incident CVD (fatal CHD, nonfatal MI, stroke, hospitalization for HF).⁷⁰ After the CVD event, there was an acute decrement in processing speed (acute drop in cognitive score, -1.97 [95% CI, -2.53 to -1.41]) followed by declines in global cognitive function (annual change in cognitive score, -0.56 [95% CI, -0.76 to -0.36]), delayed recall (annual change in cognitive score, -0.10 [95% CI, -0.16 to -0.04]), and verbal fluency (annual change in cognitive score, -0.19 [95% CI, -0.30 to -0.01]).
- Similarly, in the 171 adults with a hospitalization for HF, there was an acute decrement in processing speed (acute drop in cognitive score, -2.85 [95% CI, -4.07 to -1.63]) followed by declines in global cognitive function (annual change in cognitive

score, -0.51 [95% CI, -0.99 recall (annual change in [95% CI, -0.36 to -0.01]), and (annual change in cognitive -0.63 to -0.09)).

Atrial Fibrillation

- AF is a potential risk factor cognitive decline and (N=12 515: mean age, 57 participants; 56% females), AF was associated with greater cognitive decline over 20 years (global cognitive Z score, 0.115 [95% CI, 0.014 – 0.215]). Risk of dementia was also elevated in participants with AF compared with those without (HR, 1.23 [95% CI, 1.04 – 1.45]).⁷¹ Among 25 980 adults in REGARDS, those with AF at baseline declined in mean word list learning score over 10 years of follow-up (decline in mean±SD score from 16.3 ± 0.15 to 16.0 ± 0.23), whereas those without AF at baseline increased in mean word list learning score (increase in mean±SD score from 16.3 ± 0.05 to 16.9 ± 0.06 ; $P=0.03$ for AF versus no AF); however, there were no significant differences in trajectories of semantic fluency, word list delayed recall, or MoCA score.⁷² Among 98 484 patients with AF in the Kaiser system and 98 484 matched controls without incident AF (2010–2017; median follow-up time, 3.3 years), incidence rates for dementia were higher for those with AF (2.79 [95% CI, 2.72 – 2.85] per 100 PY) versus without (2.04 [95% CI, 1.99 – 2.08] per 100 PY).⁷³ In a meta-

with nonusers with AF.⁷⁶ In a studies including 613 920 aqualant treatment was (14%–40% lower) risk of with no treatment, albeit with of study-specific findings a study of 407 871 older Veterans Health with increased risk of CI, 1.07 – 1.22): anticoagulant

analysis of 18 studies including 3.5 million participants with >900 000 cases of incident dementia, AF was associated with 41% higher (28%–54%) hazard of dementia ($I^2=94\%$ indicating high heterogeneity, although 15 of 18 study-specific HRs fell between 1.10 and 2.00).⁷⁴

- In the UK Biobank, of the 433 746 participants without baseline dementia or AF, having a younger age at AF onset during the median 12.6 years of follow-up was associated with a higher risk of all-cause dementia (aHR per 10-year decrease, 1.23 [95% CI, 1.16 – 1.32]), AD (aHR per 10-year decrease, 1.27 [95% CI, 1.13 – 1.42]), and vascular dementia (aHR per 10-year decrease, 1.35 [95% CI, 1.20 – 1.51]) compared with participants with older age at

- with AF also was associated with increased risk of dementia (OR, 1.44 [95% CI, 1.27–1.63]).⁷⁷
- Among 39 200 new users of oral anticoagulants in the General Practice Research Database in the United Kingdom with 1258 cases of incident dementia, treatment with DOACs was associated with 16% lower hazard of dementia (95% CI, 2%–27% lower) and 26% lower hazard of MCI (95% CI, 16%–35% lower) than treatment with vitamin K antagonists.⁷⁹ Among 53 236 new users of oral anticoagulants in the Korean National Health Insurance Service database identified in 2013 to 2016 with 2194 cases of incident dementia through the end of 2016, treatment with DOACs was associated with 22% lower hazard of dementia (95% CI, 10%–31% lower) than treatment with warfarin.⁸⁰ Among 12 068 patients with AF in the Taiwan National Health Insurance Research database, treatment with DOACs was associated with 18% lower hazard (8%–27% lower) of dementia than treatment with warfarin.⁸¹ In the Belgian nationwide cohort study (2013–2019), DOAC use was associated with a lower risk of dementia (HR 0.91 [95% CI, 0.85–0.98]) compared with vitamin K antagonist use among 237 012 participants with AF.⁸² However, in another analysis among 72 846 new users of oral anticoagulants in the Korean National Health Insurance Service database identified in 2014 to 2017 with 4437 cases of incident dementia through the end of 2018, treatment with DOACs compared with warfarin was not associated with dementia risk (HR, 0.99 [95% CI, 0.93–1.06]).⁸³ Last, in a meta-analysis of 9 studies including 611 069 participants, treatment with DOACs was associated with 44% lower odds (85% CI, 6%–66% lower) of incident dementia than treatment with warfarin.⁸⁴
 - Evidence for the possible benefits of anticoagulant therapy to mitigate this risk relationship is conflicting, with some studies reporting benefits and others not.^{76,77} In SNAC-K, AF was associated with increased risk of all-cause and vascular and mixed dementia (HR, 1.40 [95% CI, 1.11–1.77]

- In a systematic review of 10 studies with 15 886 patients treated with catheter ablation and 42 684 patients treated with medical therapy (rate or rhythm control), 4 studies reported risk of dementia with the pooled-effect estimate suggesting a decreased risk of incident dementia among those who underwent ablation (HR, 0.60 [95% CI, 0.42–0.88]).⁸⁵ These results, however, were limited by an inability to assess for publication bias because of the small number of

studies included. Another systematic review of 5 studies with 30 192 in the catheter ablation group and 95 457 in the non-catheter ablation group reported a significant reduction in risk of dementia (HR, 0.63 [95% CI, 0.52–0.77]) and AD (HR, 0.78 [95% CI, 0.66–0.92]) with ablation but not vascular dementia (HR, 0.63 [95% CI, 0.38–1.06]).⁸⁶ There were more patients with HF

Coronary Disease

- In terms of coronary revascularization procedures, the evidence for an association between either CABG or PCI and later-life dementia is contradictory, although most studies do not suggest an association. One RCT did not suggest a difference in cognitive decline between PCI or CABG after 7.5 years.⁸⁷ In the HRS, there was also no significant difference in the rate of memory decline between those undergoing PCI and those undergoing CABG.⁸⁸ In CHS, there was an association between CABG and all-cause dementia (HR, 1.93 [95% CI, 1.36–2.74]) compared with those without a history of CABG.⁸⁹ Fewer studies have investigated PCI versus medical therapy and the risk of dementia, with 1 cohort study suggesting a lower risk of dementia in the PCI

in those without cognitive impairment (40.9%).

Last, among patients with NSTEMI, rates of angi-ography, PCI, and CABG were 50.3%, 27.3%, and 3.3% in those with MCI compared with 84.7%, 49.4%, and 10.9% in those without cognitive impairment.

- Among 30 465 participants in 6 different longitudinal cohort studies, points per year [95% CI, –0.21 to –0.10]), memory (–0.13 points per year [95% CI, –0.22 to –0.04]), and executive function (–0.14 points per year [95% CI, –0.20 to –0.08]) over the years after MI compared with pre-MI slopes.⁹³ It was not, however, associated with an acute decrease in any cognitive domain around the group (HR, 0.65 [95% CI, 0.46–0.84]) compared with the medically managed group.⁹⁰
- Among a prospective cohort of 3146 participants in the CARDIA study (mean age, 55; 57% females, 48% Black participants), premature CVD (≤ 60 years of age) was associated with worse midlife global cognition (–0.22 [95% CI, –0.37 to –0.08]), verbal memory (–0.28 [95% CI, –0.44 to –0.12]), processing speed (–0.46 [95% CI,

- Subclinical measures of cardiac dysfunction are also associated with brain health outcomes. For example, asymptomatic LV hypertrophy, measured by LV mass index, has been associated with increased risk of cognitive decline and dementia and worse white matter burden in late life.^{94,95} In MESA (N=4999; mean age, 61 years; 47% males; 26% Black participants, 22% Hispanic participants, and 13% Chinese participants; median follow-up, 12 years), both LV mass index and ratio of LV mass to volume were associated with increased risk of dementia (HR, 1.01 [95% CI, 1.00–1.02] and 2.37 [95% CI, 1.25–4.43], respectively).⁹⁵ LV hypertrophy and remodeling also were associated with worse global cognition, processing speed, and executive function. Studies suggest that this association is also significant for cognitive and brain MRI outcomes in middle-aged adults.⁹⁶ Early CVD was also associated with greater brain MRI WMH and lower white matter integrity, as well as accelerated cognitive decline over 5 years (aOR, 3.07 [95% CI,

- In ARIC (N=5078), a state of atrial cardiopathy was associated with an increased risk of dementia (HR, 1.35 [95% CI, 1.16–1.58]), and only a small portion of the effect was mediated by either AF (4%; 1.56–5.71]).
 $P=0.005$) or ischemic stroke (9%; $P=0.048$).⁹⁷
- In a study from the NCDR Chest Pain–MI Registry of 43 812 participants >65 years of age with MI, MCI was found in 3.9% of those presenting with an STEMI and in 5.7% of those presenting with an NSTEMI.⁹² After adjustment for potential confounders, MCI was associated with a higher risk of all-cause in-hospital mortality (STEMI cohort: OR, 1.3 [95% CI, 1.1–1.5]; NSTEMI cohort: OR, 1.3 [95% CI, 1.2–1.5]). In addition, among those presenting with STEMI, PCI use was relatively similar in those with MCI (92.8%) and those with-out cognitive impairment (92.1%), but fibrinolytic

- In CARDIA, among 2653 participants with echo-cardiogram evaluation 25 years apart, a greater increase (≥ 1 SD above the mean slope) in LV mass index and LA volume index and a greater decrease (≥ 1 SD below the mean slope) in LVEF were found.⁹⁸ After adjustment for demographics and vascular risk factors, a greater increase in LV mass index over 25 years was associated with lower cognition on some but not all cognitive tests (eg, MoCA ≥ 1 -SD change mean -0.24 [95% CI, -0.35 to -0.12) with no differences in cognitive performance for either a larger LA volume index or lower LVEF. use was lower in those with MCI

Poststroke
(See Chapter 15 [Stroke
Diseases]).)

Diabetes

- Diabetes is associated with
tioning and faster cognitive
tional analysis of UK Biobank
participants with diabetes
than matched healthv

executive function, processing speed, abstract
rea- soning, and numeric memory; they
scored similarly on a measure of reaction time
(Chart 16-1B).⁹⁹ In meta-analyses of 34 studies
conducted by the same authors, 4735

participants with diabetes scored sig- nificantly
lower than 17 496 healthy participants on 10 of
11 cognitive domains assessed (Chart 16-1C).⁹⁹

In a longitudinal analysis of ELSA par- ticipants
with a median follow-up of 13 years, 576

participants experiencing incident diabetes
declined faster on measures of global cognition
(0.035 SD/y faster [95% CI, 0.015–0.054]),
orientation (0.031 SD/y faster [95% CI, 0.002–
0.060]), memory (0.016 SD/y faster [95% CI,
0.003–0.029]), and executive function (0.027
SD/y faster [95% CI, 0.013–0.042]) after
diabetes onset than partici- pants without
diabetes.¹⁰⁰

- Among 63 117 postmenopausal females in the

of 5 longitudinal studies
ticipants with diabetes with a
years. risk of dementia was
0.3%–12% higher) per
HbA1c coefficient of variation
19% higher (95% CI, 6%–

- A history of hypoglycemia is
worse brain health outcomes.
of 9 studies of older adults

WHI observational study in the
United States with 8340 cases of
incident AD over a median follow-up
of 20 years, baseline diabetes was
associated with 22% higher hazard
(95% CI, 13%–31% higher) of AD.
Incidence of AD was 8.5 cases per
1000 PY (95% CI, 8.0–9.0) for
females who had diabetes versus 7.1
cases per 1000 PY (95% CI, 6.9–7.2)
for females without diabetes.¹⁰¹

- In a mendelian randomization study
of 115 875 adults, the RR for
1–mmol/L (18–mg/dL) higher
plasma glucose level and risk of
dementia was 2.40 (95% CI,
1.18–4.89). The results were not
signifi-

lowering drugs, experiencing hypoglycemic episodes was associated with 50% higher odds (95% CI, 29%–74% higher) of dementia.¹⁰⁷ In another meta-analysis of 10 studies including >1.4 million participants with diabetes, hypoglycemic episodes were associated with 44% higher risk (95% CI, 26%–65% higher) of dementia.¹⁰⁸ In a meta-analysis of 7 studies including 981 812 participants with diabetes, increasing number of hypoglycemic episodes was associated with higher risk of incident dementia (RR, 1.29 [95% CI, 1.15–1.44] for 1 hypoglycemic episode; 1.68 [95% CI, 1.38–2.04] for 2 hypoglycemic episodes; 1.99 [95% CI, 1.48–2.68] for ≥3 hypoglycemic episodes).¹⁰⁹

- In the PPSW (N=1212 females without diabetes; mean age, 48 years), fasting serum insulin at baseline was categorized into tertiles. Among those in the lowest tertile of fasting insulin, there was an increased risk of dementia over 34 years (HR, 2.34 [95% CI, 1.52–3.58]) compared with those with fasting insulin in the middle tertile.¹¹⁰

- Late-life diabetes, poor glycemic control among those with diabetes, and diabetes duration (≥5 years) were also associated with greater risk of MCI/dementia in ARIC (HR, 1.14 [95% CI, 1.00–1.31], 1.31 [95% CI, 1.05–1.63], and 1.59 [95% CI, 1.23–2.07], respectively). Late-life higher HbA1c (>7.5%, 58 mmol/mol) and lower HbA1c (<5.8%, 40 mmol/mol) were also associated with increased risk of MCI/dementia compared with HbA1c in the

midrange.¹¹¹

- Studies also have demonstrated an association between elevated glucose levels in early adulthood to midlife and worse midlife cognitive outcomes among participants without diabetes.^{103,104}
- HbA1c variability may be an indicator of increased risk for worse cognitive outcomes. In a study that pooled cohort data from the HRS and ELSA (N=6237; mean age, 63 years; 58% females; median follow-up, 11 years), the highest quartile

of HbA1c variability compared with the lowest quartile was associated with greater decline in memory (β =−0.094 SD/y [95% CI, −0.185 to −0.003]) and executive function (−0.083 SD/y [95% CI, −0.125 to −0.041]). This association was significant even among those without diabetes.¹⁰⁵ In a meta-analysis

- Among 11 656 adults in ARIC (mean age, 57 years; 55% female), earlier age at diagnosis of incident diabetes was associated with higher risk of incident dementia (HR, 2.92 [95% CI, 2.06-4.14] for diabetes diagnosis at <60 years of age; HR, 1.73 [95% CI, 1.47–2.04] for diabetes diagnosis at 60–69 years of age; HR, 1.23 [95% CI, 1.08–1.40] for diabetes diagnosis at 70-79 years of age).¹¹²
- Among 356 052 participants <60 years of age in the UK Biobank (mean age, 55 years; 55% female) with 485 cases of young-onset incident dementia (<65 years of age) over a median follow-up of 9.18 years, having diabetes was associated with 65% higher risk of young-onset dementia (HR, 1.65 [95% CI, 1.15–2.36]).¹¹³

Obesity

• Midlife overweight and obesity are associated with increased risk of cognitive impairment and dementia. In a meta-analysis of 11 longitudinal studies including >64 000 participants, those who were overweight in midlife compared with those who were normal weight did not have a higher risk of the combined end point of cognitive impairment or all-cause dementia (1.23–2.18) and 1.49 times the risk of vascular dementia (95% CI, 1.06–2.10). Midlife obesity compared with normal weight was associated with 1.31 times the risk of cognitive impairment

to 70 years old with other poorly controlled risk factors).¹²² There was no association between obesity and risk of dementia in participants 60 to 70 years of age without other poorly controlled risk factors or in participants ≥70 years of age compared with healthy adults with normal weight.

- In an analysis combining data from 39 studies, obesity was associated with 2.23 times the risk of AD (95% CI, 1.58–3.14), and 3.18 times the risk of vascular dementia (95% CI, 1.81–5.57).¹¹⁴

increase in BMI increased as the time between BMI assessment and dementia diagnosis increased (BMI assessed <10 years before dementia diagnosis: HR, 0.71 [95% CI, 0.66–0.77]; BMI assessed 10–20 years before dementia diagnosis: HR, 0.94 [95% CI, 0.89–0.99]; BMI assessed >20 years before dementia diagnosis: HR, 1.16 [95% CI,

- In NOMAS, abdominal adiposity, measured as waist-hip ratio, in middle-aged adults was associated with cognitive decline over 6 years. For each increase in SD for waist-hip ratio, the associated decline in global cognition was equivalent to a 2.6-year increase in age. There was also a significant association with decline in processing speed and executive function.¹¹⁵ In a separate analysis of NOMAS cohort data, BMI and WC were associated with reduced cortical thickness on brain MRI at follow-up.¹¹⁶
- In 9652 participants from the UK Biobank (mean age, 55 years; 48% males), BMI, waist-hip ratio, and fat mass were cross-sectionally associated with worse gray matter volume (β per 1 SD of measure = -4113 [95% CI, -4862 to -3364], -4272 [95% CI, -5280 to -3264], and -4590 [95% CI, -5386 to -3793], respectively).¹¹⁷ In a systematic review of 34 studies, of which 30 were cross-sectional and 4 were prospective, obesity was associated with lower gray matter volume or cortical thickness in most studies; no quantitative meta-analysis was conducted because of the heterogeneity of obesity measures (BMI, WC, waist-to-hip ratio, plasma leptin levels) and of brain MRI mea-

- One study showed that obesity may be associated with poorer cognition at baseline but slower cognitive decline over time.¹²⁴ In a meta-analysis of individual participant data consisting of 6 pooled cohorts with 28 867 participants free of dementia at baseline (mean age, 61 years; 55% female; 29% obese), participants with obesity had 0.36 point lower global cognition scores (95% CI, 0.17–0.56 point lower) and 0.56 point lower executive function scores (95% CI, 0.37–0.76 point lower) than participants with normal weight at baseline. Over a median follow-up of 6.5 years, participants with obesity had 0.03 point/y (95% CI, 0.01–0.05) slower decline in global cognition and 0.02 point/y (95% CI, 0.006–0.03) slower decline in executive function compared with participants with normal weight after adjustment for SBP and FPG. On the basis of those estimated trajectories, it would take adults with obesity 0.74 year longer (for global cognition) and 1.05 years longer (for executive function) than adults with normal weight to reach ≥ 0.5 -SD decline from the baseline cognition score.

measures used in the included studies.¹¹⁸

- The evidence for obesity and BMI in late life is less clear,¹¹⁹ with some studies suggesting that obesity is protective or that weight loss may be a prodrome of late-life dementia.^{120,121}
- In the Whitehall II Study (N=17 175), participant age modified the association between obesity and risk of dementia. Compared with healthy adults

Smoking

with normal weight, obesity at <60 years of age and 60 to 70 years of age was associated with increased risk of dementia (HR 1.69 [95% CI, 1.16–2.45] and 1.46 [95% CI, 1.02–2.08] for participants with obesity <60 years of age without and with other poorly controlled risk factors, respectively; HR, 1.47 [95% CI, 1.05–2.04] for participants with obesity 60

- Smoking is a risk factor for dementia and poor cognitive outcomes, and studies suggest that quitting smoking is beneficial for brain health.^{125–127}
- In an analysis from the NACC UDS, current smoking was associated with incident dementia (HR, 1.88 [95% CI, 1.08–3.27]) compared with non-smoking. Participants who quit within the past 10 years compared with nonsmokers were not more likely to develop dementia.¹²⁶
- Early adult trajectories of smoking are also associated with worse cognitive outcomes. In CARDIA (N=3364; mean age at cognitive assessment, 50 years; 46% Black participants; 56% female), investigators identified 5 smoking trajectories over 25

years from early adulthood to 40% minimal-stable, 20% heavy-stable, and 5% heavy. Compared with nonsmokers, had worse performance on cognitive function, and memory at CI, 1.53–3.22], 1.58 [95% CI, 1.05–2.10], and moderate-stable smokers cessation speed (OR, 1.95

1.56 [95% CI, 1.11–2.19]). Minimal stable smokers and quitters were not more likely than nonsmokers to have worse cognitive performance at midlife.¹²⁵ Among 2993 participants in the Framingham Offspring Study, those exposed to >1 pack/d of secondhand smoke during the first 18 years of life had 2.86 times the risk of dementia (HR, 2.86 [95% CI, 2.00–4.09]) and 3.13 times the risk of AD (HR, 3.13 [95% CI, 1.80–5.42]) compared with those with no exposure to secondhand smoke.¹²⁸

- Among 353 756 nonsmokers in the UK Biobank with 4113 developing incident dementia over a median 11.8 years of follow-up, secondhand smoke exposure was associated with increased risk of all-cause dementia compared with no exposure to second-hand smoke (HR, 1.11 [95% CI, 1.02–1.20] and 1.31 [95% CI, 1.13–1.52] for ≤4 and >4 h/wk of secondhand smoke exposure, respectively).¹²⁹

Cardiovascular Risk Factor Burden (See Table 16-1)

- The AHA's ideal CVH metrics are associated with reduced cognitive decline. In a meta-analysis of 14 studies including >300 000 participants, of whom

factors, 57% had 3 to 4 ideal 5 to 7 ideal factors. Ideal CVH lower risk of developing CI, 0.84–0.97] per each risk factor (OR, 0.84–0.97) and with better global cognitive function at follow-up.¹³³

- Among 229 976 participants in the Atherosclerosis Risk in Communities (ARIC) study, 2143 cases of incident dementia were identified during follow-up of 9 years. Each 1-point increase in the Life's Simple 7 score was associated with a 1-point increase in the Life's Simple 7 CVH score was associated with 6% lower rate of dementia (95% CI, 4%–8% lower).¹³⁰ The inverse relationship of higher CVH score with dementia risk was more pronounced for midlife CVH than for late-life CVH. These results are consistent with findings in ARIC showing that ideal midlife vascular risk factors were associated with less cognitive decline over 20 years.¹³¹

- Ideal CVH metrics at 50 years of age were similarly associated with lower incidence of dementia over 25 years of follow-up in the Whitehall II Study.¹³² Those with poor CVH (scores 0–6) had 3.2 cases of dementia per 1000 PY (95% CI, 2.5–4.0); those with intermediate CVH (scores 7–11) had 1.5 cases per 1000 PY (95% CI, 0.7–2.3 fewer); and

ard of dementia (HR, 0.89 [95% CI, 0.88–0.91]).¹³⁴ Each 1-point increment in the biological component score (based on BP, cholesterol, and glucose) was associated with 7% lower hazard of dementia (HR, 0.93 [95% CI, 0.89–0.96]). However, a 1-point increment in the lifestyle component score (based on smoking, BMI, diet, and PA) was not associated with dementia (HR, 0.99 [95% CI, 0.96–1.02]).

- Among 259 718 participants in the UK Biobank with 4958 cases of incident dementia over a median 10.6 years of follow-up, lower AHA's Life's Essential 8 score was associated with higher risk of vascular dementia (HR, 1.86 [95% CI, 1.44–2.42]) for participants in the lowest versus highest quartile of AHA's Life's Essential 8 score.¹³⁵ There was no association between AHA's Life's Essential 8 score and risk of AD (HR, 0.98 [95% CI, 0.84–1.16]) for participants in the lowest versus highest quartile of AHA's Life's Essential 8 score.
- Among 316 669 participants in the UK biobank with 4238 incident cases of all-cause dementia (mean age, 56 years) over a median 12.6 years of follow-up, an optimal AHA's Life's Essential 8 score (score of 80–100 on a 100-point scale) was associated with a 14% lower risk of incident all-cause dementia (HR, 0.86 [95% CI, 0.83–0.89]) and 30% lower risk of vascular dementia (HR, 0.70 [95% CI, 0.65–0.75]) compared with a poor AHA's Life's Essential 8 score (score of 0–49).¹³⁶ The association between AHA's Life's Essential 8 score and risk of dementia varied by *APOE* status ($P_{\text{interaction}} < 0.001$). In participants without an *APOE*ε4 allele, the HR of all-cause dementia or vascular dementia associated with an optimal AHA's Life's Essential 8 score was 0.39 (95% CI, 0.31–0.49) and 0.18 (95% CI, 0.12–0.29), respectively. In participants with at least 1 *APOE*ε4 allele, the HR of all-cause dementia or vascular dementia associated with an optimal AHA's Life's Essential 8 score was 0.71 (95% CI, 0.56–0.90) and 0.41 (95% CI, 0.27–0.63), respectively. those with optimal CVH (scores 12–14) had 1.9 fewer cases per 1000 PY (95% CI, 1.1–2.8 fewer), with an HR for dementia of 0.89 per 1-point incre-

- Greater cardiovascular risk factor burden is associated with increased risk of cognitive decline and dementia.^{137,138}
ment in CVH score (95% CI, 0.85–0.95).
- In the 3C Study of 6626 older adults (mean age, 74 years; 63% female), 37% had 0 to 2 ideal CVH

- In CARDIA,¹³⁷ Framingham 10-Year Coronary Heart Disease Risk Score ≥ 10 was associated with

accelerated cognitive decline 5 years later in midlife (OR, 2.29 [95% CI, 1.21–4.34]).

- In the Harvard Aging Brain Study,¹³⁹ greater Framingham 10-Year Cardiovascular Disease Risk Score was associated with greater late-life cognitive decline (-0.064 [95% CI, -0.094 to -0.033]) over almost 4 years. There was also a significant interactive effect between cardiovascular risk and amyloid burden ($\beta = -0.040$ [95% CI, -0.062 to -0.018]).
- In the Insight 46 cohort, higher Framingham 10-Year Cardiovascular Disease Risk Score in early adult-hood (36 years of age) also was associated with lower late-life total brain volume (β per 1%

BMI) did not differ in the incidence of AD compared with participants without vascular risk factors (OR,

Chronic Kidney Disease

- Among 90 369 adults in the CGPS, of whom 2468 developed dementia over 15 years of follow-up, age- and sex-standardized percentile of eGFR below the median versus above was associated with 9% increase in risk score= -3.6 mL [95% CI, -7.0 to -0.3]) and higher WMH volume (exponentiated β [mean ratio] per 1% increase in risk score= 1.09 [95% CI, 1.01 – 1.18]).¹⁴⁰ The association between vascular risk

a meta-analysis of >460 000 Scandinavian adults conducted by the same authors, there was a dose-response pattern: Risk of dementia was 1.14 times as high (95% CI, 1.06–1.22) for eGFR 60 to 90 mL·min⁻¹·1.73 m⁻², 1.31 times as high (95% CI, 0.92–1.87) for eGFR 30 to 59 mL·min⁻¹·1.73 m⁻², and 1.91 times as high (95% CI, 1.21–3.01) for eGFR <30 mL·min⁻¹·1.73 m⁻² relative to eGFR >90 mL·min⁻¹·1.73 m⁻².¹⁴⁴

score and markers of brain health was strongest in early adulthood compared with midlife and late life. • In the HRS, cognitive impairment-free life expectancy at 55 years of age was estimated as 23.0 years (95% CI, 22.6–23.4) for participants with no hypertension, HD, diabetes, or stroke; 21.2 years (95% CI, 20.9–21.5) for those with any 1 of those conditions; 18.1 years (95% CI, 17.7–18.4) for those with any 2 conditions; and 14.0 years (95% CI, 13.5–14.5) for those with any 3 or all 4 conditions.¹⁴¹ The association of CVD burden with lower cognitive impairment-free life expectancy was also observed at 65, 75,

and 85 years of age with lower absolute life expectancies (Table 16-1).

- Among adults in the ARIC (n=11 460) and AGES (n=3907) cohorts over a median follow-up of 22.3 and 10.5 years respectively, participants with a high CVH score in midlife (CVH measured by smoking, BMI, PA, healthy diet, BP, FPG, and TC; high score defined as a score of 10–14 on a 14-point scale in ARIC or score of 8–12 on a 12-point scale in AGES) had a lower risk of incident dementia than participants with a low CVH score (defined as a score of 0–5 in ARIC or a score of 0–4 in AGES) in midlife (HR, 0.60 [95% CI, 0.52–0.69] in ARIC and 0.83 [95% CI, 0.66–0.99] in AGES).¹⁴²

- Among 6050 adults in the Whitehall II Study, of whom 306 developed dementia over a mean 10 years of follow-up, eGFR $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ at baseline was associated with 37% higher risk of dementia (95% CI, 1%–85% higher), and decline in eGFR of $\geq 4 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ over ≈ 4 years was associated with 37% higher risk of subsequent dementia (95% CI, 2%–85% higher).¹⁴⁵
- In a meta-analysis of 16 studies (some longitudinal and some cross-sectional) including $>120\,000$ participants, of whom 5488 had or developed cognitive impairment and 1266 had or developed dementia, albuminuria was associated with 1.18 times the odds of cognitive impairment (95% CI, 1.09–1.27), 1.32 times the odds of dementia (95% CI, 1.10–1.58), 1.33 times the odds of AD (95% CI, 1.06–1.67), and 2.32 times the odds of vascular dementia (95% CI, 1.59–3.38).¹⁴⁶
- Among 10 567 older adults undergoing hemodialysis with 1302 cases of incident dementia over a median follow-up of 3.8 years, patients in the highest quartile of dialysis adequacy had 31% lower hazard of dementia (HR, 0.69 [95% CI, 0.58–0.82]) and 31% lower hazard of AD (HR, 0.69 [95% CI, 0.57–0.84]) than patients in the lowest quartile of dialysis adequacy.¹⁴⁷
- The association between cardiovascular risk factors and incident dementia may depend on the cardiovascular risk factors included in the burden score. Among 12 412 adults in the NACC dataset (mean age, 71 years), over a mean 65 months of follow-up, participants with vascular-dominant cardiovascular risk factors (diagnoses of hypertension and hyperlipidemia) had higher odds of incident AD than participants without vascular risk factors (OR, 1.74 [95% CI, 1.28–2.36]).¹⁴³ Participants with vascular-metabolic cardiovascular risk factors (diagnoses of hypertension, hyperlipidemia, diabetes, and high

- In a secondary analysis of SPRINT, higher serum creatinine was associated with increased risk of incident dementia or amnestic MCI over a median of 4.13 years of follow-up (HR, 1.24 [95% CI, 1.19–1.29] per 1 SD of baseline serum creatinine).¹⁴⁸• Among 1354 participants in MAP (mean age, 79 years; 75% female), lower eGFR was associated with higher risk of incident AD (HR, 1.27 [95% CI, 1.09–1.48] for every 1-SD decrease in eGFR).¹⁴⁹ Participants with an eGFR <60 mL·min⁻¹·1.73 m⁻² were diagnosed with AD a median of 1.57

(95% CI, 0.25–2.89) years with normal kidney function.

SDB/Sleep Apnea (See also Chapter 13 [Sleep].)

- In a meta-analysis of 18 (N=246 786 participants), reported or objective snoring, was associated with all-cause mortality (RR, 1.20 [95% CI, 1.03–1.41]), (pooled RR, 1.23 [95% CI, 1.03–1.41]).¹⁵⁰
- In another meta-analysis of 6 (follow-up between 3 and 15 years) as AHI ≥ 15 or based on ICD-9 codes associated with increased risk of dementia (RR, 1.26 [95% CI, 1.03–1.54], study also reported cross-studies) between SDB and executive function.¹⁵¹
- Pooling data from 5 prospective studies up to 5 years of follow-up (mean age, 62.1 years; 58–89 years; 31.5% female; Osteoporotic Fractures in Women Study, the Osteoporotic Fractures in Women Study Consortium found that adults with OSA (AHI ≥ 5) had worse cognitive function ($\beta = -0.06$ [95% CI, -0.11 to -0.01] compared with the reference).
- Greater OSA severity, based on AHI, was associated with β -amyloid 42 over 2 years in a sample of adults with normal cognition (62% females).¹⁵³ There was no significant association between OSA and Pittsburgh compound B-radioligand uptake.
- Sleep apnea, assessed by AHI

Education index, was cross-sectionally associated with greater predicted brain age, a calculated score based on patterns of 169 regions of brain volume, in SHIP (N=690; mean age, 53 years; 49% females)¹⁵⁴ and with brain WMH, most notably periventricular frontal and dorsal WMH volumes (N=529 participants; mean age, 52 years; 53% females).¹⁵⁵

- In a retrospective study of Medicare beneficiaries with OSA (ICD-9 codes; N=53 321 adults ≥ 65 years of age; 41% females), the odds of incident AD and dementia not otherwise specified

Social Determinants of

Race and Ethnicity

(See Prevalence, Incidence, Cumulative Incidence, and Secular

Sexual Orientation and Gender

- Among 108 152 NHIS respondents aged 18–74, 2421 individuals (2.2%) identified as bisexual, or something else, other than straight.¹⁵⁸ Difficulty concentrating (subjective) was reported by 24.5% (95% CI, 22.5%–26.5%), sexual minority individuals (95% CI, 18.6%–19.6%) of 1.5 [95% CI, 1.3–1.8], education, race and ethnicity, Frequency, severity, and cognitive impairment were all higher by sexual minority individuals. “Confusion” because of difficulty of confusion was reported by 8.7% (95% CI, 7.7%–9.7%) of sexual minority 5.4% (95% CI, 5.2–5.6) of 1.7 [95% CI, 1.4–2.1].¹⁵⁹ from the Canadian (N=36 849; mean age, 62.1 years) association between sexual function and better among lesbian/gay adults (0.35) and bisexual adults (0.50) compared with (0.07).
- Among 452 transgender adults identified in the OneFlorida Consortium, 3.5% had been compared with 2.2% of age-matched cisgender adults (OR, 1.6 [95% CI, 0.56–0.76]).
- In a meta-analysis of 9 RCTs (N=1901), CPAP treatment was not associated with benefits for cognition; however, study designs were heterogeneous, and all of the interventions were ≤ 1 year.¹⁵⁷

over 3 years were lower among older adults prescribed treatment for positive airway pressure therapy (OR, 0.65 [95% CI, 0.56–0.76] and 0.69 [95% CI, 0.5–0.85]).¹⁵⁶

- In a meta-analysis of 31 studies conducted in Latin America, prevalence of dementia among participants without a formal education was 21.4%, whereas prevalence of dementia among participants with at least 1 year of formal education was 9.9%.¹⁶²
- In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest education level (ie, quintile) was associated with 22% higher risk for cognitive impairment and dementia (95% CI, 10%–25% higher) relative to highest education level; lowest education versus highest education was also associated with higher risk for all-cause dementia (RR, 1.66 [95% CI, 1.20–2.32]).¹⁶³
- In a harmonized cross-national dataset of the HRS family of studies including the HRS, ELSA, MHAS, CHARLS, and LASI (N=14 980; age, ≥65 years), the association between higher educational attainment and better cognition in late-life was consistently

observed in both high- and middle-income countries. Compared with the reference group of those with lower secondary education, adults with post-secondary education scored better on global cognition overall: males in the United States, $\beta=0.80$ (95% CI, 0.62–0.99); England, $\beta=0.55$ (95% CI, 0.39–0.71); Mexico, $\beta=0.29$ (95% CI, –0.03 to 0.61); China, $\beta=0.29$ (95% CI, 0.10–0.48); and India, $\beta=0.54$ (95% CI, 0.35–0.72); and females in the United States, $\beta=1.00$ (95% CI, 0.84–1.15); England, $\beta=0.63$ (95% CI, 0.44–0.83); Mexico, $\beta=0.86$ (95% CI, 0.56–1.15); China, $\beta=0.77$ (95% CI, 0.58–0.97); and with a proxy measure, the number of teachers with graduate degrees) was associated with worse phonemic fluency, animal fluency, and immediate recall after 58 years of follow-up (β comparing schools with 0–5 teachers with graduate training versus schools with ≥ 24 teachers with graduate training ($\beta=-0.24$ [95% CI, –0.37 to –0.11]; $\beta=-0.22$ [95% CI, –0.35 to –0.09]; $\beta=-0.20$ [95% CI, –0.32 to –0.08], respectively) in the Project Talent Aging Study (N=2289; mean age, 74.8 years).¹⁶⁵

- PARs for established potentially modifiable risk factors for dementia among different groups were calculated with data from the SADHS 2016 study. The risk factor contributing the greatest PAR was low education (weighted

risk for cognitive impairment and dementia (RR, 1.06 [95% CI, 0.83–1.36]) relative to highest occupation level or with risk for all-cause dementia (RR, 1.03 [95% CI, 0.77–1.36]).¹⁶³

- In the KHANDLE cohort (N=1536; mean age, 76 years; 29% White participants; mean follow-up, 2.4 years), there were cross-sectional associations between occupational complexity using data and executive function (β highest tertile compared with lowest=0.11 [95% CI, 0.00–0.22]) and semantic memory ($\beta=0.14$ [95% CI, PAR, 12% [95% CI, 7%–18%]). The PAR for low education differed by wealth strata but not sex ($P_{\text{interaction with sex}}=0.1880$, $P_{\text{interaction with wealth}}<0.0000$).¹⁶⁶

Occupation

- Among 10 195 adults in studies included in the COSMIC collaboration, high occupational complexity (eg, managers and professionals) versus low (eg, individuals performing simple and routine manual tasks) was associated with 19% longer dementia-free survival time (95% CI, 5%–33% longer).¹⁶⁷ Intermediate occupational complexity (eg, clerical and craft jobs) versus low was associated with 7% longer dementia-free survival time (95% CI, 1% lower–16% higher).
- Among 8941 ELSA participants, low occupational attainment (routine/manual) was associated with

CI, 0.12–0.34], respectively).¹⁶⁹

Income/Wealth

- In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest income level (ie, quintile) was associated with 21% higher risk for cognitive impairment and dementia (95% CI, 4%–41% higher) relative to highest income level; lowest income versus highest was not significantly associated with risk for all-cause dementia (RR, 1.19 [95% CI, 0.78–1.82]).¹⁶³

- Among 8941 ELSA participants, self-reported household wealth was measured as the total value of home (minus outstanding mortgage), physical items such as jewelry, business assets such as investments, and financial assets, including cash and savings (minus debts and loans).¹⁶⁸ The lowest tertile of wealth was associated with 1.63 times the risk of dementia (95% CI, 1.26–2.12) and middle tertile of wealth with 1.22 times the risk of dementia (95% CI, 0.93–1.60) compared with the highest wealth tertile.

- Cross-national comparisons (N=9465; age, ≥65 years) of negative wealth shock in late life defined as a loss of wealth ≥75% differed by country. In the United States and China, negative wealth shock was associated with worse cognition (β =−0.16 SD units [95% CI, −0.29 to −0.040] and β =−0.14 [95% CI, −0.21 to −0.07]), but this association was not significant in England or in Mexico (β =−0.01 [95% CI, −0.24 to 0.22] or β =−0.11 [95% CI, −0.24 to 0.03]).¹⁷⁰

1.60 times the risk of dementia (95% CI, 1.23–

2.09) and intermediate occupational attainment with 1.53 times the risk of dementia (95% CI, 1.15–2.06)

Composite SES

compared with high occupational attainment (managerial or professional) after adjustment for

- Composite SES is a measure that incorporates education, occupation, and income levels into an index, with higher values indicating higher SES. In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest composite SES level (ie, age and sex).¹⁶⁸
- In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest occupation level (ie, quintile) was not significantly associated with

quintile) was associated with 1.75 times the risk for cognitive impairment and dementia (95% CI, 1.37–2.23) relative to highest composite SES level

and with 2.00 times the risk (95% CI, 1.27–3.15).¹⁶³

- Adults living in neighborhoods with advantage, assessed by the composite area-based disadvantage, were more likely (reference, lowest quintile Index; second quintile aHR, 1.10; third quintile aHR, 1.14; fourth quintile aHR, 1.16 [95% CI, 1.01–1.33]; highest quintile aHR, 1.22 [95% CI, 1.01–1.47]) with adjustment for age, sex, education, and medical comorbidities in a prospective study of Veterans patients (N=1 637 484; mean age, 65.0 years; mean follow-up, 11.0 years). In the Mayo Clinic Study of Aging (mean age, 72.9 years), residence in a high-deprivation Area Deprivation Index was associated with risk of dementia (HR for each Area Deprivation Index state 1.01–1.11) and slightly higher annualized rate of decline (annualized rate of decline per decile increase in score β = -0.035 [95% CI, -0.045 to -0.024]).¹⁶⁴

Geography/Dementia Belt/Rural-Urban

- Among 152 444 HRS participants ≥ 50 years of age, those living in a rural county that had decreased or increased population size over the previous 20 years, living in a rural county that had decreased or increased population size was associated with 0.22-point lower TICS score ($P < 0.01$), and living in a rural county that had decreased or increased population size was associated with 0.36-point lower TICS score ($P < 0.01$).¹⁷³
- In a US nationwide ecological study of Medicare beneficiaries from 2008 to 2015, county-level annual prevalence of AD/ADRD was ≈ 0.5 to 1.0 case per 100 population lower in rural counties than in urban counties, whereas county-level annual incidence of AD/ADRD was ≈ 0.4 new case per 100 population higher in rural counties than in urban counties, adjusted for county-level demographic

- Among 20 878 participants in the Health and Retirement Study (≥ 45 years; 57% female), 79% lived in rural areas.¹⁷⁶ Small rural versus large rural areas were associated with 24% higher odds of incident dementia (95% CI, 2%–53% higher) after adjustment for demographics, health behaviors, and socioeconomic characteristics. Large rural versus small rural areas were associated with incident

Risk Prediction

- The LIBRA index for predicting incident dementia, depression, diabetes, PA, smoking, and moderate alcohol use. Among the Finnish CAIDE study, higher LIBRA score was associated with a 27% higher risk of dementia (95% CI, 13%–41%) and a 13% higher risk of depression (95% CI, 0.84–1.02).¹⁷⁴
- Among 4392 adults in MESA, at baseline—CAIDE score, Profile score, and ASCVD score—were associated with lower mean time to incident dementia (10 years) and health care factors.¹⁷⁴
- Geospatial analysis of HRS data (N=96 848; mean age, 75.0 years) indicates that dementia prevalence was highest in the South (10.7%–13.6%) and lowest in the Northeast (7.8%–9.3%), with similar patterns for incidence based on region of birth (13.5%–14.7% and 6.6%–7.0%, respectively). In models adjusted for age, sex, survey year, demographics, education, and region of residence, birth in the Northeast United States was significantly associated with lower dementia compared with birth in the South (OR, 0.57 [95% CI, 0.49–0.65]).¹⁷⁵

Symbol Coding, and Digit Span.¹⁷⁸ For example, mean CASI score was 2.41 points lower (95% CI, 2.19–2.64), mean Digit Symbol Coding score was 7.46 points lower (95% CI, 6.97–7.95), and mean Digit Span score was 0.95 points lower (95% CI, 0.83–1.07) per 1-SD increment in CAIDE score.

These associations varied by race and ethnicity. For example, the association of SD increment in base-line CAIDE score with mean CASI score 10 years later was 1.61 points lower in White individuals (95% CI, 1.28–1.95), 2.52 points lower in Chinese American individuals (95% CI, 1.81–3.24), 2.30 points lower in Black individuals (95% CI, 1.84–2.77), and 3.28 points lower in Hispanic individuals (95% CI, 2.82–3.74).

- Among 34 083 female and 39 998 male patients with AF with no history of dementia, CHA₂DS₂-VASc scores ≥ 3 (versus ≤ 1) were associated with 7.8 times the risk of dementia in females (95% CI, 5.9–10.2) and 4.8 times the risk of dementia in males (95% CI, 4.2–5.4). Similarly, the blood bio-marker-based Intermountain Mortality Risk Score (high versus low) was associated with 3.1 times the risk of dementia in females (95% CI, 2.7–3.5) and 2.7 times the risk of dementia in males (95% CI, 2.4–3.1).¹⁷⁹
- The FDRS includes age, marital status, BMI, stroke/ TIA, diabetes, and cancer. The FDRS, which had previously been shown to predict dementia with a C statistic of 0.72 in a general population sample of 2383 adults ≥ 60 years of age in the FHS,¹⁸⁰

was shown to have dementia risk in newly diagnosed HF and in adults ≥ 50 years of age in a population-based study in

Subclinical/ Unrecognized Disease

MRI Abnormalities/Covert Vascular Brain Injury

• MRI measures of brain age were assessed in 2 community-based cohorts of middle-aged and older

adults (WHICAP: mean age, 75 years; and Offspring:

mean age, 55 years; combined $N=1467$).¹⁸¹

Cortical

thickness in AD-related regions and WMH volume differed significantly

by race and ethnicity and $P=0.03$) and White $\beta=0.005$ [95% CI, volume: $\beta=-0.021$ $P=0.07$].

- In a meta-analysis of participants with AD, brain microbleeds with Studies conducted prevalence of 33%–45%]) than MRI (26% [95% CI, ducted with a greater prevalence [95% CI, 38%–52%]) non-susceptibility-23%–29%]).

• Among 1881 dent dementia, in the risk of dementia over 2-fold higher among bination of larger (3–infarcts compared observed on MRI

- In a meta-analysis of was associated with tion on the MMSE to -0.22).¹⁸⁴ In the 4 studies, covert cognitive dysfunction -3.36 [95% CI, -5.90 to -0.82]

- Among 630 participants without dementia in the Alzheimer's Disease Neuroimaging Initiative who underwent an assessment for neuropsychiatric symptoms with the Neuropsychiatric Inventory and 3-T MRI at baseline ($n=631$) and follow-up ($n=616$), a higher burden of cerebral small-vessel disease was associated with neuropsychiatric symptoms in follow-up.¹⁸⁵ Lacunar infarcts predicted hyperactivity ($P=0.0092$), psychosis ($P=0.0402$), affective symptoms ($P=0.0156$), and apathy ($P\leq 0.0001$). WMHs were associated with hyperactivity ($P=0.0377$) and apathy ($P=0.0343$), whereas cerebral microbleeds correlated with apathy ($P=0.0141$).
- Among 552 dementia- and stroke-free participants from the FHS, lighter sleep, as characterized by longer N1 sleep duration and shorter slow-wave sleep on polysomnography, was associated with higher enlarged perivascular spaces burden in the centrum semiovale on brain MRI (OR of higher burden per minute of N1 sleep, 1.03 [95% CI, 1.10–1.05]), and longer N3 sleep duration was associated with lower enlarged perivascular spaces burden in the centrum semiovale (OR, 0.99 [95% CI, 0.98–1.00]).¹⁸⁶ These findings suggest that sleep architecture may be involved in glymphatic clearance and cerebral small-vessel disease.

Subclinical Cortical Abnormalities (Not MRI)

- Among 4399 cognitively unimpaired adults 65 to 85 years of age enrolled in the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease Study, the β -amyloid standard uptake value ratio on positron emission tomography imaging was associated with anxiety scores on the State Trait Anxiety Inventory (range, 6–24) but not depression scores on the Geriatric Depression Scale.¹⁸⁷ For each 0.5-point increase in cortical β -amyloid standard uptake value ratio, the mean anxiety score increased by 0.25 points (95% CI, 0.04–0.53).
- Transcranial magnetic stimulation applied to the primary motor cortex and coupled with electromyography provides a subclinical measure of cortical excitability and plasticity. In a meta-analysis of the value of transcranial magnetic stimulation–derived excitability and plasticity measures to distinguish AD, MCI, and normal cognition, 61 studies ($n=2728$ participants) included 1454 patients with AD, 163 patients with MCI, and 1111 cognitively normal individuals.¹⁸⁸ Patients with AD had significantly lower resting motor threshold (Cohen $d=1.05$ [$P<0.0001$]), lower active motor threshold (Cohen $d=0.77$ [$P<0.0001$]), lower short latency afferent inhibition (Cohen $d=1.89$ [$P<0.0001$]), lower short-latency intracortical inhibition (Cohen $d=0.68$ [$P<0.01$]), and lower long-term potentiation-like plasticity (Cohen $d=1.20$ [$P<0.0001$]) compared with cognitively normal individuals. Patients with MCI

had lower resting motor threshold (Cohen $d=0.39$ [$P<0.005$]) and lower long-term potentiation-like plasticity (Cohen $d=0.86$ [$P<0.05$]) compared with cognitively normal individuals.

- In a single-center study, among 288 Chinese patients (mean age, 80.5 years; 60.4% females) with AD, subclinical epileptiform discharge on scalp electroencephalography was present in 57 patients (19.8%).¹⁸⁹ Subclinical epileptiform discharge was associated with greater decline in CASI (−9.32 versus −3.52 points; $P=0.0001$) and MMSE (−2.52 versus −1.12 points; $P=0.0042$) scores at 1 year.

Subclinical Cardiac and Arterial Disease

- Abnormal P-wave parameters on ECG are associated with brain MRI findings. Among 1715 participants in the ARIC Neurocognitive Study (mean age, 76.1 years; 61% female), including 797 (46%) who had at least 1 abnormal P-wave parameter, abnormal P-wave terminal force in lead I was associated with higher odds of cortical infarcts (OR, 1.41 [95% CI, 1.14–1.37]) and lacunar infarcts (OR, 1.36 [95% CI, 1.15–1.63]); prolonged P-wave duration was associated with higher odds of cortical infarcts (OR, 1.30 [95% CI, 1.04–1.63]) and lacunar infarcts (OR, 1.37 [95% CI, 1.15–1.65]).¹⁹⁰
- Greater arterial stiffness, measured by PWV, is another vascular risk factor consistently associated with worse measures of brain health. In a meta-analysis of 9 longitudinal studies, greater arterial stiffness was associated with worse global cognition (effect size, −0.21 [95% CI, −0.36 to −0.06]), executive function (effect size, −0.12 [95% CI, −0.22 to −0.02]), and memory (effect size, −0.05 [95% CI, −0.12 to 0.03]).¹⁹¹
- Among 623 community-dwelling adults from the Whitehall II Imaging Substudy who underwent multimodal MRI, higher mean arterial pressure throughout midlife ($\beta=3.36$ [95% CI, 0.42–6.30]) and faster cognitive decline in letter fluency ($\beta=-0.07$ [95% CI, −0.13 to −0.01]) and verbal reasoning ($\beta=-0.05$ [95% CI, −0.11 to −0.001]) were associated with severe small-vessel disease burden in older age.¹⁹²
- In a study that combined longitudinal data from 3 clinical trials (B-Vitamin Atherosclerosis Intervention Trial, Women's Isoflavone Soy Health Trial, and Early Versus Late Intervention Trial With Estradiol), among participants (308 males and 1187 females; mean age, 61 years) free of CVD and diabetes, participants underwent the same standardized protocol for ultrasound measurement of carotid IMT, as well as cognitive assessment, at baseline and 2.5 years. Although no associations were found between carotid IMT and cognitive function at baseline or at 2.5 years, there was a weak inverse association

between
global
[SE, 0.028]
−0.110 to
sis was
inverse
for

Genetics and

- AD is highly heritable. With >65 years of age from the Swedish Twin Registry, AD heritability was estimated to range from 58% to 79%.¹⁹⁴
- Rare forms of early-onset autosomal dominant AD may reflect highly penetrant variations in *APP*, *PSEN1*, or *PSEN2*.¹⁹⁵

APOE

- The *APOE*ε4 risk factor, lifetime risk in
- The *APOE*ε4 dementia and 552 controls associated with 1.85 times the alleles was vascular
- The frequency variation populations.²⁰¹
- Among 8263 Latino people higher risk for cognitively (9.6%–12.5%) 12.6% (95% CI, 17.5% individuals, Mexican 14.6%) in Puerto Rican

(95% CI, 9.4%–13.0%) in South American individuals.²⁰² Prevalence of ≥ 1 *APOE* ϵ 2 alleles (associated with lower risk for late-onset AD) was highest in Dominican individuals (8.6% [95% CI, 7.2%–10.1%]) and lowest in Mexican individuals (2.9% [95% CI, 2.4%–3.3%]).

Other Dementia Loci

- The largest GWAS of clinically diagnosed AD was performed by the International Genomics of Alzheimer's Project Consortium.²⁰³ With a final $n=35\,274$ cases and $n=59\,163$ controls, this study identified 25 AD loci, 5 of which were novel. Pathway analyses implicated tau binding proteins and amyloid precursor protein metabolism in late-onset AD, suggesting a shared genetic architecture with early-onset autosomal dominant AD.
- Although not examining clinically diagnosed AD, other GWASs have examined AD proxy traits. As an example, a GWAS of 116 196 UK Biobank participants compared participants who reported having a parent with AD (proxy cases) with control subjects. This study identified 4 novel loci ($P<5\times 10^{-8}$) on chromosomes 5 (near *HBEFGF*), 10 (near *ECHDC3*), 15 (near *SPPL2A*), and 17 (near *SCIMP*).
- GWASs also have combined clinically diagnosed with proxy AD cases. For example, a study of $n=111\,326$ clinical diagnosed or proxy AD cases and $n=677\,663$ controls identified 75 loci, including 42 new loci.²⁰⁵ In addition to confirming involvement of amyloid/tau pathways, this study suggested new mechanisms, including the tumor necrosis factor- α pathway. These results also were used to develop new GRSs to predict AD/dementia incidence or progression from MCI to AD/dementia.
- To increase ancestral diversity, a GWAS of AD and ADRD was performed in the Million Veteran

Program although a healthy lifestyle was associated with lower risk of incident dementia among participants with low or high genetic risk, no significant interaction between dementia genetic risk and lifestyle factors on incident dementia was detected ($P=0.99$).

- A PRS for AD developed from GWASs in a European population was associated with risk of AD in a sample of 1634 Korean participants, of whom 716 had AD (OR of AD per increment in PRS, 1.95 [95% CI, 1.40–2.72]), suggesting that GRSs for AD may be transferable across different ethnic populations.²⁰⁸ In the UK Biobank with 206 646 participants 37 to 73 years of age at baseline and 5750 incident dementia cases over a median of 12.5 years of follow-up, a PRS for dementia based on European ancestry GWAS was categorized into high, medium, and low risk.²⁰⁹

Program biobank, restricted to participants of African ancestry ($n=4012$ cases).²⁰⁶ To increase statistical power, the authors combined their AD and ADRD GWAS with a proxy dementia GWAS that used survey-reported paternal AD or dementia ($n=4385$ maternal cases, $n=2256$ paternal cases). Three loci in *APOE*, *ROBO1*, and *RP11-340A13.2* were identified. *ROBO1* participates in the regulation of axon guidance. Lack of association between *ROBO1* when a strict AD phenotype was examined suggests that this locus may be relevant for dementia more broadly.

Polygenic Risk Scores

- All-cause dementia GRSs have been used to examine whether lifestyle factors can offset high dementia genetic risk.²⁰⁷ In a study of $N=196\,383$ participants,

Exercise

- A 2019 randomized, parallel-group, community-based clinical trial of 132 multiracial, multiethnic, cognitively normal individuals (mean age, 40 years) with below-median aerobic capacity in New York found that aerobic exercise, compared with stretching and toning, for 6 months improved executive function with greater improvement as age increased (increase at 40 years of age, 0.228 SD [95% CI, 0.007–0.448]; increase at 60 years of age, 0.596 SD [95% CI, 0.219–0.973]) and less improvement among those with ≥ 1 APOE ϵ 4 alleles.²¹⁰
- In a trial of adults ≥ 65 years of age with subjective cognitive concerns (N=585), participants were randomized to exercise training, mindfulness-based stress reduction, both exercise training and mindfulness-based stress reduction, or health education. At 6 and 18 months, there was no difference in executive function or episodic memory among the intervention groups.²¹¹
- Meta-analyses examining RCTs indicate that PA interventions benefit cognition in both AD (7 RCTs; N=501; with improvement on the MMSE, 0.458 [95% CI, 0.097–0.819]) and MCI (15 RCTs; N=1156; improvement on the MMSE, 0.631 [95% CI, 0.244–1.018]).²¹²

BP Control

- Among 9361 participants (SPRINT) with hypertension and high cardiovascular risk in the United States and Puerto Rico (mean age, 67.9 years; 35%

females; 58% White
uals, 10% Hispanic
<120 mm Hg compared with
<140 mm Hg for a median of
the risk of MCI (14.6 cases
1000 PY; HR, 0.81 [95% CI,
combined rate of MCI or
cases versus 24.1 cases per
[95% CI, 0.74–0.97]) but not
probable dementia (7.2 cases
1000 PY; HR, 0.83 [95% CI,

total median follow-up of 5.11 years.²¹³ A
secondary analysis from SPRINT suggests
that antihypertensive treatment regimens that
stimulate angiotensin II receptors were
associated with reduced risk of cognitive
impairment compared with angiotensin
inhibitor-only regimens (HR for amnesic MCI,
0.74 [95% CI, 0.64–0.87]; HR for probable
dementia, 0.80 [95% CI, 0.57–1.14]).²¹⁴

- A post hoc analysis from the PreDIVA trial (54%

control was associated with a
dementia or cognitive
of patients over a mean trial
OR, 0.93 [95% CI, 0.88–0.98];
tion, 0.39% [95% CI, 0.09%–

- In a meta-analysis of 5 RCTs
69.1 years; median follow-up,
SYST-EUR, PROGRESS,
antihypertensive treatment
reduced risk of incident
CI, 0.75–0.99]).²²⁰

females; mean age, 74.5 years) also
found that angiotensin II–stimulating
antihypertensive medica- tions were
significantly associated with reduced
risk of dementia (HR, 0.86 [95%
CI, 0.64–1.16]) com- pared with
angiotensin II–inhibiting medications.²¹⁵•
In a systematic review of 15 prospective
cohort studies and 7 RCTs (N=649
790), treatment with

- A 2021 Cochrane review of hypertension treatment in adults without prior cerebrovascular disease reported low-certainty evidence for a small benefit in cognition (4 placebo-controlled trials; mean difference on MMSE score, 0.20 [95% CI, 0.10–0.29]) but no significant benefit for dementia (5 placebo-controlled trials).²²¹

Blood Lipid Control/Statin Therapy

- A secondary analysis of the HPS suggests that disease or diabetes (mean age, 63 years; 25% ing a nonfatal stroke or TIA and 2.4% avoiding a reduction in cognitive aging of 0.15 year (95% CI, calcium channel blockers and angiotensin II receptor blockers was associated with a reduced risk of incident dementia compared with other antihypertensive classes.²¹⁶ For calcium channel blockers, the HR versus ACE inhibitors was 0.84 (95% CI, 0.74–0.95), the HR versus β -blockers was 0.83 (95% CI, 0.81–0.97), and the HR versus diuretics was 0.89 (95% CI, 0.78–1.01). For angiotensin II receptor blockers, the HR versus ACE inhibitors was 0.88 (95% CI, 0.81–0.97), the HR versus β -blockers was 0.87 (95% CI, 0.77–0.99), and the statin therapy for 5 years in adults with vascular females) resulted in 2.0% of participants avoiding a nonfatal cardiac event, which yielded an expected 0.11–0.19).²²²
 - HR versus diuretics was 0.93 (95% CI, 0.83–1.05).
- In a randomized clinical trial of older adults with MCI and hypertension (N=176; mean age, 66 years; 57% females; 64% Black individuals), participants treated with candesartan over 1 year had better outcomes on executive function (–0.03 [95% CI, –0.08 to 0.03]) compared with those treated with

- In an observational study of 18 846 older adults (median age, 74 years; 56% females) with no history of cardiovascular events, statin therapy was not associated with risk of dementia, MCI, or cognitive decline.²²³
- A meta-analysis of 14 double-blind trials (4 phase 2 and 10 phase 3) for the PCSK9 inhibitor alirocumab found a low incidence of neurocognitive adverse events, with no significant differences between the alirocumab and control groups and no association between neurocognitive adverse events and LDL-C <25 mg/dL.²²⁴ Another meta-analysis of 35 RCTs for alirocumab and evolocumab similarly found no significant associations between PCSK9 inhibitor use and neurocognitive adverse events (OR, 1.12 [95% CI, 0.88–1.42]).²²⁵
- A randomized placebo-controlled trial of evolocumab in addition to statin therapy (N=1204; age, 69 years; 42% females), BP lowering with antihypertensive agents compared with treatment with placebo.²¹⁸
- In a subset of participants in the International Polycap Study 3 who underwent cognitive assessment (N=2098; mean±SD age, 70.1±4.5 years), treatment with a polypill (antihypertensives and a statin), aspirin alone, or polypill plus aspirin over 5 years did not reduce the risk of cognitive decline or dementia compared with

40–85 years) found no significant differences in cognitive function between the evolocumab group and the placebo group.²²⁶ Another RCT (N=22 655) involving evolocumab added to statin therapy found no significant effect on self-reported cognition, even among patients who had LDL-C <20 mg/dL.²²⁷• A meta-analysis of 33 RCTs found no association between lipid-lowering treatments (PCSK9 inhibitors, statins, and ezetimibe) and cognitive impairment and no significant effects of low LDL-C levels

on cognitive disorder likelihood or global cognitive performance.²²⁸

Aspirin and Antiplatelet Therapy

- In a randomized placebo-controlled trial, the ASPREE study, rates of incident dementia, probable AD, and MCI did not differ between the low-dose daily aspirin treatment group and the placebo group after almost 5 years of follow-up (N=19 114; age, 65–98 years; 44% male).²²⁹
- In a meta-analysis of 11 randomized trials of anti-platelet therapy (N=109 860; mean age, 66.2 years; mean follow-up, 5.8 years), there was no protective benefit for risk of cognitive impairment or dementia (OR, 0.94 [95% CI, 0.88–1.00]; absolute risk reduction, 0.2% [95% CI, –0.4% to

Glycemic Control

- In adults ≥60 years of age with type 1 diabetes, continuous glucose monitoring compared with standard blood glucose monitoring resulted in a small but statistically significant reduction in hypoglycemia but no differences in cognitive outcomes over 6 months.²³¹
- A meta-analysis of RCTs found that intensive glucose control compared with conventional glucose control may delay cognitive decline slightly

n=4617; mean difference on composite cognitive Z score based on neuropsychological test battery, 0.03 [95% CI, 0.01–0.06]).²³⁵

- A meta-analysis of RCTs for older adults with MCI (28 RCTs; N=2711; mean±SD age, 71.6±3.4 years; mean±SD duration of intervention, 19.8±14.6 weeks) suggests that compared with single-domain interventions, multidomain interventions, targeting at least 2 nonpharmacological strategies, benefit cognition, including global cognition (20 RCTs; SMD, 0.41 [95% CI, 0.23–0.59]), executive function (17 RCTs; SMD, 0.20 [95% CI, 0.04–0.36]), memory (15 RCTs; SMD,

in patients with type 2 diabetes (4 cohorts with N=5444; β =–0.03 [95% CI, –0.05 to –0.02]).²³²

Multidomain Prevention Strategies

- In the 4-year DR's EXTRA trial (N=1401; mean age, 66.5 years), there was a trend toward better cognition in older adults randomized to a combined aerobic exercise and healthy diet intervention compared with the control group (global cognition [CERAD-TS] increase, 1.4 points [95% CI, 0.1–2.7]; $P=0.06$).²³³ Effects were not significant for the resistance exercise alone, aerobic exercise alone, diet alone, or combined resistance exercise and diet

75.8 years; 79% females), behavioral activation, which aimed to increase cognitive, physical, and social activity, compared with supportive therapy, an attention control treatment, reduced the 2-year incidence of memory decline (absolute difference, 7.1%; RR, 0.12 [95% CI, 0.02–0.74]; $P=0.02$).²³⁷ Compared with supportive therapy, behavioral activation also was associated with improvement in executive function and preservation of everyday function.

- SMARRT (N=172; age, 70–89 years; with ≥ 2 of 8 targeted risk factors) compared personalized risk reduction, targeting physical inactivity, poorly controlled hypertension, poor sleep, adverse prescription medication use, high depressive symptoms, poorly controlled diabetes, social isolation, and smoking, with a health education control.²³⁸ In this 2-year RCT, participants in the intervention group demonstrated a 74% greater improvement on the composite cognitive score compared with the control group (average treatment effect of SD, 0.14 [95% CI, 0.03–0.25]; $P=0.02$).
- A Basque multidomain RCT, GOIZ ZAINDU (“coming early” in Basque), modeled after FINGER, targeting early cognitive decline (MMSE score <26 ; $n=250$; mean difference in change, 0.84 [95% CI, 0.15–1.54]; $P<0.001$).
- A 2021 Cochrane review of RCTs found no conclusive evidence that multidomain interventions reduce the incidence of dementia in older adults (2 RCTs; $n=7256$); however, there was high-certainty evidence for a small effect on cognition (3 RCTs; $n=1,111$).
- A pooled analysis of 2 multidomain intervention trials focused on cardiovascular and lifestyle strategies (MAPT and PreDIVA; N=4162 participants; median age, 74 years) found no significant overall association between multidomain prevention and cognitive decline.²³⁴ Cognitive benefits were observed among participants with lower baseline cognitive function.

geted cardiovascular risk factors, nutrition, PA, ≥60 years; CAIDE risk score ≥6 and poor cognitive performance). In the intervention group, fewer participants experienced decline in executive function Z score after 1 year (40%) compared with the health advice control group (64%; OR, 2.58 [95% CI, 1.17–5.71]; $P=0.019$), and fewer intervention participants declined in processing speed Z score (39%) compared with control participants (61%; OR, 2.44 [95% CI, 1.11–5.36]; $P=0.026$).²³⁹

•In the AgeWell.de cluster randomized trial, the multifactor management, nutrition, PA, social activity,

and cognitive training in older adults (N=125; age, ≥60 years; CAIDE risk score ≥6 and poor cognitive performance). In the intervention group, fewer participants experienced decline in executive function Z score after 1 year (40%) compared with the health advice control group (64%; OR, 2.58 [95% CI, 1.17–5.71]; $P=0.019$), and fewer intervention participants declined in processing speed Z score (39%) compared with control participants (61%; OR,

2.44 [95% CI, 1.11–5.36]; $P=0.026$).²³⁹

•In the AgeWell.de cluster randomized trial, the multidomain intervention focused on cardiovascular risk

and cognitive training and the German primary care participants (N=819: age. 60–77 score ≥ 9), changes in not differ between the control group receiving health (average marginal effect. 0.133)].²⁴⁰

- Among 5989 NHANES 1999 to 2014 with mortality lower cognitive test scores higher all-cause mortality 1-SD decrement on the Digit Test was associated with 36% 25%–48% higher) mortality differences by education level.

less than high school education, mortality rates were

46% higher (95% CI, 9%–97% higher) per 1-SD decrement in animal fluency, 34% higher (95% CI, 7%–67% higher) per 1-SD decrement in word list learning, and 38% higher (95% CI, 5%–82% higher) per 1-SD decrement in word list delayed recall; those associations were not observed for individuals with high school diploma or higher education. Similarly, SD decrements in animal fluency, word list learning, and word list delayed recall were associated with higher mortality among low-income individuals but not high-income individuals.

participants who had probable dementia with a mean 82 years of age and median follow-up of 3.9 years; it was then externally validated in NHATS participants.²⁴³ In the external validation, the risk score had an AUC of 73% (95% CI, 70%–76%) for predicting death within 1 year and an AUC of 74% (95% CI, 71%–76%) for predicting death within 5 years. Factors included in this mortality risk score model were age, sex, BMI, smoking status, activities of daily living dependency count, instrumental activity of daily living difficulty count, difficulty walking several blocks, participation in vigorous PA, and chronic conditions (cancer, HD, diabetes, lung disease).

Mortality

(See Table 16-2)

- In 2022 (unpublished NHLBI tabulations using CDC WONDER²⁴¹ and the NVSS²⁴²):
 - On average, every 1 minute 48 seconds, someone died of dementia.
 - Dementia accounted for ≈ 1 of every 11 deaths in the United States. the age-adjusted death rate for dementia as an underlying cause of death was 70.4 per 100 000 (Table 16-2), whereas the age-adjusted rate for any mention of dementia as a cause of death was 109.1 per 100 000.
 - More females than males die of dementia each year because of the higher prevalence of elderly females compared with males. Females accounted for 66.7% of US dementia deaths in 2022.
- Conclusions about changes in dementia death rates from 2012 to 2022 are as follows²⁴¹:
 - The age-adjusted dementia death rate increased 11.2% (from 63.3 per 100 000 to 70.4 per 100 000), whereas the actual number of dementia deaths increased 31.1% (from 223 404 to 292 881 deaths).
 - Age-adjusted dementia death rates increased 9.1% for males and 12.9% for females.
- A mortality risk score for people having probable dementia was developed among 4267 HRS par-

Mortality in Hospitalized Patients

- In a 5-year retrospective review of 9519 adult diagnosis of dementia at an American College of Surgeons–verified level I trauma center,²⁴⁵ patients with dementia (n=195) were matched with dementia-free patients (n=195) and compared on mortality, ICU length of stay, and hospital length of stay. The comorbidities and complications were similar between the groups (11.8% versus 12.4%). Mortality was 5.1% in both the dementia and control groups. The study found that dementia did not increase the risk of mortality in patients with trauma.
- In a cohort of >1 million Medicare beneficiaries hospitalized in 2016, of whom 211 698 had diagnosed dementia, those with dementia were more likely to die (5.7%) than those without dementia (3.1%) within 30 days after discharge (aOR, 1.21 [95% CI, 1.17–1.24]).²⁴⁶
- In an analysis of 3.7 million hospitalizations of adults ≥65 years of age throughout Italy, of whom 278 149 were patients diagnosed with dementia, those with dementia were more likely to die while in the hospital than those without dementia (age-, sex-, and comorbidity-adjusted OR, 1.98 [95% CI, 1.95–2.00]).²⁴⁷ Among patients with dementia, the comorbidities most strongly associated with higher risk for in-hospital mortality were HF, pneumonia, and kidney disease.
- Among 7118 patients ≥65 years of age, including 3559 individuals with dementia and 3559 controls without dementia, admitted to an ED in Italy from 2014 to 2019, in-hospital mortality was more frequent among those with dementia (18.7% versus 16.0%; aHR, 1.13 [95% CI, 1.01–1.27]).²⁴⁸

Complications

Suicide

• In a national cohort of Medicare fee-for-service beneficiaries ≥ 65 years of age with newly diagnosed ADRD ($n=2\,667\,987$) linked to the National Death Index, the rate of suicide was 26.42 per 100 000

PY.²⁴⁹ The overall standardized mortality ratio for suicide was 1.53 (95% CI, 1.42–1.65). The highest risk for suicide was among those 65 to 74 years of age (SMR, 3.40 [95% CI, 2.94–3.86]) and during the first 90 days after diagnosis. Rural residence

1.85–4.97]); the combination of all 3 conditions—cognitive impairment, mobility impairment, and orthostatic hypotension—was associated with the highest odds of falls (OR, 4.33 [95% CI, 2.59–7.24]) compared with having none of the 3 conditions.²⁵³

Mobility

• In a registry-based longitudinal study in Sweden, among 23 759 patients >50 years of age with a nonpathological hip fracture previously able to walk, 25% of patients

Stroke

• In a meta-analysis of 29 studies including 61 824 individuals with AD followed up for incident stroke, incidence of total stroke (20 studies) was 15.4 per 1000 PY (95% CI, 10.6–20.3), incidence of ischemic stroke (11 studies) was 13.0 per 1000 PY (95% CI, 7.6–18.5), and incidence of ICH (16 studies) was 3.4 per 1000 PY (95% CI, 2.3–4.6).²⁵⁰ Individuals with AD compared with controls without AD (3 studies) had 1.31 times the incidence of total stroke (95% CI, 1.07–1.59), 1.22 times the incidence of ischemic stroke (95% CI, 0.95–1.57), and 1.67 times the incidence of ICH (95% CI, 1.43–1.96).

Postoperative Complications

• Among 53 studies ($N=196\,491$ patients) included

in a systematic review and meta-analysis, preoperative cognitive impairment was associated with a significant risk of delirium in patients ≥ 60 years of age after noncardiac surgery (25.1% versus 10.3%; OR, 3.84 [95% CI, 2.35–6.26]).²⁵¹ Cognitive impairment was also associated with an increased risk of discharge to assisted care (44.7% versus 38.3%; OR, 1.74 [95% CI, 1.05–2.89]) and postoperative complications (40.7% versus 18.8%; OR, 1.85 [95% CI, 1.37–2.49]).

Frailty

• In a meta-analysis of 16 studies of patients ≥ 65 years of age living with dementia in acute care, community, and residential care settings, the prevalence of frailty (variously defined) ranged from 50.8% to 91.8% in acute care settings across studies (overall 77.6% in 6 studies for which detailed data were available).²⁵²

increased risk of loss of walking ability at 4 months (OR, 1.80 [95% CI, 1.57–2.06]).

Instrumental Activities of Daily Living

• Among 3111 community-dwelling older adults in the Taiwan Longitudinal Study on Aging, prevalence of disability in instrumental activities of daily living was 71.8% among participants who had cognitive impairment without stroke, 56.8% among participants who had stroke without cognitive impairment, and 91.5% among participants who had cognitive impairment and stroke compared with 24.2% among participants who were cognitively intact with no stroke ($P<0.001$).²⁵⁵

Sleep

• In a meta-analysis of 24 studies of polysomnographic changes in patients with AD compared with healthy control subjects, patients with AD had significant reductions in total sleep time (SMD, -0.60 [95% CI, -0.86 to -0.34]), sleep efficiency (SMD, -0.96 [95% CI, -1.36 to -0.57]), and percentage of slow-wave sleep (SMD, -0.86 [95% CI, -1.14 to -0.58]) and rapid eye movement sleep (SMD, -0.77 [95% CI, -1.14 to -0.40]), as well as increases in sleep latency (SMD, 0.45 [95% CI, 0.29 – 0.61]), wake time after sleep onset (SMD, 0.74 [95% CI, 0.38 – 1.10]), number of awakenings (SMD, 0.55 [95% CI, 0.25 – 0.86]), and rapid eye movement latency (SMD, 0.35 [95% CI, 0.13 – 0.58]).²⁵⁶ Decreased slow-wave sleep and rapid eye movement sleep were significantly associated with the severity of cognitive impairment.

Falls

• Unexplained falls are those that occur not because of slips or trips, with no clear reason for the fall. Among 2108 community-dwelling adults ≥ 65 years of age, cognitive impairment was

Periodontitis

associated with higher odds of unexplained falls (OR, 1.38 [95% CI, 0.99–1.93]), especially when coupled with mobility impairment (OR, 2.92 [95% CI, 1.73–4.92]) or

- In a retrospective cohort study (n=8640 patients with dementia without prior periodontitis and 8640 propensity score-matched control individuals without dementia), 2670 patients with dementia developed periodontitis.²⁵⁷ The risk of periodontitis was significantly higher in those with dementia compared with those without dementia (aHR, 1.92 with orthostatic hypotension (OR, [95% CI, 1.77–2.08])).

Pseudobulbar Affect

- In a series of meta-analyses of the prevalence of uncontrolled episodes of crying and laughing (pseudobulbar affect) in patients with neurodegenerative disorders, the prevalence of pseudobulbar affect in AD was 16.4% (95% CI, 7%–25%).²⁵⁸

Health Care Use

Dementia Care

- A structured dementia care program was examined with regard to health care use and cost outcomes.²⁵⁹ The program included structured needs assessments of patients and caregivers, individualized care plans, coordination with primary care, referrals to community organizations for dementia-related services and support, and continuous access to clinicians for assistance and advice. Compared with community control subjects (n=2163), those in the program (n=1083) were less likely to be admitted to a long-term care facility (HR, 0.60 [95% CI, 0.59–0.61]). There were no differences between groups in terms of hospitalizations, ED visits, or 30-day readmissions.

Stroke Care

- Patients with stroke with preexisting cognitive impairment or dementia may receive different care compared with cognitively normal patients with stroke. Among 836 adults with AIS in the Brain Attack Surveillance in Corpus Christi project, having preexisting dementia compared with being cognitively normal was associated with lower odds of receiving antithrombotic therapy by day 2 (OR, 0.39 [95% CI, 0.16–0.96]) and echocardiogram (OR, 0.42 [95% CI, 0.26–0.67]).²⁶⁰ Preexisting MCI compared with normal cognition was associated with lower odds of receiving intravenous tPA (OR, 0.36 [95% CI, 0.14–0.96]), rehabilitation assessment (OR, 0.28 [95% CI, 0.10–0.79]), and echocardiogram (OR, 0.48 [95% CI, 0.32–0.73]). A composite quality measure of care received compared with care eligible to receive was not significantly associated with dementia (OR, 0.79 [95% CI, 0.55–1.12]) or with MCI (OR, 1.06 [95% CI, 0.77–1.45]).

- Among 464 710 patients with AIS in the Japanese Diagnosis Procedure Combination Database, including 57 905 who had dementia, those with dementia were less likely to receive intravenous thrombolysis (5.2% versus 6.9%; aOR, 0.79 [95% CI, 0.76–0.82]) and more likely to receive early rehabilitation as acute care (76.1% versus 73.0%; aOR, 1.06 [95% CI, 1.04–1.09]).²⁶¹

- Among 7070 patients with acute stroke in the

Hospital

- Among 490 dementia MD, area, in the falls (12.4%)
- In Japan, a general cognitive errate times (95% sion within impairment CI, 1.21–days
- Use of ED the past 6 race and with linked with ED care and 76.8% 70.7% of hospitalizations and with 67.5% tion, among individuals (57.1%); all care Black (18.4%) than

Telemedicine

- In Italy, who were neurological connected unable to nection for child or the absence

Hospice Care

- Australian Stroke Foundation national audit, those with dementia were more likely to receive no rehabilitation (OR, 1.88 [95% CI, 1.25–2.83]) and to be discharged to residential care (OR, 2.36 [95% CI,

• Use of hospice care during the past 6 months of life with dementia varies by race, sex, and level of education. Among 5058 participants in HRS with linked Medicare claims who were diagnosed with dementia and died between 2000 and 2016, NH Black individuals had 35% lower odds (95% CI, 22%–45% lower) of using hospice care than NH White individuals.²⁶⁵ Females had 19% higher odds (95% CI, 5%–35% higher) of using hospice care than males. Individuals with high school education had 17% higher odds (95% CI, 1%–36% higher) and those with more than high school education had 1.50–3.72 times higher odds (95% CI, 1.50–3.72).²⁶²

had 32% higher odds (95% CI, 13%–54% higher) of using hospice care compared with those with less than high school education.

Cost

Total Costs Including Social Care and Informal (Unpaid) Care

• Among an estimated 690 000 people with dementia in England, 565 000 received unpaid care, received community care, or lived in a care home (assisted living residence or nursing home).²⁶⁷ Total annual cost of dementia care in England was estimated to be £24.2 billion in 2015, of which 42% (£10.1 billion) was attributable to unpaid care. Social care costs (£10.2 billion) were 3 times larger than health care costs (£3.8 billion), and £6.2 billion of the total social care

costs was met by

- Estimated US health care spending on dementias more than doubled from \$38.6 (95% CI, \$34.1–\$42.8) billion in 1996 to \$79.2 (95% CI, \$67.6–\$90.8) billion in 2016. Spending on dementias was among the top 10 health care costs in the United States in 2016.²⁷⁰
- Among 2779 HRS participants with incident dementia, mean Medicare spending in the

individuals (+\$8709) versus NH White individuals (+\$8388), for college graduates (+\$7265) versus those with less than college graduation (+\$8639), and for those living in rural areas (+\$8849) versus those living in nonrural areas (+\$8666).

- Based on 3653 HRS participants with dementia linked to Medicare claims data for 1992 to 2015, compared with demographically matched HRS participants without dementia, mean Medicare cost attributable to dementia was \$15 632 (95% CI, \$12 780–\$18 588) during the first 5 years after diagnosis, with \$9288 (95% CI, \$8241–\$10 357), or 59%, occurring during the first year after diagnosis.²⁷²• Among 3619 HRS participants with incident dementia, during the first 8 years after diagnosis, mean estimated total out-of-pocket spending on medical costs was \$22 795 (95% CI, \$21 236–\$24 398), which was \$8751 more (95% CI, \$7354–\$10 217) than the expected mean 8-year total out-of-pocket spending without dementia of \$14 044 (95% CI,

\$13 544–\$14 597).²⁷³ Additional out-of-pocket spending attributed to dementia was much higher for NH White individuals (mean, \$16 766 [95% CI, \$14 305–\$19 380]) than for Black or Hispanic individuals (mean, \$853 [95% CI, –\$441 to \$2209]) and was higher for females (mean, \$13 706 [95% CI, \$11 393–\$16 322]) than for males (mean \$5744 [95% CI, \$3815–\$7801]). Additional out-of-pocket spending attributed to dementia and the race, ethnicity, and sex differences were largely the result of out-of-pocket nursing home costs.

- Inpatient hospitalization costs during the past 6 months of life with dementia vary by race and ethnicity. Among 5058 participants in HRS with linked Medicare claims who were diagnosed with dementia and died between 2000 and 2016, mean inpatient hospitalization costs were \$23 279 for Black individuals (95% CI, \$20 690–\$25 868) and \$23 471 for Hispanic individuals (95% CI, \$19 532–\$27 410) compared with \$14 609 for White individuals (95% CI, \$13 800–\$15 418).²⁶⁵

quarter during which the diagnosis occurred was \$13 794, which was \$8400 more ($P<0.001$) than mean

Medicare spending of \$5394 in the quarter before the diagnosis.²⁷¹ The additional costs in the quarter containing the diagnosis were not significantly different (all group differences $P>0.1$) for females (+\$7899) versus males (+\$9248), for NH Black

Global Burden

All prevalence and mortality estimates cited here are courtesy of the GBD Study 2021 based on 204 countries and territories and pertain to all types of dementia combined.²⁷⁴

Prevalence: GBD Study 2021

(See Table 16-3 and Chart 16-2)

- There were 56.86 (95% UI, 49.38–64.98) million prevalent cases of AD and other dementias in 2021, with 20.75 (95% UI, 17.77–23.80) million among males and 36.10 (95% UI, 31.47–41.12) million among females (Table 16-3).

- In 2021, the highest age-rates of AD and other were found for East Asia North America, North Africa tropical Latin America, and Africa (Chart 16-2).

Mortality: GBD Study 2021

(See Table 16-3 and Chart 16-3)

- There were 1.95 (95% UI, 0.51–deaths attributable to AD and 2021 (Table 16-3).
- In 2021, among regions, mortality for AD and other dementias sub-Saharan Africa followed was lowest for Andean Latin America (Chart 16-3)

months.²⁷⁸ Compared with with adjustment for ties, survivors of severe the odds of cognitive decline by remaining stable through 3.30–7.20). 7.58 times the only at 12 months after being (95% CI, 3.58–16.03), and of progressive cognitive months (95% CI, 9.14–39.51).

- COVID-19 is also a risk factor dementia. Among 7133 299 444 control subjects Korean National Health base, all free of dementia at survivors had 1.39 times the dementia compared with

COVID-19

COVID-19 as a Risk Factor for Cognitive Decline and Dementia

- In a meta-analysis of 19 studies of post-COVID-19 syndrome (long COVID) with 11 324 participants with COVID-19, prevalence of cognitive dysfunction was assessed ≥ 3 months after COVID-19 onset.²⁷⁵ Prevalence of memory issues (5 studies; 5268 participants) was 27% (95% CI, 18%–36%); prevalence of attention disorder (3 studies; 1207 participants) was 22% (95% CI, 10%–34%); and prevalence of brain fog (3 studies; 4329 participants) was 32% (95% CI, 9%–55%). In another meta-analysis of 43 studies, prevalence of cognitive impairment ≥ 12 weeks after COVID-19 diagnosis was 22% (95% CI, 17%–28%).²⁷⁶
- In a study of 401 UK Biobank participants who had brain imaging before and after COVID-19 infection and 385 control subjects who had brain imaging at 2 time points on average 2 years apart without COVID-19 infection, those who had COVID-19

experienced 7.8% greater increase in time to complete Trails A (uncorrected $P=0.0002$; family-wise error-corrected $P=0.005$) and 12.2% greater increase in time to complete Trails B (uncorrected $P=0.0007$; family-wise error-corrected $P=0.002$) relative to control subjects without COVID-19. Those with COVID-19 also had significantly reduced gray matter thickness in certain regions, changes in tissue damage biomarker levels, and reduced global brain size, suggesting that COVID-19 infection affected brain structure.²⁷⁷

- In a cohort study evaluating cognitive decline during the first year after COVID-19 infection among 1438 COVID-19 survivors and 438 uninfected spouses, the authors found that 12.5% of those with COVID-19 had incident cognitive impairment within 12

Dementia and Breakthrough COVID-19 Infection

COVID-19 infection in fully vaccinated older adults.

Among 225 763 fully vaccinated older adults (mean age, 73.8 years), including 2764 with AD, 1244 with vascular dementia, and 4385 with MCI, after adjust-ment for comorbidities, risk of breakthrough infec-tion was similar to nondementia for AD (aOR, 1.07 [95% CI, 0.87–1.32]) and vascular dementia (aOR, 1.05 [95% CI, 0.78–1.41]) but was elevated for MCI (aOR, 1.16 [95% CI, 1.00–1.35]).²⁸⁰

Mortality in Relation to Dementia and COVID-19

with COVID-19. In a meta-analysis of 3 stud-dementia and 805 patients with COVID-19 with-with 3.69 times the odds of mortality (95% CI,

- Mortality among 223 patients with COVID-19 >50 dementia was 33.6% compared with 20.2% among who did not have dementia (aOR, 3.05 [95% CI, requiring a ventilator (24.1% versus 22.0% without

- In a meta-analysis of 10 studies including 56 577 dementia, having dementia was associated with 1.45–2.24).²⁸³

- In a meta-analysis of 9 studies, the mortality rate in with COVID-19 was significantly higher than in those with-11.59]).²⁸⁴

- Dementia was assessed in relation to breakthrough

- Dementia is a risk factor for mortality in patients ies including 130 patients with COVID-19 with

out dementia, having dementia was associated 1.99–6.83).²⁸¹

years of age in South Korea who had underlying 223 propensity-matched patients with COVID-19 1.80–5.30]); dementia was also associated with dementia; $P<0.001$).²⁸²

patients with COVID-19 with 10% prevalence of 1.80 times the adjusted odds of death (95% CI,

individuals with dementia after being infected out dementia (OR, 5.17 [95% CI, 2.31–

Table 16-1. Health Expectancies by Number of Cardiovascular Conditions Across Age Groups, HRS in the United States, 1996 to 2014

	No. of cardiovascular conditions*			
	0; y (95% CI)	1; y (95% CI)	2; y (95% CI)	≥3; y (95% CI)
At 55 y of age				
CIFLE	23.0 (22.6–23.4)	21.2 (20.9–21.5)	18.1 (17.7–18.4)	14.0 (13.5–14.5)
CILE	6.7 (6.4–7.0)	6.2 (6.0–6.4)	5.5 (5.3–5.8)	4.6 (4.2–5.0)
TLE	29.7 (29.3–30.2)	27.4 (27.0–27.8)	23.6 (23.1–24.0)	18.6 (18.0–19.2)
At 65 y of age				
CIFLE	15.0 (14.6–15.3)	13.3 (13.1–13.6)	10.9 (10.7–11.2)	7.9 (7.6–8.3)
CILE	6.4 (6.1–6.7)	5.8 (5.6–6.0)	5.2 (5.0–5.4)	4.3 (4.0–4.6)
TLE	21.3 (20.9–21.8)	19.2 (18.9–19.5)	16.1 (15.8–16.4)	12.2 (11.9–12.6)
At 75 y of age				
CIFLE	8.4 (8.1–8.6)	7.1 (6.9–7.3)	5.6 (5.4–5.7)	3.7 (3.5–3.9)
CILE	5.7 (5.4–5.9)	5.1 (4.9–5.3)	4.5 (4.3–4.6)	3.7 (3.5–3.9)
TLE	14.0 (13.7–14.4)	12.2 (12.0–12.5)	10.0 (9.8–10.3)	7.4 (7.1–7.6)
At 85 y of age				
CIFLE	3.8 (3.6–4.0)	3.1 (2.9–3.2)	2.3 (2.1–2.4)	1.4 (1.2–1.5)
CILE	4.5 (4.3–4.7)	3.9 (3.8–4.1)	3.4 (3.3–3.6)	2.7 (2.5–2.8)
TLE	8.3 (8.0–8.6)	7.0 (6.8–7.2)	5.7 (5.5–5.8)	4.1 (3.9–4.2)

CIFLE indicates cognitive impairment-free life expectancy; CILE, cognitive impairment life expectancy; HRS, Health and Retirement Study; and TLE, total life expectancy.

*Cardiovascular conditions included hypertension, heart disease, diabetes, and stroke.

Source: Adapted from Zheng et al,¹⁴¹ by permission of Oxford University Press. Copyright © 2021 The Authors.

Table 16-2. Dementia Mortality in the United States

Population group	Mortality, 2022: all ages*	Age-adjusted mortality rates per 100 000 (95% CI)
Both sexes	292 881	70.4 (70.1–70.6)
Males	97 470 (33.3%)†	59.7 (59.3–60.1)
Females	195 411 (66.7%)†	76.8 (76.4–77.1)
NH White males	80 270	63.4 (62.9–63.8)
NH White females	159 862	82.6 (82.2–83.1)
NH Black males	7687	62.5 (61.0–63.9)
NH Black females	15 912	69.9 (68.8–71.0)
Hispanic males	6209	45.7 (44.5–46.9)
Hispanic females	13 004	59.2 (58.2–60.2)
NH Asian males	2463‡	30.0 (28.8–31.1)‡
NH Asian females	5128‡	39.8 (38.7–40.9)‡
NH American Indian or Alaska Native	897	39.8 (37.2–42.4)
NH Native Hawaiian or Other Pacific Islander	202	42.5 (36.6–48.5)

Data represent underlying cause of death only using ICD-10 codes F01, F03, and G30 through G31. (ICD-10 codes F00 and F02 are not listed as underlying or multiple causes of death in the NVSS.)

ICD-10 indicates *International Classification of Diseases, 10th Revision*; NH, non-Hispanic; and NVSS, National Vital Statistics System.

*Mortality for American Indian or Alaska Native people and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native decedents, Asian and Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses. †These percentages represent the portion of total mortality that is for males vs females.

‡Includes Chinese, Filipino, Japanese, and other Asian people.

Source: Mortality: Unpublished National Heart, Lung, and Blood Institute tabulation using NVSS²⁴² and CDC WONDER.²⁴¹

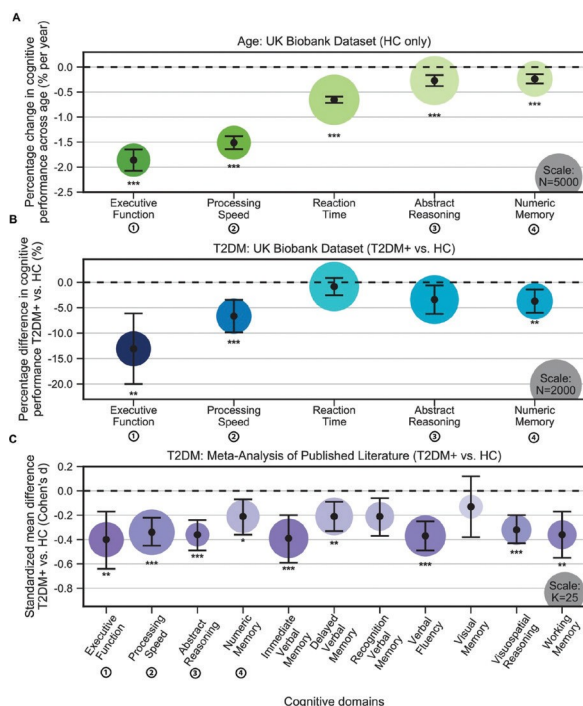
Table 16-3. Global Mortality and Prevalence of AD and Other Dementias, by Sex, 2021

	Both sexes		Male	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	1.95 (0.51 to 4.98)	56.86 (49.38 to 64.98)	0.63 (0.15 to 1.68)	20.75 (17.77 to 23.80)
Percent change (%) in total	194.39 (176.93 to 220.09)	160.81 (156.09 to 165.90)	212.84 (193.81 to 240.83)	171.06 (164.66 to 176.63)
Percent change (%) in total	50.32 (44.65 to 57.92)	45.50 (44.03 to 46.99)	54.84 (47.22 to 64.60)	47.16 (45.55 to 48.84)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; GBD, Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved. 274

**Chart 16-1. Domain-specific cognitive deficits associated with age and type 2 diabetes.**

A, In the UK Biobank, among participants without type 2 diabetes, age was associated with statistically significant deficits in executive function, processing speed, abstract reasoning, numeric memory, and reaction time. **B**, In the UK Biobank, type 2 diabetes was associated with statistically significant deficits in executive function, processing speed, abstract reasoning, and numeric memory but not in reaction time.

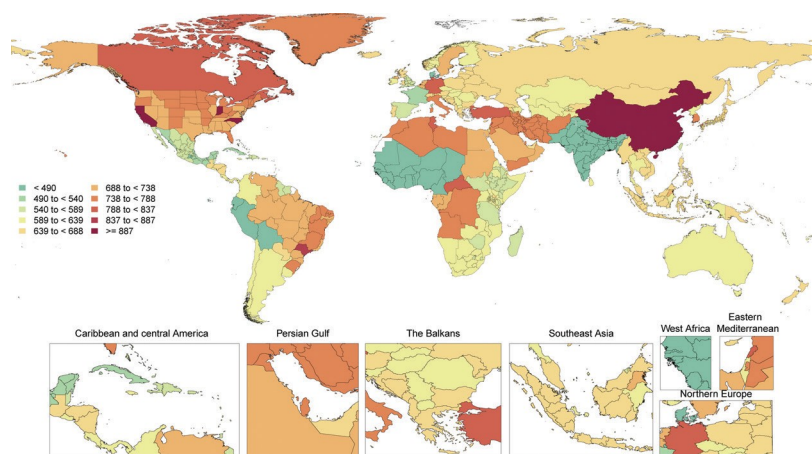


Chart 16-2. Age-standardized global prevalence rates of AD and other dementias per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AD indicates Alzheimer disease; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²⁷⁴

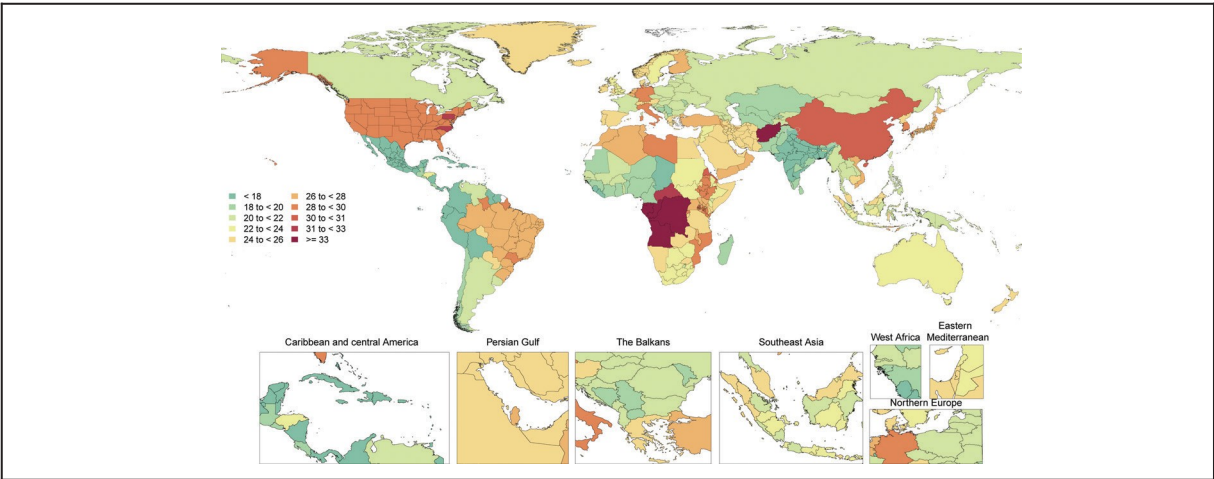


Chart 16-3. Age-standardized global mortality rates of AD and other dementias per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

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Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²⁷⁴

REFERENCES

1. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, Bae HJ, Bauman MA, Dichgans M, Duncan PW, et al; on behalf of the American Heart Association/American Stroke Association. Defining optimal brain health in adults: a presidential advisory from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e284–e303. doi: 10.1161/STR.000000000000148

2. Hachinski V, Avian A, Gilliland J, Oveissharan S. A new definition of brain health. *Lancet Neurol*. 2021;20:335– doi: 10.1016/S1474-4422(21)00102-2

3. World Health Organization. Optimizing brain health across the life course: WHO position paper. 2022. Accessed April 27, 2024.

4. Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol*. 2006;63:674–681. doi: 10.1001/archneur.63.5.674

5. Wolters FJ, Ikram MA. Epidemiology of vascular dementia. *Arterioscler Thromb Vasc Biol*. 2019;39:1542–1549. doi: 10.1161/ATVBAHA.119.311908

6. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol*. 2017;134:171–186. doi: 10.1007/s00401-017-1717-7

7. GBD Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:88–106. doi: 10.1016/S1474-4422(18)30403-4

8. National Institute of Neurological Disorders. Focus on Alzheimer's disease and related dementia. Accessed April 27, 2024.

9. Feigin VL, Vos T, Alahdab F, Amit AML, Barniohausen TW, Beahi E, Beheshti M, Chavan PP, Criqui MH, Desai R, et al; GBD 2017 US Neurological Disorders Collaborators. Burden of neurological disorders across the US from 1990–2017: a Global Burden of Disease Study. *JAMA Neurol*. 2021;78:165–176. doi: 10.1001/jamaneurol.2020.4152

10. Manly JJ, Jones RN, Langa KM, Ryan LH, Levine DA, McCammon R, Heeringa SG, Weir D. Estimating the prevalence of dementia and mild cognitive impairment in the US: The 2016 Health and Retirement Study Harmonized Cognitive Assessment Protocol Project. *JAMA Neurol*. 2022;79:1242–1249. doi: 10.1001/jamaneurol.2022.3543

11. Matthews KA, Xu W, Gadloti AH, Holt JB, Croft JB, Mack D, McGuire LC. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥ 65 years. *Alzheimers Dement*. 2019;15:17–24. doi: 10.1016/j.jalz.2018.06.3063

12. Prince MJ. World Alzheimer report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. 2015. Accessed April 27, 2024.

13. Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, Jonsson L, Liu Z, Prince M. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement*. 2017;13:1–7. doi: 10.1016/j.jalz.2016.07.150

14. Mattao SM, Mohan D, McGrattan AM, Allotey P, Stephan BC, Reidpath DD, Siervo M, Robinson L, Chaivakunabruk N. The economic burden of dementia in low- and middle-income countries (LMICs): a systematic review. *BMJ Glob Health*. 2022;7:e007409. doi: 10.1136/bmjgh-2021-007409

15. Hendriks S, Peetoom K, Bakker C, van der Flier WM, Paasma JM, Koopmans R, Verheij FRJ, de Vugt M, Kohler S, Withall A, et al; Young-Onset Dementia Epidemiology Study Group. Global prevalence of young-onset dementia: a systematic review and meta-analysis. *JAMA Neurol*. 2021;78:1080–1090. doi: 10.1001/jamaneurol.2021.2161

16. Wooten KG, McGuire LC, Olivari BS, Jackson EMJ, Croft JB. Racial and ethnic differences in subjective cognitive decline—United States, 2015–2020. *MMWR Morb Mortal Wkly Rep*. 2023;72:249–255. doi: 10.15585/mmwr.mm7210a1

17. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20:e3708–3821. doi: 10.1002/alz.13809

18. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020–2060). *Alzheimers Dement*. 2021;17:1966–1975. doi: 10.1002/alz.12362

19. Chang Wong E, Chang Chui H. Vascular cognitive impairment and dementia. *Continuum (Minneapolis)*. 2022;28:750–780. doi: 10.1212/CON.0000000000001124

20. Cao Q, Tan CC, Xu W, Hu H, Cao XP, Dong Q, Tan L, Yu JT. The prevalence of dementia: a systematic review and meta-analysis. *J Alzheimers Dis*. 2020;73:1157–1166. doi: 10.3233/JAD-191092

38. Gao S, Burney HN, Callahan CM, Purnell CE, Hendrie HC. Incidence of dementia and Alzheimer disease over time: a meta-analysis. *J Am Geriatr Soc*. 2019;67:1361–1369. doi: 10.1111/jgs.16027

39. Power MC, Bennett EE, Turner RW, Dowling NM, Ciarleglio A, Glymour MM, Gianattasio KZ. Trends in relative incidence and prevalence of dementia across non-Hispanic Black and White individuals in the United States, 2000-2016. *JAMA Neurol*. 2021;78:275–284. doi: 10.1001/jamaneurol.2020.4471

40. Yoseph M, Paddick SM, Gray WK, Andrea D, Barber R, Colgan A, Dotchin C, Urasa S, Kisoli A, Kissima J, et al. Prevalence estimates of dementia in

- older adults in rural Kilimanjaro 2009-2010 and 2018-2019: is there evidence of changing prevalence? *Int J Geriatr Psychiatry*. 2021;36:950–959. doi: 10.1002/gps.5498
41. Akinyemi RO, Yaria J, Ojagbemi A, Guerchet M, Okubadejo N, Njamnshi AK, Sarfo FS, Akpalu A, Ogbale G, Ayantayo T, et al; African Dementia Consortium (AfDC). Dementia in Africa: current evidence, knowledge gaps, and future directions. *Alzheimers Dement*. 2022;18:790–809. doi: 10.1002/alz.12432
42. Grodstein F, Leurgans SE, Capuano AW, Schneider JA, Bennett DA. Trends in postmortem neurodegenerative and cerebrovascular neuropathologies over 25 years. *JAMA Neurol*. 2023;80:370–376. doi: 10.1001/jamaneurol.2022.5416
44. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med*. 2016;374:523–532. doi: 10.1056/NEJMoa1504327
58. Li C, Ma Y, Hua R, Yang Z, Zhong B, Wang H, Xie W. Dose-response relationship between long-term blood pressure variability and cognitive decline. *Stroke*. 2021;52:3249–3257. doi: 10.1161/STROKEAHA.120.033697
59. Ernst ME, Ryan J, Chowdhury EK, Margolis KL, Beilin LJ, Reid CM, Nelson MR, Woods RL, Shah RC, Orchard SG, et al. Long-term blood pressure variability and risk of cognitive decline and dementia among older adults. *J Am Heart Assoc*. 2021;10:e019613. doi: 10.1161/jaha.120.019613
60. den Brok M, van Dalen JW, Marcum ZA, Busschers WB, van Middelaar T, Hilken N, Klijn CJM, Moll van Charante EP. 45. Ou Y-N, Tan C-C, Shen X-N, Xu W, Hou X-H, Dong Q, Tan L, Yu J-T. Blood pressure and risks of cognitive impairment and dementia. *Hypertension*. 2020;76:217–225. doi: 10.1161/HYPERTENSIONAHA.120.14993
46. Kim H, Ang TFA, Thomas RJ, Lyons MJ, Au R. Long-term blood pressure patterns in midlife and dementia in later life: findings from the Framingham Heart Study. *Alzheimers Dement*. 2023;19:4357–4366. doi:

- Xia ZL. Associations of changes in late-life blood pressure with cognitive impairment among older population in China. *BMC Geriatr.* 2021;21:536. doi: 10.1186/s12877-021-02479-1
62. Walker KA, Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, Bandeen-Roche K, Coresh J, Gross AL, Windham BG, et al. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA.* 2019;322:535–545. doi: 10.1001/jama.2019.10575
 63. Levine DA, Gross AL, Briceno EM, Tilton N, Kabeto MU, Hingtgen SM, Giordani BJ, Sussman JB, Hayward RA, Burke JF, et al. Association between blood pressure and later-life cognition among Black and White individuals. *JAMA Neurol.* 2020;77:810–819. doi: 10.1001/jamaneurol.2020.0568
 64. Lennon MJ, Lam BCP, Lipnicki DM, Crawford JD, Peters R, Schutte AE, Brodaty H, Thalamuthu A, Rydberg-Sterner T, Najjar J, et al. Use of an- doi: 10.1007/s11606-022-07951-1
 47. Ding L, Zhu X, Xiong Z, Yang F, Zhang X. The association of age at diagnosis of hypertension with cognitive decline: the China Health and Retirement Longitudinal Study (CHARLS). *J Gen Intern Med.* 2023;38:1431–1438.
 48. Zhou H, Zhu Z, Liu C, Bai Y, Zhan Q, Huang X, Zeng Q, Ren H, Xu D. Effect of hypertension duration and blood pressure control during early adulthood on cognitive function in middle age. *J Alzheimers Dis.* 2022;85:779–789.

tihypertensives, blood pressure, and estimated risk of dementia in late life: an individual participant data meta-analysis. *JAMA Network Open*.

2023;6:e23333353. doi: 10.1001/jamanetworkopen.2023.33353

65. Li S, Jiang C, Wang Y, Lai Y, Zhao M, Li Q, Bai Y, Dai W, Guo Q, He L, et al. Systolic blood pressure time in target range and cognitive outcomes: insights from the SPRINT MIND trial. *Hypertension*. 2023;80:1628–1636.

doi: 10.1161/HYPERTENSIONAHA.122.20711

doi: 10.3233/JAD-215070

49. Yaffe K, Vittinghoff E, Hoang T, Matthews K, Golden SH, Al Hazzouri AZ. Cardiovascular risk factors across the life course and cognitive decline: a pooled cohort study. *Neurology*. 2021;96:e2212–e2219. doi: 10.1212/wnl.00000000000011747

50. Samara AA, Liampas I, Dadouli K, Siokas V, Zintzaras E, Stefanidis I,

66. Hammond CA, Blades NJ, Chaudhry SI, Dodson JA, Longstreth W Jr, Daponte A, Sotiriou S, Dardiotis E. Preeclampsia, gestational hypertension and incident dementia: a systematic review and meta-analysis of published evidence. *Pregnancy Hypertens*. 2022;30:192–197. doi: 10.1016/j.preghy.2022.10.008

51. Sánchez-Nieto JM, Rivera-Sánchez UD, Mendoza-Núñez VM. Relationship between arterial hypertension with cognitive performance in elderly:

- Heckbert SR, Psaty BM, Arnold AM, Dublin S, Sitlani CM, et al. Long-term cognitive decline after newly diagnosed heart failure: longitudinal analysis in the CHS (Cardiovascular Health Study). *Circ: Heart Fail*. 2018;11:e004476. doi: 10.1161/CIRCHEARTFAILURE.117.004476 67. Wolters FJ, Segufa RA, Darweesh SKL, Bos D, Ikram MA, Sabayan B, Hofman A, Sedaghat S. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. *Alzheimers Dement*. 2018;14:1493–1504. doi: 10.1016/j.jalz.2018.01.007
68. Manemann SM, Knopman DS, St Sauver J, Bielinski SJ, Chamberlain AM, Weston SA, Jiang R, Roger VL. Alzheimer's disease and related dementias and heart failure: a community study. *J Am Geriatr Soc*. 2022;70:1664–1672. doi: 10.1111/jgs.17752
- 10.3390/brainsci11111445
52. Legdeur N, Heymans MW, Comijs HC, Huisman M, Maier AB, Visser PJ. Age dependency of risk factors for cognitive decline. *BMC Geriatr*.

69. Manemann SM, Chamberlain AM, Bielinski SJ, Jiang R, Weston SA, Roger VL. Predicting Alzheimer's disease and related dementias in heart failure and atrial fibrillation. *Am J Med.* 2023;136:302–307. doi: 10.1016/j.amjmed.2022.11.010
53. Deckers K, Köhler S, van Boxtel M, Verhey F, Brayne C, Fleming J. Lack of associations between modifiable risk factors and de-mentia in the very old: findings from the Cambridge City Over-75s cohort study. *Aging Ment Health.* 2018;22:1272–1278. doi: 10.1080/13607863.2017.1280767
54. van Dalen JW, Brayne C, Crane PK, Fratiglioni L, Larson EB, Lobo A, Lobo E, Marcum ZA, Moll van Charante EP, Qiu C, et al. Association of systolic blood pressure with dementia risk and the role of age, U-shaped associations, and mortality. *JAMA Intern Med.* 2022;182:142–152. doi: 10.1001/jamainternmed.2021.7009
55. Chen R, Morris BJ, Donlon TA, Ross GW, Kallianpur KJ, Allsopp RC, Nakagawa K, Willcox BJ, Masaki KH. Incidence of Alzheimer's disease in men with late-life hypertension is ameliorated by FOXO3 longevity geno-type. *J Alzheimers Dis.* 2023;95:79–91. doi: 10.3233/JAD-230350
56. Nasrallah IM, Gaussoin SA, Pomponio R, Dolui S, Erus G, Wright CB, Launer LJ, Detre JA, Wolk DA, Davatzikos C, et al; SPRINT Research Group. Association of intensive vs standard blood pressure control with magnetic

70. Vishwanath S, Hopper I, Wolfe R, Polekhina G, Reid CM, Tonkin AM, Murray AM, Shah RC, Storey E, Woods RL, et al. Cognitive trajectories and incident dementia after a cardiovascular event in older adults. *Alzheimers Dement*. 2023;19:3670–3678. doi: 10.1002/alz.13006
71. Chen LY, Norby FL, Gottesman RF, Mosley TH, Soliman EZ, Agarwal SK, Loehr LR, Folsom AR, Coresh J, Alonso A. Association of atrial fibrillation with cognitive decline and dementia over 20 years: the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). *J Am Heart Assoc*. 2018;7:e007301. doi: 10.1161/JAHA.117.007301
72. Bailey MJ, Soliman EZ, McClure LA, Howard G, Howard VJ, Judd SE, Unverzagt FW, Wadley V, Sachs BC, Hughes TM. Relation of atrial fibrillation to cognitive decline (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol*. 2021;148:60–68. doi: 10.1016/j.amjcard.2021.02.036
73. Bansal N, Zelnick LR, An J, Harrison TN, Lee MS, Singer DE, Fan D, Go AS. Incident atrial fibrillation and risk of dementia in a diverse, community-based population. *J Am Heart Assoc*. 2023;12:e028290. doi: 10.1161/JAHA.122.028290
57. Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, Berrut G, et al. Resonance imaging biomarkers of Alzheimer disease: secondary analysis of the SPRINT MIND randomized trial. *JAMA Neurol*. 2021;78:568–577. doi: 10.1001/jamaneurol.2021.0178

74. Zuin M, Roncon L, Passaro A, Bosi C, Cervellati C, Zuliani G. Risk of dementia in patients with atrial fibrillation: short versus long follow-up: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2021;36:1488–1500.
- Corruble E, Derumeaux G, Falissard B, et al; S.AGES Investigators. Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: the S.AGES cohort. *Hypertension*. 2020;76:1280–1288. doi: 10.1002/gps.5582
- doi: 10.1161/HYPERTENSIONAHA.119.14553

75. Zhang W, Liang J, Li C, Gao D, Ma Q, Pan Y, Wang Y, Xie W, Zheng F. Age at diagnosis of atrial fibrillation and incident dementia. *JAMA Netw Open*. 2023;6:e2342744. doi: 10.1001/jamanetworkopen.2023.42744

Circulation. 2025;151:e41–e660. DOI:

February 25, 2025 e405

76. Ding M, Fratiglioni L, Johnell K, Santoni G, Marengoni A, Oiu C. Atrial fibrillation. five aging: a population-based study. doi: 10.1212/WNL.00000000000006456
77. Rouch L, Xia F, Bahorik A, Olin J, Yaffe with greater risk of dementia in older 2021;29:1092–1098. doi: 10.1111/jicn.14269
78. Lin M, Han W, Zhong J, Wu L. A systematic to determine the effect of oral in patients with atrial fibrillation. *Int J Clin* 2021;107:1898–1904. doi: 10.1136/heartjnl-2021-319672 80.
79. Cadogan SL, Powell E, Wing K, Wong AY. Anticoagulant prescribing for atrial Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Sung JH, Pak HN, Lee MH, et al. Association of anticoagulant therapy with risk of de- mentia among patients with atrial fibrillation. *Europace*. 2021;23:184–195. doi: 10.1093/europace/euaa192
80. Hsu JY, Liu PP, Liu AB, Lin SM, Huang HK, Loh CH. Lower risk of demen- tia in patients with atrial fibrillation taking non-vitamin K antagonist oral anticoagulants: a nationwide population-based cohort study. *J Am Heart Assoc*. 2021;10:e016437. doi: 10.1161/JAHA.120.016437
81. Grymonprez M, Petrovic M, De Backer TL, Ikram MA, Steurbaut S, Lahousse L. Comparing the risk of dementia in subjects with atrial 2023;52:afad038. doi: 5210.1093/ageing/afad038
82. Lee SR, Choi EK, Park SH, Jung JH, Han KD, Oh S, Lip GYH. Comparing warfarin and 4 direct oral anticoagulants for the risk of dementia in patients with atrial fibrillation. *Stroke*. 2021;52:3459–3468. doi: 10.1161/STROKEAHA.120.033338
83. Lee ZX, Ang E, Lim XT, Arain SJ. Association of risk of dementia with direct oral anticoagulants versus warfarin use in patients with non-valvular atrial 2023;52:afad038. doi: 5210.1093/ageing/afad038
84. Norby FL, Chen LY, Soliman EZ. Association of left ventricular dementia risk over 20 years: the Neurocognitive Study (ARIC-NCs). 10.1016/j.ahj.2018.07.007
85. Moazzami K, Ostovaneh MR, Ambale Wu C, Liu K, Pimenta I, Fitzpatrick A. nhv and remodeling and risk of (Multi-Ethnic Study of doi: 10.1161/STROKEAHA.120.033338
86. Razavi AC, Fernandez C, He J, Kelly SP, Carmichael OT, Bazzano LA. Left is associated with cognitive function in fibrillation using non-vitamin K antagonist oral anticoagulants versus vitamin K antagonists: a Belgian nationwide cohort study. *Age Ageing*. 2023;52:afad038. doi: 5210.1093/ageing/afad038

- Heart Study. *Circ Cardiovasc Imaging*. 2020;13:e010335. doi: 10.1161/circimaging.119.010335
97. Johansen MC, Wang W, Zhang M, Knopman DS, Ndumele C, Mosley TH, Selvin E, Shah AM, Solomon SD, Gottesman RF, et al. Risk of dementia associated with atrial cardiopathy: the ARIC study. *J Am Heart Assoc*. 2022;11:e025646. doi: 10.1161/jaha.121.025646
98. Rouch L, Hoang T, Xia F, Sidney S, Lima JAC, Yaffe K. Twenty-five-year change in cardiac structure and function and midlife cognition: the CARDIA study. *Neurology*. 2022;98:e1040–e1049. doi: 10.1212/WNL.00000000000013249
99. Antal B, McMahon LP, Sultan SF, Lithen A, Wexler DJ, Dickerson B, Ratai EM, Mujica-Parodi LR. Type 2 diabetes mellitus accelerates brain aging and cognitive decline: complementary findings from UK Biobank and meta-analyses. *Elife*. 2022;11:e73138. doi: 10.7554/eLife.73138
100. Ji X, Gao H, Sun D, Zhuang J, Fang Y, Wang K, Ahmadizar F. Trajectories of cognition and daily functioning before and after incident diabetes. *Diabetes Care*. 2023;46:75–82. doi: 10.2337/dc22-1190
101. Liu L, Gracely EJ, Yin X, Eisen HJ. Impact of diabetes mellitus and cardiometabolic syndrome on the risk of Alzheimer's disease among postmenopausal women. *World J Diabetes*. 2021;12:69–83. doi: 10.4239/wjd.v12.i1.69
- fibrillation: a systematic review and meta-analysis. *J Cardiovasc Pharmacol*. 2021;77:22–31. doi: 10.1097/FJC.0000000000000925
85. Bodagh N, Yap R, Kotadia I, Sim I, Bhalla A, Somerville P, O'Neill M, Williams SE. Impact of catheter ablation versus medical therapy on cognitive function in atrial fibrillation: a systematic review. *J Interv Card Electrophysiol*. 2022;65:271–286. doi: 10.1007/s10840-022-01196-y
86. Jaiswal V, Ang SP, Deb N, Roy P, Chauhan S, Halder A, Rajak K, Raj N, Patel N, Soni S, et al. Association between catheter ablation and dementia among patients with atrial fibrillation: a systematic review and meta-analysis. *Curr Probl Cardiol*. 2024;49:102154. doi: 10.1016/j.cpcardiol.2023.102154
87. Sauer AC, Nathoe HM, Hendrikse J, Peelen LM, Regieli J, Veldhuijzen DS, Kalkman CJ, Grobbee DE, Doevendans PA, van Dijk D; Octopus Study Group. Cognitive outcomes 7.5 years after angioplasty compared with off-pump coronary bypass surgery. *Ann Thorac Surg*. 2013;96:1294–1300. doi: 10.1016/j.athoracsur.2013.05.001
88. Whitlock EL, Diaz-Ramirez LG, Smith AK, Boscardin WJ, Covinsky KE, Avidan MS, Glymour MM. Association of coronary artery bypass grafting vs percutaneous coronary intervention with memory decline in older adults undergoing coronary revascularization. *JAMA*. 2021;325:1955–1964. doi: 10.1001/jama.2021.5150
89. Kuzma E, Airdrie J, Littlejohns TJ, Lourida I, Thompson-Coon J, Lang IA, Scrobotovici M, Thacker EL, Fitzpatrick A, Kuller LH, et al. Coronary artery bypass graft surgery and dementia risk in the Cardiovascular Health Study. *Alzheimer Dis Assoc Disord*. 2017;31:120–127. doi:

102. Benn M, Nordestgaard BG, Tybjaerg-Hansen A, Frikke-Schmidt R. Impact of glucose on risk of dementia: mendelian randomisation studies in 115,875 individuals. *Diabetologia*. 2020;63:1151–1161. doi: 10.1007/s00125-020-05124-5
103. Carmichael O, Stuchlik P, Pillai S, Biessels G-J, Dhullipudi R, Madden-Rusnak A, Martin S, Hsia DS, Fonseca V, Bazzano L. High-normal adolescent fasting plasma glucose is associated with poorer midlife brain health: Bogalusa Heart Study. *J Clin Endocrinol Metab*. 2019;104:4492–4500. doi: 10.1210/je.2018-02750
104. Cohen-Manheim I, Sinnreich R, Doniger GM, Simon ES, Pinchas-Mizrachi R, Kark JD. Fasting plasma glucose in young adults free of diabetes is associated with cognitive function in midlife. *Eur J Public Health*. 2018;28:496–503. doi: 10.1093/eurpub/ckx194
105. Yu ZB, Zhu Y, Li D, Wu MY, Tang ML, Wang JB, Chen K. Association between visit-to-visit variability of HbA(1c) and cognitive decline: a pooled analysis of two prospective population-based cohorts. *Diabetologia*. 2020;63:85–94. doi: 10.1007/s00125-019-04986-8
106. Song J, Bai H, Xu H, Xing Y, Chen S. HbA1c variability and the risk of dementia in patients with diabetes: a meta-analysis. *Int J Clin Pract*. 2022;2022:7706330. doi: 10.1155/2022/7706330
107. Mattishent K, Loke YK. Meta-analysis: association between hypoglycemia and serious adverse events in older patients treated with glucose-lowering agents. *Front Endocrinol*. 2021;12:571568. doi: 10.1097/WAD.0000000000000191
90. Mutch WA, Fransoo RR, Campbell BI, Chateau DG, Sirski M, Warrian RK. Dementia and depression with ischemic heart disease: a population-based longitudinal study comparing interventional approaches to medical management. *PLoS One*. 2011;6:e17457. doi: 10.1371/journal.pone.0017457
91. Jiang X, Lewis CE, Allen NB, Sidney S, Yaffe K. Premature cardiovascular disease and brain health in midlife: the CARDIA study. *Neurology*. 2023;100:e1454–e1463. doi: 10.1212/WNL.00000000000206825
92. Bagai A, Chen AY, Udell JA, Dodson JA, McManus DD, Maurer MS, Enriquez JR, Hochman J, Goyal A, Henry TD, et al. Association of cognitive impairment with treatment and outcomes in older myocardial infarction patients: a report from the NCDR Chest Pain-MI Registry. *J Am Heart Assoc*. 2019;8:e012929. doi: 10.1161/JAHA.119.012929
93. Johansen MC, Ye W, Gross A, Gottesman RF, Han D, Whitney R, Briceno EM, Giordani BJ, Shore S, Elkind MSV, et al. Association between acute myocardial infarction and cognition. *JAMA Neurol*. 2023;80:723–731. doi: 10.1001/jamaneurol.2023.1331

108. Huang L, Zhu M, Ji J. Association between hypoglycemia and dementia in patients with diabetes: a systematic review and meta-analysis of 1.4 million patients. *Diabetol Metab Syndr*. 2022;14:31. doi: 10.1186/s13098-022-00799-9

109. Gomez-Guijarro MD, Alvarez-Bueno C, Saz-Lara A, Sequi-Dominguez I, Luceron-Lucas-Torres M, Cavero-Redondo I. Association between severe hypoglycaemia and risk of dementia in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2023;39:e3610. doi: 10.1002/dmrr.3610

110. Mehlig K, Lapidus L, Thelle DS, Waern M, Zetterberg H, Björkelund C, Skoog I, Lissner L. Low fasting serum insulin and dementia in nondiabetic women followed for 34 years. *Neurology*. 2018;91:e427–e435. doi: 10.1212/WNL.0000000000005911

111. Rawlings AM, Sharrett AR, Albert MS, Coresh J, Windham BG, Power MC, Knopman DS, Walker K, Burgard S, Mosley TH, et al. The association of late-life diabetes status and hyperglycemia with incident mild cognitive

- impairment and dementia: the ARIC study. *Diabetes Care*. 2019;42:1248–1254. doi: 10.2337/dc19-0120
112. Hu J, Fang M, Pike JR, Lutsey PL, Sharrett AR, Wagenknecht LE, Hughes TM, Seegmiller JC, Gottesman RF, Mosley TH, et al. Prediabetes, intervening diabetes and subsequent risk of dementia: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*. 2023;66:1442–1449. doi: 10.1007/s00125-023-05930-7
113. Hendriks S, Ranson JM, Peetoom K, Lourida I, Tai XY, de Vugt M, Llewellyn DJ, Kohler S. Risk factors for young-onset dementia in the UK Biobank. *JAMA Neurol*. 2024;81:134–142. doi: 10.1001/jamaneurol.2023.4929
114. Qu Y, Hu HY, Ou YN, Shen XN, Xu W, Wang ZT, Dong Q, Tan L, Yu JT. Association of body mass index with risk of cognitive impairment and dementia: a systematic review and meta-analysis of prospective studies. *Neurosci Biobehav Rev*. 2020;115:189–198. doi: 10.1016/j.neubiorev.2020.05.012
- Wright CB, Sacco RL. Obesity measures in relation to cognition in the Northern Manhattan Study. *J Alzheimers Dis*. 2020;78:1653–1660. doi: 10.3233/JAD-201071
116. Caunca MR, Gardener H, Simonetto M, Cheung YK, Alperin N, population-based cohort study. *Neuroepidemiology*. 2024;58:166–173. doi: 10.1159/000535828
130. Wu J, Xiong Y, Xia X, Orsini N, Qiu C, Kivipelto M, Rizzuto D, Wang R. Can dementia risk be reduced by following the American Heart Association's Life's Simple 7? A systematic review and dose-response meta-analysis. *Ageing Res Rev*. 2023;83:101788. doi: 10.1016/j.arr.2022.101788
131. González HM, Tarraf W, Harrison K, Windham BG, Tingle J, Alonso A, Griswold M, Heiss G, Knopman D, Mosley TH. Midlife cardiovascular health and 20-year cognitive decline: Atherosclerosis Risk in Communities Study results. *Alzheimers Dement*. 2018;14:579–589. doi: 10.1016/j.jalz.2017.11.002
- Yoshita M, DeCarli C, Elkind MSV, Sacco RL, Wright CB, et al. Measures of obesity are associated with MRI markers of brain aging. *Neurology*. 2019;93:e791–e803. doi: 10.1212/WNL.0000000000007966
117. Hamer M, Batty GD. Association of body mass index and waist-to-hip ratio

133. Samieri C, Perier M-C, Gaye B, Proust-Lima C, Helmer C, Dartigues J-F, Berr C, Tzourio C, Empana J-P. Association of cardiovascular health level in older age with cognitive decline and incident dementia. *JAMA*. 2018;320:657–664. doi: 10.1001/jama.2018.11499
134. Malik R, Georgakis MK, Neitzel J, Rannikmäe K, Ewers M, Seshadri S, Sudlow CLM, Dichgans M. Midlife vascular risk factors and risk of incident dementia: longitudinal cohort and mendelian randomization analyses in the UK Biobank. *Alzheimers Dement*. 2021;17:1422–1431. doi: 10.1002/alz.12320
118. Fernández-Andújar M, Morales-García E, García-Casares N. Obesity and gray matter volume assessed by neuroimaging: a systematic review. *Brain Sciences*. 2021;11:999. doi: 10.3390/brainsci11080999
119. Danat IM, Clifford A, Partridge M, Zhou W, Bakre AT, Chen A, McFeeters D, Smith T, Wan Y, Copeland J, et al. Impacts of overweight and obesity in older age on the risk of dementia: a systematic literature review and a meta-analysis. *J Alzheimers Dis*. 2019;70:S87–S99. doi: 10.3233/JAD-180763

135. Petermann-Rocha F, Deo S, Lyall D, Orkaby AR, Quinn TJ, Sattar N, Celis-Morales C, Pell JP, Ho FK. Association between the AHA Life's Essential 8 score and incident all-cause dementia: a prospective cohort study from UK Biobank. *Curr Probl Cardiol.* 2023;48:101934. doi: 10.1016/j.cpcardiol.2023.101934
136. Zhou R, Chen H-W, Li F-R, Zhong Q, Huang Y-N, Wu X-B. "Life's Essential 8" cardiovascular health and dementia risk, cognition, and neuroimaging markers of brain health. *J Am Med Dir Assoc.* 2023;24:1791–1797. doi: 10.1016/j.jamda.2023.05.023
120. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S, Kivimaki M. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. *Alzheimers Dement.* 2018;14:178–186. doi: 10.1016/j.jalz.2017.06.2637
- E, Chalmers J, Clarke R, Dartigues JF, et al. Association of anthropometry and weight change with risk of dementia and its major subtypes: a meta-analysis consisting 2.8 million adults with 57 294 cases of dementia. *Obes Rev.*
121. Lee CM, Woodward M, Batty GD, Beiser AS, Bell S, Berr C, Bjertness

137. Yaffe K, Bahorik AL, Hoang TD, Forrester S, Jacobs DR, Lewis CE, Lloyd-Jones DM, Sidney S, Reis JP. Cardiovascular risk factors and accelerated cognitive decline in midlife: the CARDIA study. *Neurology*. 2020;95:e839–e846. doi: 10.1212/WNL.00000000000010078
138. Fayosse A, Nguyen DP, Dugravot A, Dumurgier J, Tabak AG, Kivimäki M, Sabia S, Singh-Manoux A. Risk prediction models for dementia: role of age and cardiometabolic risk factors. *BMC Med*. 2020;18:107. doi: 10.1186/s12916-020-01578-x
122. Machado-Fragua MD, Sabia S, Fayosse A, Hassen CB, van der Heide F, Kivimäki M, Singh-Manoux A. Is metabolic-healthy obesity associated with risk of dementia? An age-stratified analysis of the Whitehall II cohort study. *BMC Med*. 2023;21:436. doi: 10.1186/s12916-023-03155-4
123. Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, Shipley MJ, Alfredsson L, Fransson EI, Goldberg M, et al. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement*. 2018;14:601–609. doi: 10.1016/j.jalz.2017.09.016
124. Quaye E, Galecki AT, Tilton N, Whitney R, Briceno EM, Elkind MSV, Fitzpatrick AL, Gottesman RF, Griswold M, Gross AL, et al. Association of obesity with cognitive decline in Black and White Americans. *Neurology*. 2023;100:e220–e231. doi: 10.1212/WNL.000000000000201367
125. Bahorik AL, Sidney S, Kramer-Feldman J, Jacobs DR, Mathew AR, Reis JP, Yaffe K. Early to midlife smoking trajectories and cognitive function in mid-dle-aged US adults: the CARDIA study. *J Gen Intern Med*. 2022;37:1023–1030. doi: 10.1007/s11606-020-06450-5
126. Johnson AL, Nystrom NC, Piper ME, Cook J, Norton DL, Zuelsdorff M, Wyman MF, Flowers Benton S, Lambrou NH, O'Hara J, et al. Cigarette smoking status, cigarette exposure, and duration of abstinence predicting

139. Rabin JS, Schultz AP, Hedden T, Viswanathan A, Marshall GA, Kilpatrick E, Klein H, Buckley RF, Yang HS, Properzi M, et al. Interactive associations of vascular risk and β -amyloid burden with cognitive decline in clinically normal elderly individuals: findings from the Harvard Aging Brain Study. *JAMA Neurol.* 2018;75:1124–1131. doi: 10.1001/jamaneurol.2018.1123
140. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Malone IB, Parker TD, Keshavan A, Buchanan SM, Keuss SE, et al. Associations between vascular risk across adulthood and brain pathology in late life: evidence from a British birth cohort. *JAMA Neurol.* 2020;77:175–183. doi: 10.1001/jamaneurol.2019.3774
141. Zheng L, Matthews FE, Anstey KJ. Cognitive health expectancies of cardiovascular risk factors for cognitive decline and dementia. *Age Ageing.* 2021;50:169–175. doi: 10.1093/ageing/afaa111
142. Sedaghat S, Lutsey PL, Ji Y, Empiana JP, Sorond F, Hughes TM, Mosley TH, Gottesman RF, Knopman DS, Walker KA, et al. Association of change in cardiovascular risk factors with incident dementia. *Alzheimers Dement.* 2023;19:1821–1831. doi: 10.1002/alz.12818
143. Ruthirakuhan M, Cogo-Moreira H, Swardfager W, Herrmann N, Lanctot KL, Black SE. Cardiovascular risk factors and risk of Alzheimer disease and mortality: a latent class approach. *J Am Heart Assoc.* 2023;12:e025724. doi: 10.1161/jaha.122.025724
127. Deal JA, Power MC, Palta P, Alonso A, Schneider ALC, Perryman K, Bandeen-Roche K, Sharrett AR. Relationship of cigarette smoking and time of quitting with incident dementia and cognitive decline. *J Am Geriatr Soc.* 2021;80:1013–1023. doi: 10.3233/JAD-201332
128. Zhou S, Wang K. Childhood secondhand smoke exposure and risk of dementia, Alzheimer's disease and stroke in adulthood: a prospective cohort study. *J Prev Alzheimers Dis.* 2021;8:345–350. doi: 2020;68:337–345. doi: 10.1111/jgs.16228

144. Kjaergaard AD, Ellervik C, Witte DR, Nordestgaard BG, Frikke-Schmidt R, Bojesen SE. Kidney function and risk of dementia: observational study, meta-analysis, and two-sample mendelian randomization study. *Eur J Epidemiol.* 2022;37:1273–1284. doi: 10.1007/s10654-022-00923-z
145. Singh-Manoux A, Oumarou-Ibrahim A, Machado-Fragua MD, Dumurgier J, Brunner EJ, Kivimaki M, Fayosse A, Sabia S. Association between kidney function and incidence of dementia: 10-year follow-up of the Whitehall II cohort study. *Age Ageing.* 2022;51:afab259. doi: 10.1093/ageing/afab259
146. Li H, Zhao S, Wang R, Gao B. The association between cognitive impairment/dementia and albuminuria: a systematic review and meta-analysis. *Clin Exp Nephrol.* 2022;26:45–53. doi: 10.1007/s10157-021-02127-3
129. Wan Z, Zhang X, He H, Zhang Y, Chen GC, Qin LQ, Zhang N, Li FR. Secondhand smoke exposure and risk of dementia in non-smokers: a

147. Kim HW, Jhee JH, Joo YS, Yang KH, Jung TH, Kang SW, Park JT. Dialysis adequacy derived hemodialysis patients. *Front Med* 10:3389/fmed.2021.769490
148. Ghazi L, Shen J, Ying J, Derington CG, JS, King JB, Cheung AK, Williamson JD, et al. Intensive blood pressure treatment based on an analysis of the SPRINT randomized 2023;6:e2314443. doi:
149. Wang S, Wang J, Dove A, Guo J, Yang W. Association of impaired kidney function with dyes: a community-based cohort study. 2773. doi: 10.1002/alz.12910
150. Shi L, Chen S-J, Ma M-Y, Bao Y-P, Han Y, Wang Y-M, Shi J, Vitiello MV, Lu L. Sleep disturbances increase the risk of dementia: a system-Harmonized Cognitive Assessment *Sci*. 2024;79:0bae005. doi:
165. Seblova D, Enn C, Avila-Rieder JF, Zahodne LB, Chanman B, Prescott quality is associated with cognition 58 (*Amst*). 2023;15:e12424. doi:
166. Bobrow K, Hoang T, Barnes DE. sex and wealth on population Africa. *Front Neurol*. 2021;12:766705.
167. Hyun J, Hall CB, Katz MJ, Derby CA, A, Vaccaro R, Davin A, Kim KW, et al: International Consortium (COSMIC). and incident dementia: a COSMIC atic review and meta-analysis. *Sleep Med Rev*. 2018;40:4–16. doi:

- Dis.* 2022;85:179–196. doi: 10.3233/JAD-210627
168. Geraets AFJ, Leist AK. Sex/gender and socioeconomic differences in modifiable risk factors for dementia. *Sci Rep.* 2023;13:80. doi: 10.1016/j.smr.2017.06.010
151. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. *JAMA Neurol.* 2017;74:1237–1245. doi: 10.1001/jamaneurol.2017.2180

169. Soh Y, Eng CW, Mayeda ER, Whitmer RA, Lee C, Peterson RL, Mungas DM, Glymour MM, Gilsanz P. Association of primary lifetime occupational cognitive complexity and cognitive decline in a diverse cohort: results from the KHANDLE study. *Alzheimers Dement*. 2023;19:3926–3935. doi: 10.1002/alz.13038
152. Pase MP, Harrison S, Misialek JR, Kline CE, Cavaoto M, Baril AA, Yiallourou S, Bisson A, Himali D, Leng Y, et al. Sleep architecture, obstructive sleep apnea, and cognitive function in adults. *JAMA Netw Open*. 2023;6:e2325152. doi: 10.1001/jamanetworkopen.2023.25152
153. Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, Wohlleber M, Miller MD, Andrade A, Lewis C, et al. Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly: a longitudinal study. *Am J Respir Crit Care Med*. 2018;197:933–943. doi: 10.1164/rccm.201711-2283OC

170. Cho TC, Yu X, Gross AL, Zhang YS, Lee J, Langa KM, Kobayashi LC. Negative wealth shocks in later life and subsequent cognitive function in older adults in China, England, Mexico, and the USA, 2012-18: a population-based, cross-nationally harmonised, longitudinal study. *Lancet Healthy Longev.* 2023;4:e461–e469. doi: 10.1016/S2666-7568(23)00113-7 171. Dintica CS, Bahorik A, Xia F, Kind A, Yaffe K. Dementia risk and disadvantaged neighborhoods. *JAMA Neurol.* 2023;80:903–909. doi: 10.1164/rccm.201704-0704OC 10.1001/jamaneurol.2023.2120
154. Weihs A, Frenzel S, Wittfeld K, Obst A, Stubbe B, Habes M, Szentkirályi A, Berger K, Fietze I, Penzel T, et al. Associations between sleep ap-nea and advanced brain aging in a large-scale population study. *Sleep.* 2021;44:zsaa204. doi: 10.1093/sleep/zsaa204
155. Zacharias HU, Weihs A, Habes M, Wittfeld K, Frenzel S, Rashid T, Stubbe B, Obst A, Szentkirályi A, Bulow R, et al. Association between obstruc-

172. Vassilaki M, Aakre JA, Castillo A, Chamberlain AM, Wilson PM, Kremers WK, Mielke MM, Geda YE, Machulda MM, Alhurani RE, et al. Association of neighborhood socioeconomic disadvantage and cognitive impairment. *Alzheimers Dement*. 2023;19:761–770. doi: 10.1002/alz.12702
173. Glauber R. Rural depopulation and the rural-urban gap in cognitive functioning among older adults. *J Rural Health*. 2022;38:696–704. doi: 10.1111/jrh.12650
- tive sleep apnea and brain white matter hyperintensities in a population-based cohort in Germany. *JAMA Netw Open*. 2021;4:e2128225. doi: 10.1001/jamanetworkopen.2021.28225
156. Dunietz GL, Chervin RD, Burke JF, Conceicao AS, Braley TJ. Obstructive

174. Rahman M, White EM, Mills C, Thomas KS, Jutkowitz E. Rural-urban differences in diagnostic incidence and prevalence of Alzheimer's disease and related dementias. *Alzheimers Dement*. 2021;17:1213–1230. doi: 10.1002/alz.12285
- sleep apnea treatment and dementia risk in older adults. *Sleep*. 2021;44:zsab076. doi: 10.1093/sleep/zsab076
157. Franks KH, Rowsthorn E, Nicolazzo J, Boland A, Lavale A, Baker J, Rajaratnam SMW, Cavuoto MG, Yiallourou SR, Naughton MT, et al. The treatment of sleep dysfunction to improve cognitive function: a meta-analysis of randomized controlled trials. *Sleep Med*. 2023;101:118–126. doi: 10.1016/j.sleep.2022.10.021
158. Fredriksen-Goldsen KI, Jung H, Kim HJ, Petros R, Emlen C. Disparities in subjective cognitive impairment by sexual orientation and gender in a national population based study of U.S. adults, 2013-2018. *J Aging Health*. 2022;34:519–528. doi: 10.1177/08982643211046466
159. Hsieh N, Liu H, Lai WH. Elevated risk of cognitive impairment among older sexual minorities: do health conditions, health behaviors, and social connections matter? *Gerontologist*. 2021;61:352–362. doi: 10.1093/geront/gnaa136
160. Stinchcombe A, Hammond NG. Correlates of memory and executive function in middle-aged and older adults in the CLSA: a minority stress approach. *J Gerontol B Psychol Sci Soc Sci*. 2022;77:1105–1117. doi: 10.1093/geronb/gbab084
161. Guo Y, Li Q, Yang X, Jaffee MS, Wu Y, Wang F, Bian J. Prevalence of Alzheimer's and related dementia diseases and risk factors among trans-gender adults, Florida, 2012–2020. *Am J Public Health*. 2022;112:754–757. doi: 10.2105/AJPH.2022.306720
162. Ribeiro F, Teixeira-Santos AC, Caramelli P, Leist AK. Prevalence of dementia in Latin America and Caribbean countries: systematic review and meta-analyses exploring age, sex, rurality, and education as possible determinants.

175. Zacher M, Brady S, Short SE. Geographic patterns of dementia in the United States: variation by place of residence, place of birth, and sub-population. *J Gerontol B Psychol Sci Soc Sci*. 2023;78:1192–1203. doi: 10.1093/geronb/gbad045
176. Harris ML, Bennion E, Magnusson KR, Howard VJ, Wadley VG, McClure LA, Levine DA, Manly JJ, Avila JF, Glymour MM, et al. Rural versus urban residence in adulthood and incident cognitive impairment. *Neuroepidemiology*. 2023;57:218–228. doi: 10.1159/000530961
177. Deckers K, Barbera M, Kohler S, Ngandu T, van Boxtel M, Rusanen M, Laatikainen T, Verhey F, Soininen H, Kivipelto M, et al. Long-term dementia risk prediction by the LIBRA score: a 30-year follow-up of the CAIDE study. *Int J Geriatr Psychiatry*. 2020;35:195–203. doi: 10.1002/gps.5235
178. Schaich CL, Yeboah J, Espeland MA, Baker LD, Ding J, Hayden KM, Sachs BC, Craft S, Rapp SR, Luchsinger JA, et al. Association of vascular risk scores and cognitive performance in a diverse cohort: the Multi-Ethnic Study of Atherosclerosis. *J Gerontol A Biol Sci Med Sci*. 2022;77:1208–1215. doi: 10.1093/gerona/glab189
179. Graves KG, May HT, Jacobs V, Knowlton KU, Muhlestein JB, Lappe DL, Anderson JL, Horne BD, Bunch TJ. CHA2DS2-VASc scores and Intermountain Mortality Risk Scores for the joint risk stratification of dementia among patients with atrial fibrillation. *Heart Rhythm*. 2019;16:3–9. doi: 10.1016/j.hrthm.2018.10.018
180. Li J, Ogrodnik M, Devine S, Auerbach S, Wolf PA, Au R. Practical risk score for 5-, 10-, and 20-year prediction of dementia in elderly persons: Framingham Heart Study. *Alzheimers Dement*. 2018;14:35–42. doi: 10.1016/j.arr.2022.101703
163. Wang AY, Hu HY, Ou YN, Wang ZT, Ma YH, Tan L, Yu JT. Socioeconomic status and risks of cognitive impairment and dementia: a systematic re-view and meta-analysis of 39 prospective studies. *J Prev Alzheimers Dis*. 2023;10:83–94. doi: 10.14283/jpad.2022.81
164. Zhang YS, O'Shea B, Yu X, Cho TC, Zhang KP, Kler J, Langa KM, Weir DR, Gross AL, Kobayashi LC. Educational attainment and later-life cognitive function in high- and middle-income countries: evidence from the

181. Turney IC, Lao PJ, Rentería MA, Igwe KC, Berroa J, Rivera A, Benavides A, Morales CD, Rizvi B, Schupf N, et al. Brain aging among racially and ethnically diverse middle-aged and older adults. *JAMA Neurol.* 2023;80:73–81.
doi: 10.1001/jamaneurol.2022.3919

182. Chin KS, Holper S, Loveland P, Churilov L, Yassi N, Watson R.
Prevalence of cerebral microbleeds in Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia: a

systematic review and meta-analysis. *Neurobiol Aging*. 2024;134:74–83. doi: 10.1016/j.neurobiolaging.2023.11.006

183. Sullivan KJ, Griswold ME, Ghelani K, Rajesh A, Shrestha S, Gottesman RF, Knopman D, Mosley TH, Windham BG. Late midlife subclinical infarct burden and risk of dementia: the Atherosclerosis Risk in Communities Neurocognitive Study. *J Alzheimers Dis*. 2023;91:543–549. doi: 10.3233/JAD-220746

184. Lei C, Deng Q, Li H, Zhong L. Association between silent brain infarcts and cognitive function: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2019;28:2376–2383. doi: 10.1016/j.jstrokecerebrovasdis.2019.03.036

185. Cao QL, Sun Y, Hu H, Wang ZT, Tan L, Yu JT; Alzheimer's Disease Neuroimaging Initiative. Association of cerebral small vessel disease burden with neuropsychiatric symptoms in non-demented elderly: a longitudinal study. *J Alzheimers Dis*. 2022;89:583–592. doi: 10.3233/JAD-220128

186. Baril AA, Pinheiro AA, Himali JJ, Beiser A, Sanchez E, Pase MP, Seshadri S, Demissie S, Romero JR. Lighter sleep is associated with higher enlarged perivascular spaces burden in middle-aged and elderly individuals. *Sleep Med*. 2022;100:558–564. doi: 10.1016/j.sleep.2022.10.006

187. Lewis CK, Bernstein OM, Grill JD, Gillen DL, Sultzer DL. Anxiety and

- Investigation of Neurocognitive Aging results (HCHS/SOL). *Sci Rep*. 2018;8:17578. doi: 10.1038/s41598-018-35573-3
203. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, Disease Genetics Consortium (ADGC). Genetic meta-analysis of dementia, immunity and lipid processing. *Nat Genet*. 2019;51:414–430. doi: 10.1038/s41588-019-0358-2
 204. Liu JZ, Erlich Y, Pickrell JK. Case-control association mapping by proxy using family history of disease. *Nat Genet*. 2017;49:325–331. doi: 10.1038/ng.3766
188. Chou YH, Sundman M, Ton That V, Green J, Trapani C. Cortical excitability and plasticity in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis of transcranial magnetic stimulation studies. *Ageing Res Rev*. 2022;79:101660. doi: 10.1016/j.arr.2022.101660
 189. Yeh WC, Hsu CY, Li KY, Chien CF, Huang LC, Yang YH. Association between subclinical epileptiform discharge and the severity of cognitive decline in Alzheimer's disease: a longitudinal cohort study. *J Alzheimers Dis*. 2022;90:305–312. doi: 10.3233/JAD-220567
 190. Reyes JL, Norby FL, Ji Y, Wang W, Parikh R, Zhang MJ, Oldenburg NC, Lutsey PL, Jack CR Jr, Johansen M, et al. Association of abnormal p-wave parameters with brain MRI morphology: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Pacing Clin Electrophysiol*. 2023;46:951–959. doi: 10.1111/pace.14687
 191. Alvarez-Bueno C, Cunha PG, Martinez-Vizcaino V, Pozuelo-Carrascosa DP, Visier-Alfonso ME, Jimenez-Lopez E, Cervero-Redondo I. Arterial stiffness and cognition among adults: a systematic review and meta-analysis of observational and longitudinal studies. *J Am Heart Assoc*. 2020;9:e014621. doi: 10.1161/JAHA.119.014621
 192. Jansen MG, Griffanti L, Mackay CE, Anatórk M, Melazzini L, Lange AG, Filippini N, Zsoldos E, Wiegertjes K, Leeuw FE, et al. Association of cerebral small vessel disease burden with brain structure and cognitive and vascular risk trajectories in mid-to-late life. *J Cereb Blood Flow Metab*. 2023;46:951–959. doi: 10.1161/JAHA.119.014621
 193. Lin F, Pa J, Karim R, Hodis HN, Han SD, Henderson VW, St John JA, Mack WJ. Subclinical carotid artery atherosclerosis and cognitive function in older adults. *Alzheimers Res Ther*. 2022;14:63. doi: 10.1186/s13195-022-00997-7
 194. Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, Fiske A, Pedersen NL. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry*. 2006;63:168–174. doi: 10.1001/archpsyc.63.2.168
 195. Lanoiselee HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, Richard AC, Pasquier F, Rollin-Sillaire A, Martinaud O, et al; Collaborators of the CNR-MAJ Project. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: a genetic screening study of familial and sporadic cases. *PLoS Med*. 2017;14:e1002270. doi: 10.1371/journal.pmed.1002270
 196. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillon M, Marechal E, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383:707–710. doi: 10.1038/383707a0
 197. Maia LF, Mackenzie IR, Feldman HH. Clinical phenotypes of cerebral amyloid angiopathy. *J Neurol Sci*. 2007;257:23–30. doi: 10.1016/j.jns.2007.01.054
 198. Bergem AL, Engedal K, Kringlen E. The role of heredity in late-onset Alzheimer disease and vascular dementia: a twin study. *Arch Gen Psychiatry*. 1997;54:264–270. doi: 10.1001/archpsyc.1997.01830150090013
 199. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921–923. doi: 10.1126/science.8346443

205. Bellenguez C, Kucukali F, Jansen IE, Kleiendam L, Moreno-Grau S, Amin N, Naj AC, Campos-Martin R, Grenier-Boley B, Andrade V, et al; EADB. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet.* 2022;54:412–436. doi: 10.1038/s41588-022-01024-z
206. Sherva R, Zhang R, Sahelijo N, Jun G, Anglin T, Chanfreau C, Cho K, Fonda JR, Gaziano JM, Harrington KM, et al. African ancestry GWAS of dementia in a large military cohort identifies significant risk loci. *Mol Psychiatry.* 2023;28:1293–1302. doi: 10.1038/s41380-022-01890-3
207. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hypponen E, Kuzma E, Llewellyn DJ. Association of lifestyle and genetic risk with incidence of dementia. *JAMA.* 2019;322:430–437. doi: 10.1001/jama.2019.9879
208. Jung SH, Kim HR, Chun MY, Jang H, Cho M, Kim B, Kim S, Jeong JH, Yoon SJ, Park KW, et al. Transferability of Alzheimer disease polygenic risk score across populations and its association with Alzheimer disease-related phenotypes. *JAMA Netw Open.* 2022;5:e2247162. doi: 10.1001/jamanetworkopen.2022.47162
209. Chen Y, Zhang Y, Li S, Zhou L, Li H, Li D, Wang Y, Yang H. Cardiometabolic diseases, polygenic risk score, APOE genotype, and risk of incident dementia: a population-based prospective cohort study. *Arch Gerontol Geriatr.* 2023;105:104853. doi: 10.1016/j.archger.2022.104853
210. Stern Y, MacKay-Brandt A, Lee S, McKinley P, McIntyre K, Razlighi Q, Agarunov E, Bartels M, Sloan RP. Effect of aerobic exercise on cognition in younger adults: a randomized clinical trial. *Neurology.* 2019;92:e905–e916. doi: 10.1212/WNL.0000000000007003
211. Lenze EJ, Voegtle M, Miller JP, Ances BM, Balota DA, Barch D, Depp CA, Diniz BS, Eyler LT, Foster ER, et al. Effects of mindfulness training and exercise on cognitive function in older adults: a randomized clinical trial. *JAMA.* 2022;328:2218–2229. doi: 10.1001/jama.2022.21680
212. Pisani S, Mueller C, Huntley J, Aarsland D, Kempton MJ. A meta-analysis of randomised controlled trials of physical activity in people with Alzheimer's disease and mild cognitive impairment with a comparison to donepezil. *Int J Geriatr Psychiatry.* 2021;36:1471–1487. doi: 10.1002/gps.5581
213. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, et al; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA.* 2019;321:553–561. doi: 10.1001/jama.2018.21442
214. Marcum ZA, Cohen JB, Zhang C, Derington CG, Greene TH, Ghazi L, Herrick JS, King JB, Cheung AK, Bryan N, et al; Systolic Blood Pressure Intervention Trial (SPRINT) Research Group. Association of antihypertensives that stimulate vs inhibit types 2 and 4 angiotensin II receptors with cognitive impairment. *JAMA Netw Open.* 2022;5:e2145319. doi: 10.1001/jamanetworkopen.2021.45319
215. van Dalen JW, Marcum ZA, Gray SL, Barthold D, Moll van Charante EP, van Gool WA, Crane PK, Larson EB, Richard E. Association of angiotensin II-stimulating antihypertensive use and dementia risk: post hoc analysis of the PreDIVA trial. *Neurology.* 2021;96:e67–e80. doi: 10.1212/WNL.00000000000010996
216. den Brok M, van Dalen JW, Abdulrahman H, Larson EB, van Middelaar T, van Gool WA, van Charante EPM, Richard E. Antihypertensive

- medication classes and the risk of work meta-analysis. *J Am Med Dir Assoc*. 10.1016/j.jamda.2020.12.019
217. Haijar I, Okafor M, McDaniel D, Obideen M, AA, Levev A, Goldstein F. Effects of cognitive function in older adults with a randomized clinical trial. *JAMA Netw*. 10.1001/jamanetworkopen.2020.12252
 218. Bosch JJ, O'Donnell MJ, Gao P, Joseph P, Lopez Jaramillo P, Yusuf S. Effects of a tion of both on cognitive and functional al. *JAMA Neurol*. 2023;80:251–259. doi: 10.1001/jamaneuro.2023.12252
 219. Hughes D, Judge C, Murphy R, Loughlin F, J, O'Donnell MJ, Canavan M. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA*. 2020;323:1934–1944. doi: 10.1001/jama.2020.4249
 220. Peters R, Xu Y, Fitzgerald O, Aung HL, Beckett N, Bulpitt C, Chalmers J, Forette F, Gong J, Harris K, et al; Dementia risk REDuCTion for Seniors With Diabetes Mellitus
tenuous glucose monitoring on diabetes: a randomized clinical trial. 10.1001/jama.2020.6928
 232. Tang X, Cardoso MA, Yang J, Zhou control on brain health: meta-analysis tients with type 2 diabetes mellitus. 10.1007/s13300-021-01009-x
 233. Komulainen P, Tuomilehto J, Savonen TA, Hanninen T, Kiviniemi V, Jacobs and cognition in a 4-year randomized Exercise Training (DR's EXTRA). *Am* doi: 10.1093/ajcn/nqah018 (DIRECT) Collaboration. Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis. *Eur Heart J*. 2022;43:4980–4990. doi: 10.1093/eurheartj/ehac584

234. den Brok M, Hoevenaar-Blom MP, Coley N, Andrieu S, van Dalen J, Meiller Y, Guillemont J, Brayne C, van Gool WA, Moll van Charante EP, et al. The effect of multidomain interventions on global cognition, symptoms of de-pression and apathy: a pooled analysis of two randomized controlled trials. *J Prev Alzheimers Dis*. 2022;9:96–103. doi: 10.14283/jpad.2021.53

235. Hafdi M, Hoevenaar-Blom MP, Richard E. Multi-domain interventions for the prevention of dementia and cognitive decline. *Cochrane Database Syst Rev*. 2021;11:CD013572. doi: 10.1002/14651858.CD013572.pub2

221. T, Sarquis-Y, Son S, Montero-M,

Pharmacological treatment of hypertension in people without prior cerebrovascular disease for the prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2021;5:CD004034. doi: 10.1002/14651858.CD004034.pub4

222. Offer A, Arnold M, Clarke R, Bennett D, Bowman L, Bulbulia R, Haynes R, Li J, Hopewell JC, Landray M, et al; Heart Protection Study (HPS), Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), and Treatment of HDL (High-Density Lipoprotein) to Reduce the Incidence of Vascular Events (HPS2-THRIVE) Collaborative Group. Assessment of vascular event prevention and cognitive function among older adults with preexisting vascular disease or diabetes: a secondary analysis of 3 randomized clinical trials. *JAMA Netw Open*. 2019;2:e190223. doi: 10.1001/jamanetworkopen.2019.0223

223. Zhou Z, Ryan J, Ernst ME, Zoungas S, Tonkin AM, Woods RL, McNeil JJ, Reid CM, Curtis AJ, Wolfe R, et al; ASPREE Investigator Group. Effect of statin therapy on cognitive decline and incident dementia in older adults. *J Am Coll Cardiol*. 2021;77:3145–3156. doi: 10.1016/j.jacc.2021.04.075

224. Harvey PD, Sabbagh MN, Harrison JE, Ginsberg HN, Chapman MJ, Manvelian G, Moryusef A, Mandel J, Farnier M. No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized phase 2 and 3 controlled trials: a meta-analysis of individual patient data. *Eur Heart J*. 2018;39:374–381. doi: 10.1093/eurheartj/ehy001

Fraser S. Associations of multidomain interventions with improvements in cognition in mild cognitive impairment: a systematic review and meta-analysis. *JAMA Network Open*. 2022;5:e226744. doi: 10.1001/jamanetworkopen.2022.6744

237. Rovner BW, Casten RJ, Hegel MT, Leiby B. Preventing cognitive decline in Black individuals with mild cognitive impairment: a randomized clinical trial. *JAMA Neurol*. 2018;75:1487–1493. doi: 10.1001/jamaneurol.2018.2513

238. Yaffe K, Vittinghoff E, Dublin S, Peltz CB, Fleckenstein LE, Rosenberg DE, Barnes DE, Balderson BH, Larson EB. Effect of personalized risk-reduction strategies on cognition and dementia risk profile among older adults: the SMART randomized clinical trial. *JAMA Intern Med*. 2024;184:54–62. doi: 10.1001/jamainternmed.2023.6279

239. Tainta M, Ecay-Torres M, de Arriba M, Barandiaran M, Otaegui-Arrazola A, ZAINDU study: a FINGER-like multidomain lifestyle intervention feasibility trial. *Ther*. 2024;16:44. doi: 10.1186/s13195-024-01393-z

240. Zülke AE, Pabst A, Luppa M, Roehr S, Seidling H, Oey A, Cardona MI, Blotenberg I, Bauer A, Weise S, et al. A multidomain intervention against cognitive decline in an at-risk-population in Germany: results from the cluster-randomized AgeWell.de trial. *Alzheimers Dement*. 2024;20:615–628. doi: 10.1093/eurheartj/ehx661

225. Karatasakis A, Danek BA, Karacsonyi J, Rangan BV, Roesle MK, Knickelbine T, Miedema MD, Khalili H, Ahmad Z, Abdullah S, et al. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterol-emia: a meta-analysis of 35 randomized controlled trials. *J Am Heart Assoc*. 2017;6:e006910. doi: 10.1161/JAHA.117.006910

226. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, et al; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med*. 2017;377:633–643. doi: 10.1056/NEJMoa1701131

227. Gencer B, Mach F, Guo J, Im K, Ruzza A, Wang H, Kurtz CE, Pedersen TR, Keech AC, Ott BR, et al; FOURIER Investigators. Cognition After lowering LDL-cholesterol with evolocumab. *J Am Coll Cardiol*. 2020;75:2283–2293. doi: 10.1016/j.jacc.2020.03.039

228. Ying H, Wang J, Shen Z, Wang M, Zhou B. Impact of lowering low-density lipoprotein cholesterol with contemporary lipid-lowering medicines on cognitive function: a systematic review and meta-analysis. *Cardiovasc Drugs Ther*. 2021;35:153–166. doi: 10.1007/s10557-020-07045-2

229. Ryan J, Storey E, Murray AM, Woods RL, Wolfe R, Reid CM, Nelson MR, Chong TT, Williamson JD, Ward SA, et al; ASPREE Investigator Group. Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline. *Neurology*. 2020;95:e320–e331. doi: 10.1212/WNL.0000000000009277

230. Kitt K, Murphy R, Clarke A, Reddin C, Ferguson J, Bosch J, Whiteley W, Canavan M, Judge C, O'Donnell M. Antiplatelet therapy and incident cognitive impairment or dementia-a systematic review and meta-analysis of randomised clinical trials. *Age Ageing*. 2023;52:afad197. doi: 10.1093/ageing/afad197

231. Pratley RE, Kanapka LG, Rickels MR, Ahmann A, Aleppo G, Beck R, Bhargava A, Bode BW, Carlson A, Chaytor NS, et al; Wireless Innovation

241. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.

242. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.

243. Deardorff WJ, Barnes DE, Jeon SY, Boscardin WJ, Langa KM, Covinsky KE, Mitchell SL, Whitlock EL, Smith AK, Lee SJ. Development and external validation of a mortality prediction model for community-dwelling older adults with dementia. *JAMA Intern Med.* 2022;182:1161–1170. doi: 10.1001/jamainternmed.2022.4326

244. Adjoian Mezzaca T, Dodds LV, Rundek T, Zeki Al Hazzouri A, Caunca MR, Gomes-Osman J, Loewenstein DA, Schneiderman N, Elfassy T. Associations between cognitive functioning and mortality in a population-based sample of older United States adults: differences by sex and education. *J Aging Health.* 2022;34:905–915. doi: 10.1177/08982643221076690

245. Jordan BC, Brungardt J, Reyes J, Helmer SD, Haan JM. Dementia as a predictor of mortality in adult trauma patients. *Am J Surg.* 2018;215:48–52. doi: 10.1016/j.amjsurg.2017.07.012

246. Anderson TS, Marcantonio ER, McCarthy EP, Ngo L, Schonberg MA, Herzig SJ. Association of diagnosed dementia with post-discharge mortality and readmission among hospitalized Medicare beneficiaries. *J Gen Intern Med.* 2022;37:4062–4070. doi: 10.1007/s11606-022-07549-7

247. Zuliani G, Gallerani M, Martellucci CA, Reverberi R, Brombo G, Cervellati C, Zuin M, Pistolesi C, Pedrini D, Flacco ME, et al. Dementia and in-hospital mortality: retrospective analysis of a nationwide administrative database of elderly subjects in Italy. *Aging Clin Exp Res.* 2022;34:1037–1045. doi: 10.1007/s40520-021-02021-8

248. De Matteis G, Burzo ML, Della Polla DA, Serra A, Russo A, Landi F, Gasbarrini A, Gambassi G, Franceschi F, Covino M. Outcomes and predictors of in-hospital mortality among older patients with dementia. *J Clin Med*. 2022;12:59. doi: 10.3390/jcm12010059
249. Schmutte T, Olfson M, Maust DT, Xie M, Marcus SC. Suicide risk in first year after dementia diagnosis in older adults. *Alzheimers Dement*. 2022;18:262–271. doi: 10.1002/alz.12390
250. Pinho J, Quintas-Neves M, Dogan I, Reetz K, Reich A, Costa AS. Incident stroke in patients with Alzheimer's disease: systematic review and meta-analysis. *Sci Rep*. 2021;11:16385. doi: 10.1038/s41598-021-95821-x
251. Chen L, Au E, Saripella A. *J Clin Anesth*. 2022;80:110883. doi: 10.1016/j.jclinane.2022.110883
252. Koria LG, Sawan MJ, Redston MR, Gnjjidic D. The prevalence of frailty among older adults living with dementia: a systematic review. *J Am* at end-of-life among Medicare beneficiaries with dementia. *JAMA Netw Open*. 2022;5:e2216260. doi: 10.1001/jamanetworkopen.2022.16260
253. Arighi A, Fumagalli GG, Carandini T, Pietroboni AM, De Riz MA, Galimberti D, Scarpini E. Facing the digital divide into a dementia clinic during COVID-19 pandemic: caregiver age matters. *Neurol Sci*. 2021;42:1247–1251. doi: 10.1007/s10072-020-05009-w
254. Wittenberg R, Knapp M, Hu B, Comas-Herrera A, King D, Rehill A, Shi C, Banerjee S, Patel A, Jagger C, et al. The costs of dementia in England. *Int J Geriatr Psychiatry*. 2019;34:1095–1103. doi: 10.1002/gps.5113
255. Nandi A, Counts N, Broker J, Malik S, Chen S, Han R. *Med Dir Assoc*. 2022;23:1807–1814. doi: 10.1016/j.jamda.2022.01.084
256. Donnell DO, Romero-Ortuno R, Kennelly SP, O'Neill D, Donoghue Lavan A, Cunningham C, McElwaine P, Kenny RA, Briggs R. The

269. Lastuka A, Breshock MR, McHugh TA, Sogge WT, Swart V, Dieleman JL. U.S. dementia care spending by state: 2010-2019. *Alzheimers Dement.* 2024;20:2742–2751. doi: 10.1002/alz.13746
270. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyas T, Scott KW, et al. US health care spending by payer and health condition, 1996-2016. *JAMA.* 2020;323:863–884. doi: 10.1001/jama.2020.0734
255. Lee PH, Yeh TT, Yen HY, Hsu WL, Chiu VJ, Lee SC. Impacts of 'Bermuda Triangle' of orthostatic hypotension, cognitive impairment and reduced mobility: prospective associations with falls and fractures in the Irish Longitudinal Study on Ageing. *Age Ageing.* 2023;52:afad005. doi: 10.1093/ageing/afad005
254. Martinez-Carranza N, Lindqvist K, Modig K, Hedström M. Factors associated with non-walking 4 months after hip fracture: a prospective study of 23,759 fractures. *Injury.* 2022;53:2180–2183. doi: 10.1016/j.injury.2021.10.031

271. Hoffman GJ, Maust DT, Harris M, Ha J, Davis MA. Medicare spending associated with a dementia diagnosis among older adults. *J Am Geriatr Soc*. 2022;70:2592–2601. doi: 10.1111/jgs.17835
272. Coe NB, White L, Oney M, Basu A, Larson EB. Public spending on acute and long-term care for Alzheimer's disease and related dementias. *Alzheimers Dement*. 2023;19:150–157. doi: 10.1002/alz.12657
273. Oney M, White L, Coe NB. Out-of-pocket costs attributable to dementia: a longitudinal analysis. *J Am Geriatr Soc*. 2022;70:1538–1545. doi: 10.1111/jgs.17746
274. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed July 1, 2024.
256. Zhang Y, Ren R, Yang L, Zhang H, Shi Y, Okhravi HR, Vitiello MV, Sanford LD, Tang X. Sleep in Alzheimer's disease: a systematic review and meta-analysis of polysomnographic findings. *Transl Psychiatry*. 2022;12:136.
258. Nabizadeh F, Nikfarjam M, Azami M, Sharifkazemi H, Sodeifian F. Dementia and the risk of periodontitis: a population-based cohort study. *J Dent Res*. 2022;101:270–277. doi: 10.1177/00220345211037220
257. Ma KS, Hasturk H, Carreras I, Dedeoglu A, Veeravalli JJ, Huang JY, doi: 10.1038/s41398-022-01897-y

275. Premraj L, Kannapadi NV, Briggs J, Seal SM, Battaglini D, Fanning J, Suen J, Robba C, Fraser J, Cho SM. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: a meta-analysis. *J Neurol Sci.* 2022;434:120162. doi: 10.1016/j.jns.2022.120162
276. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, Rodrigues NB, Subramaniapillai M, Di Vincenzo JD, Cao B, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. *Brain Behav Immun.* 2022;101:93–135. doi: 10.1016/j.bbi.2021.12.020
259. Jennings LA, Laffan AM, Schlissel AC, Colligan E, Tan Z, Wenger NS, Reuben DB. Health care utilization and cost outcomes of a comprehensive dementia care program for Medicare beneficiaries. *JAMA Intern Med.* 2022;100:100–107. doi: 10.1016/j.jocn.2022.04.009
260. Levine DA, Galecki AT, Morgenstern LB, Zahuranec DB, Langa KM, Kabeto MU, Okullo D, Nallamothu BK, Giordani B, Reale BK, et al. Preexisting mild cognitive impairment, dementia, and receipt of treatments for acute ischemic stroke. *Stroke.* 2021;52:2134–2142. doi: 10.1001/jamainternmed.2018.5579

277. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, Lange F, Andersson JLR, Griffanti L, Duff E, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature*. 2022;604:697–707. doi: 10.1038/s41586-022-04569-5
278. Liu YH, Chen Y, Wang QH, Wang LR, Jiang L, Yang Y, Chen X, Li Y, Cen Y, Xu C, et al. One-year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China: a longitudinal cohort study. *JAMA Neurol*. 2022;79:509. doi: 10.1001/jamaneurol.2022.0461
279. Park HY, Song IA, Oh TK. Dementia risk among coronavirus disease survivors: a nationwide cohort study in South Korea. *J Pers Med*. 2021;11:1015. doi: 10.3390/jpm11101015
261. Matsugaki R, Muramatsu K, Fushimi K, Matsuda S. Dementia and acute care of ischemic stroke in Japan: a retrospective observational study using the Japanese Diagnosis Procedure Combination database. *Geriatr Gerontol Int*. 2023;23:270–274. doi: 10.1111/ggi.14560
262. Callisaya ML, Purvis T, Lawler K, Brodtmann A, Cadilhac DA, Kilkenney MF. Dementia is associated with poorer quality of care and outcomes after stroke: an observational study. *J Gerontol A Biol Sci Med Sci*. 2021;76:851–

280. Wang L, Davis PB, Kaelber DC, Xu R. COVID-19 breakthrough infections and hospitalizations among vaccinated patients with dementia in the United States between December 2020 and August 2021. *Alzheimers Dement*. 2023;19:421–432. doi: 10.1002/alz.12669
281. Damayanthi HDWT, Prabani KIP, Weerasekara I. Factors associated for mortality of older people with COVID 19: a systematic review and meta-analysis. *Gerontol Geriatr Med*. 2021;7:23337214211057392. doi: 10.1093/gerona/glaa139
263. Lee YJ, Johnston DM, Reuland M, Lyketsos CG, Samus Q, Amjad H. Reasons for hospitalization while receiving dementia care coordination through maximizing independence at home. *J Am Med Dir Assoc*. 2022;23:1573–1578.e2. doi: 10.1016/j.jamda.2021.12.044

282. Wang SM, Park SH, Kim NY, Kang DW, Na HR, Um YH, Han S, Park SS, Lim HK. Association between dementia and clinical outcome after COVID-19: a nationwide cohort study with propensity score matched control in South Korea. *Psychiatry Investig.* 2021;18:523–529. doi:
264. Mitsutake S, Ishizaki T, Tsuchiya-Ito R, Furuta K, Hatakeyama A, 10.30773/pi.2021.0064
Sugiyama M, Toba K, Ito H. Association of cognitive impairment cohort study of 8897 older patients. *Alzheimers Dement (Amst).* 2021;13:e12147.
severity with potentially avoidable readmissions: a retrospective doi:

283. July J, Pranata R. Prevalence of dementia and its impact on mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. *Geriatr Gerontol Int*. 2021;21:172–177. doi: 10.1111/ggi.14107
- 10.1002/dad2.12147
284. Liu N, Sun J, Wang X, Zhao M, Huang Q, Li H. The impact of dementia on the clinical outcome of COVID-19: a systematic review and meta-analysis. *J Alzheimers Dis*. 2020;78:1775–1782. doi: 10.3233/JAD-201016
265. Lin PJ, Zhu Y, Olchanski N, Cohen JT, Neumann PJ, Faul JD, Fillit HM, Freund KM. Racial and ethnic differences in hospice use and hospitalizations

17. CONGENITAL DEFECTS AND

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Congenital Cardiovascular Defects

ICD-9 745 to 747; ICD-10 Q20 to Q28

CCDs, which arise from abnormal or incomplete formation of the heart, valves, and blood vessels, are one of the most common birth defects worldwide.^{1,2} CCDs range in severity from minor abnormalities that spontaneously resolve or are hemodynamically

266 461–331 437; 60%) of

This figure represents a fairly

32nd Bethesda Conference

800 000)¹² and estimates

estimate. 1.4 million adults and

reflecting a change in GBD

prior estimates. every person

less of type or severity, was

across their life span. In 2017,

more nuanced approach that allowed for “cure” of

simple

lesions such as ASDs that undergo spontaneous

closure

insignificant to complex malformations,

including absent, hypoplastic, or atretic

portions of the heart. There is significant

variability in the presentation of CCDs,

resulting in heterogeneous morbidity,

mortality, and health care costs across the

life

for which there was no known associated morbidity or mortality, thus lowering the overall population considered to be living with a CCD.¹¹ With the same modeling strategy, 2017 estimates place the global prevalence of CCDs at 157 per 100 000 (95% CI, 143–172), with the highest prevalence estimates in countries with a low sustainable development index (238 per 100 000 [95% CI, 216–261]) and the lowest prevalence in those with a high-middle or high sustainable development index (112 per 100 000 [95% CI, 102–114] and 135 per 100 000 [95% CI, 125–145], respectively).¹¹

span. Some types of CCDs are associated with diminished quality of life,³ on par with what is **Birth Prevalence**

chronic pediatric health conditions,⁴ as well as deficits in cognitive functioning^{5,6} and neurodevelopmental outcomes.^{7,8} However, health outcomes generally continue to improve for CCDs, including survival.⁹

Overall Life Span Prevalence

It is estimated that 13.3 (95% CI, 11.5–15.4) million people globally were living with CCDs in 2019.¹⁰ CCD prevalence increased by 28% between 1990 and 2019, driven largely by increases in the number of adolescents and younger adults (15–49 years of age increased by 42%) and middle-aged adults (50–69 years of age increased by 117%) living with CCDs. The change was greatest in low- and middle-income

countries, attributed to both increasing population growth and improving survival.

In 2017, the all-age prevalence of CCDs in the United States was estimated at 466 566 (95% CI, 429 140–505 806) individuals, with 279 320 (95% CI,

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical

- In high-income North America, including the United States, the birth prevalence of CCDs is estimated to be 12.3 per 1000 (95% CI, 11.1–13.8) according to 1990 to 2017 data.¹¹

Birth Prevalence of Specific Defects

- The National Birth Defects Prevention Network showed the average birth prevalence of 29 selected major birth defects from 39 population-based birth defects surveillance programs in the United States from 2010 to 2014.¹⁴ These data indicated the following prevalence: atrioventricular septal defect (0.54 per 1000 births), coarctation of the aorta (0.56 per 1000 births), truncus arteriosus (0.067 per 1000 births), double-outlet right ventricle (0.17 per 1000 births), HLHS (0.26 per 1000 births), other single ventricle (0.079 per 1000 births), interrupted aortic arch (0.062 per 1000 births), pulmonary valve atresia/stenosis (0.97 per 1000 births), TOF (0.46 per 1000 births), total anomalous pulmonary venous connection (0.14 per 1000 births), and TGA (0.38 per 1000 births).
- Bicuspid aortic valve occurs in 13.7 of every 1000 people; these defects vary in severity, but aortic stenosis and regurgitation can progress throughout life.¹⁵

Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be

Risk Factors

used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- Numerous nongenetic risk factors are thought to contribute to CCDs.¹⁶

- Maternal exposure to first-trimester anesthesia (between 3 and 8 weeks after conception) may be associated with 1.50 times greater risk of CCDs at birth (95% CI, 1.11–2.03).¹⁷
- Maternal exposure to teratogens may be associated with CCDs at birth. In an Iranian cohort, exposure to teratogens in the first trimester of pregnancy (hair color, canned foods, detergents) increased
- Maternal lifestyle factors have been associated with increased risk of CCDs.
 - Periconceptional cigarette smoking^{19–22} 1 month before conception through 3 months after conception is associated with an increased odds of ASD (OR, 1.7 [95% CI, 1.5–2.0]), truncus arteriosus (OR, 1.7 [95% CI,

HD.²⁸ According to a population cohort study of 2 050 491 singleton infants born in Sweden between 1992 and 2012, maternal obesity was associated with a greater odds of CCD, with a clear dose-response risk rate between categories of obesity including normal weight (BMI 18.5–<25 kg/m²), overweight (BMI 25–<30 kg/m²), obese class 1 (1.0–2.7]), any septal defect (OR, 1.5 [95% CI, 1.3–1.7]), double-outlet right ventricle (OR, 1.3 [95% CI, 1.1–2.2]), peri-membranous VSD (OR, 1.3, [95% CI, 1.0–1.4]), atrioventricular septal defect (OR, 1.3 [95% CI, 1.0–1.9]), right-sided obstructive lesion (OR, 1.2 [95% CI, 1.0–1.4]), and pulmonary valve stenosis

35 to <40 kg/m² was associated with an OR of 1.51 (95% CI, 1.08–2.12), and a BMI ≥40 kg/m² was associated with an OR of 1.85 (95% CI, 1.11–3.08) of TGA. Similarly, a BMI of 30 to <35, 35 to <40, and ≥40 kg/m² was associated with an OR of 1.32 (95% CI, 1.09–1.58), 1.60 (95% CI, 1.19–2.15), and 1.87 (95% CI, 1.19–2.95) for aortic arch defect (eg, aortic arch hypoplasia), respectively. A BMI of 30 to <35 kg/m² was associated with an OR of 1.64 (95% CI, 1.13–2.38) of single-ventricle heart. Maternal diabetes, including type 1, type 2, and gestational diabetes, is associated with fetal CCDs (OR, 1.94 [95% CI, 1.59–2.35]).^{29,30}

There was not a significant association between this exposure and truncus arteriosus (OR, 1.2 [95% CI, 0.7–2.1]) and Ebstein anomaly (OR, 1.1 [95% CI, 0.7–1.8]).²³ Exposure to secondhand smoke also

has been implicated as a risk factor for CCDs.²¹

– Smoking and binge drinking together may also increase risk. Mothers who smoke and report any binge drinking in the 3 months before pregnancy may be at increased risk of giving birth to a child with a CCD compared with mothers who report only any binge drinking (aOR, 12.65 [95% CI, 3.5–45.2] versus 9.45 [95% CI, 2.5–35.3]).²⁴•

Maternal health factors have been associated with increased risk of CCDs.²⁵

– Higher maternal BMI has been identified as a risk factor for CCDs in some but not all studies. A systematic review including 8 studies that assessed the relationship between maternal obesity and CCDs found a significant association between maternal obesity and CCDs in 5 studies, whereas 3 studies found no association between CCDs and maternal obesity.²⁶ A second meta-analysis (14 studies) found a dose-response effect between overweight, moderate obesity, and severe obesity and a pregnancy with a CCD (pooled ORs: OR, 1.08 [95% CI, 1.02–1.15]; OR, 1.15 [95% CI, 1.11–1.20]; and OR, 1.39 [95% CI, 1.31–1.47], respectively), an association that persisted when controlling for the presence of

- Approximately 2670 (95% UI, 1795–3795) cases of CHDs could potentially be prevented annually if all females in the United States with pregestational diabetes achieved glycemic control before pregnancy.³¹ Uncontrolled prenatal diabetes with an HbA1c >8% was associated with a 4-fold greater risk for CCD.³²
- By 2007, folate deficiency was considered a well-documented risk for CCDs.³³ However, a more recent systematic review did not identify a relationship between folate deficiency and CCDs.³⁴—
- Maternal viral infections associated with CCDs include hepatitis B virus (OR, 2.21 [95% CI, 1.66–2.95]), coxsackievirus B (OR, 2.21 [95% CI, 1.63–3.00]), human cytomegalovirus (OR, 3.12 [95% CI, 2.44–3.98]), and rubella (OR, 2.62 [95% CI, 1.95–3.51]).³⁵
- Maternal medications associated with CCDs include receipt of antihypertensive agents (ACE inhibitors, antiadrenergic agents, β -blockers, calcium channel blockers, diuretics) during the first trimester with variable odds, depending on the lesion type and overall greater odds of CHD (OR, 2.03 [95% CI, 1.46–2.84]).¹⁶
- Additional medications associated with a greater odds of CCD if taken by females during the first trimester of pregnancy include any antibacterial agents, sulfonamides, nitrofurantoin, quinolones, urinary antiseptic, erythromycin, insulin, fertility drugs, clomiphene, chorionic gonadotropin, non-diabetes.²⁷
- A 2019 study has further highlighted the relationship between maternal obesity and congenital

steroidal anti-inflammatory drugs, benzodiazepines, lithium, anticonvulsants, selective serotonin

reuptake inhibitors (eg, antidepressants).¹⁶

- Maternal factors associated of CCD included maternal health condition 6 months nancy (OR, 1.5 [95% CI, history of CCD (OR, 2.4 [95% CI,
 - Paternal occupational associated with fetal CCDs.³⁶
 - More specifically, there are of fetal TOF attributable to paternal anesthesia (3.6%), coarctation of the aorta to parental sym- pathomimetic medication exposure (5.8%), VSDs to paternal pesticide exposure (5.5%), and HLHS to paternal solvent exposure (4.6%).³⁷
 - More recent data from the Japan Environment and Children's Study identified higher risks for

screening for critical CCDs a significant decrease (33.4% 50.3%) in infant cardiac 2013 compared with states

- Reports outside of the United high-income settings have mance of pulse oximetry critical CCDs.⁴⁹ with a pulse oximetry screening for and 99.7%, respectively.

CCDs related to paternal exposure to engine oil (OR, 1.68 [95% CI, 1.02–2.77]), lead-like sol- der (OR, 2.03 [95% CI, 1.06–3.88]), lead-free solder (OR, 3.45 [95% CI, 1.85–6.43]), and microbes (OR, 4.51 [95% CI, 1.63–12.49]).³⁸

- A more recent retrospective cohort study of CCD live births between 2004 and 2018 in Massachusetts did not find a reduction in delayed diagnosis once pulse oximetry screening became mandatory.⁵⁰ However, in this same study, prenatal screen-ing was associated with improved diagnosis rates. Between 2004 and 2018, prenatal diagnosis of CCD increased by 65% ($P_{\text{trend}} < 0.001$) and delayed diagnosis decreased by 56% ($P_{\text{trend}} = 0.021$).

Social Determinants of Health/Health Equity

Multiple studies assessing the impact of social determi-

nants of health on CCD incidence and prevalence,

Screening

It has been more than a decade since pulse oximetry screening for CCDs was instituted as part of the uniform US screening panel for newborns and endorsed by the AHA and the American Academy of Pediatrics.^{39,40}

At present, all 50 states and the District of Columbia have laws or regulations mandating newborn screening

for identification of previously unidentified CCDs,⁴¹ and several studies have demonstrated the benefit of such screening.^{42–44} However, developmental changes in skin

- A 2021 scoping review showed that lower SES and poverty were associated with higher incidence and prevalence of CCDs; reported associations between lower SES and parental education attainment and prenatal diagnosis of CCDs suggest lower rates of prenatal diagnosis in association with stated risk factors, as well as increased infant mortality, adverse postsurgical outcomes, decreased health care access, and impaired neurodevelopmental physiology and pigmentation require further study because of the potential for overestimation of oxygen saturation in babies of races with darker skin tone (Indian, outcome.⁵¹

- The importance of a healthy maternal-fetal environment and social deprivation on CCD incidence cannot be overemphasized. Among >2.4 million Black).⁴⁵
 - A simulation model estimates that screening the entire United States for critical CCDs with pulse oximetry would uncover 875 infants (95% UI, 705–1060) who have nonsyndromic CCDs versus 880 (95% UI, 700–1080) false-negative screenings (no

infants born in California, the odds of CCD were 31% greater among infants born in neighborhoods in the lowest compared with the highest SES quartile (OR, 1.31 [95% CI, 1.21–1.42]). The odds of CCD were 1.23 times (95% CI, 1.15–1.31;

CCD).⁴⁶
neighbor-
P<0.001) greater among infants born in
for detection of critical CCDs with
a false-positive rate of 0.14%
(95% CI, 0.07%–0.22%).⁴⁷ On the
basis of these

- A meta-analysis of 19 studies that included 436 758 newborns found that pulse oximetry had a sensitivity of 76.3% (95% CI, 69.5%–82.0%) and a specificity of 99.9% (95% CI, 99.7%–99.9%)

hoods with the greatest exposure to environmental pollutants (versus the lowest quartile exposure group; OR, 1.23 [95% CI, 1.15–1.31]). Together, the odds of CCD were the highest among infants in the highest quartile for environmental exposure and social deprivation (OR, 1.48 [95% CI, 1.32–1.66]; $P < 0.0001$).⁵²

data, among healthy-appearing late-preterm or full-term infants, pulse oximetry screening will detect 5 of 6 per 10 000 with critical CCDs and falsely identify an additional 14 per 10 000 screened.

- An observational study demonstrated that statewide implementation of mandatory policies for newborn

- In Ontario, CCDs were more common among children of mothers who lived in neighborhoods in the lowest compared with the highest income quartile (OR, 1.29 [95% CI, 1.20–1.38]) and neighborhoods with the lowest compared with the highest

percentage of individuals with university or advanced degrees (aOR, 1.34 [95% CI, 1.24–1.44]).⁵³ Rurality and low material wealth are risk factors for CCD. In a cohort study of 798 173 singleton births, infants living in the most socially deprived neighborhoods (SDI quintile 5) had an 18% increase in the odds of CHD (aOR, 1.18 [95% CI, 1.1–1.26]) compared with those living in quintile 1.⁵⁴ Infants living in rural counterparts living in urban areas.

- Maternal exposure to air pollutants may also increase the risk of CCDs. A systematic review and meta-analysis including 26 studies showed that risk of TOF (OR, 1.21 [95% CI, 1.04–1.41]) was associated with high versus low carbon monoxide exposure, increasing risk of ASD was

type, geographic region, or low versus high procedure complexity.

- Adolescent and adults with CHD residing in the most deprived neighborhoods had higher rates of inpatient admission, ED visits, and outpatient visits.

Among children and adults with CCD residing within the most compared with the least deprived communities, there

proportionally associated with increasing exposure to particulate matter ($\leq 10 \mu\text{m}$) and ozone (OR, 1.04 per 10 $\mu\text{g}/\text{m}^3$ [95% CI, 1.00–1.09] and 1.09 per 10 $\mu\text{g}/\text{m}^3$ [95% CI, 1.02–1.17], respectively), and increased risk of aortic coarctation was associated with high versus low nitrogen dioxide exposure (OR, 1.14 [95% CI,

- 1.47–2.34]), and a 23% greater odds of an outpatient clinic visit (OR, 1.23 [95% CI, 1.11–1.37]).^{.60}• The relationship between neighborhood household income and mortality among children with CHD is nonlinear. Higher risk for mortality exists at lower and higher income levels. The risk of death nadirs of \$72 000 and \$80 000.^{.61}
- Lower maternal education is associated with higher infant mortality in the first year among infants with critical CHDs (OR, 1.32 [95% CI, 1.2–1.45]).^{.58}
 - Lower socioeconomic quartile was associated with decreased rates of prenatal detection of HLHS and TGA, particularly among children with TGA (1.02–1.26]).^{.55}
 - Among infants with HLHS in the Metropolitan poverty cen-sus tracts (9%) compared with those Atlanta Congenital Defects Program, survival rates were worse for those residing in high- residing in low-poverty census tracts (25%; $P<0.001$).^{.56}
- Novel

(OR for socioeconomic quartile 1, 0.78 [95% CI, 0.64–0.85] compared with quartile 4). Hispanic ethnicity (RR, 0.85 [95% CI, 0.72–0.99]) and rural residence (RR, 0.78 [95% CI, 0.64–0.95]) were also associated with lower rates of prenatal detec-

technology such as remote cardiac monitoring during the interstage period (the time between the first and second palliative surgeries) might help to reduce disparities in outcome. Among families from low, middle, and high socioeconomic groups enrolled in a Cardiac High Acuity Monitoring Program, survival was no different among the highest and middle SES groups:

tion of TGA.⁶²

mortality OR of 0.997 (95% CI, 0.30–3.36) and OR of 1.7 (95% CI, 0.73–3.94), respectively.⁵⁷• Neurodevelopmental outcomes and quality of life measures were lowest among children living in poverty, children of parents with low educational attainment, and children of parents with transportation

- Gaps in care are common among youths with CCDs. According to results from a single-center study, roughly one-third of youths with CCDs experience a >3-year gap in clinical care.⁶³ Factors associated with gaps in clinical care include 14 to 29 years of age (OR, 1.20 [95% CI, 1.06–1.37]), Black race (OR, 1.50 [95% CI, 1.15–1.97]), distance of >150 miles from the hospital (OR, 1.81 [95% CI, 1.00–3.27]), mother's education of high school or less (OR, 1.17 [95% CI, 1.03–1.34]), and low neighborhood-level opportunity (eg, high deprivation; OR, 1.22 [95% CI, 1.02–1.45]).⁵¹
- SES is a major contributor to identified differences in infant mortality among infants with critical CCDs, with greater mortality among socioeconomically deprived patients (OR, 1.7 [95% CI, 1.4–2.07]).⁵⁸
- The income status of the neighborhood in which a child lives is associated with increased risk for
 - Individuals with CCDs who reside within higher-death after congenital heart surgery and resource use.⁵⁹ Among patients undergoing cardiac surgery, children from the lowest neighborhood income quartile versus the highest had a 1.31 times increased mortality risk (OR, 1.21 [95% CI, 1.14–1.51]) after cardiac surgery independently of age, race, insurance

deprivation communities are more likely to have had no health care visits within a 12-month period (OR, 1.5 [95% CI, 1.1–2.1]), more emergency department visits within a 12-month period (OR, 1.6 [95% CI, 1.1–2.3]), more hospitalizations within a 12-month period (OR, 1.6 [95% CI, 1.1–2.3]), and >1 cardiac comorbidity (OR, 1.8 [95% CI, 1.2–2.7]).⁶⁴

Genetics and Family History

- Eight percent to 10% of CCDs can be attributed to chromosomal aberrations (eg, DiGeorge syndrome, Down syndrome, Turner syndrome) and 5% to 15%

to single-nucleotide or variants.⁶⁵

- CCDs can have a heritable tal consanguinity is a known greater concordance of CCDs dizygotic twins.⁶⁶ A report data showed that ticularly increased risk for 9.2–14.5%).⁶⁷

- Among parents with ASD or VSD.

3.7%, respectively, have children who are similarly affected, 21 times the estimated population frequency.⁶⁸ However, the majority of CCDs occur in families with no other history of CCDs, which supports the possibility of de novo genetic events. In fact, a large study of next-generation sequencing in CCDs suggests that 8% of cases are attributable to de novo variation.⁶⁹

- Large chromosomal abnormalities are found in 8% to 10% of individuals with CCDs.⁶⁹ For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.⁷⁰ The specific genes responsible for CCDs that are disrupted by these abnormalities are difficult to identify.

study of nonsyndromic TOF in found rare variants in 7% of patients with TOF.⁷⁹ A including 1025 conotruncal LV obstructive tract defect conotruncal defect cases, and intronic variants in the conotruncal defects; in meta-wide significant association aenic SNP associated with LV

Studies suggest that *DSCAM* and *COL6A* contribute to Down syndrome–associated CCDs.⁷¹

- Copy number variants contribute to 3% to 25% of CCDs that occur as part of a syndrome and to 3% to 10% of isolated CCDs and have been shown to be overrepresented in larger cohorts of patients with specific forms of CCDs.⁷² The most common copy number variant is del22q11, which encompasses the *TBX1* (T-box transcription factor) gene

Whole-genome sequencing has identified additional genetic loci for CCDs. In a study of whole-genome sequencing in 749 CCD case-parent trios with 1611 unaffected trios, a burden of de novo noncoding variants was identified in cases compared with controls, including in established CCD genes (*PTPN11*, *NOTCH1*, *FBN1*, *FLT4*, *NR2F2*, *GATA4*), with higher representation of variants in RNA-binding-protein regulatory sites.⁸¹ These results suggest that non-coding de novo variants play a significant role in CCDs in addition to coding de novo variants.

- Human induced pluripotent stem cell-derived cardiomyocyte-based experiments examining the role of 6590 noncoding de novo variants revealed that 403 noncoding de novo variants affect cardiac regulatory activity through predominantly increasing enhancer activity.⁸²

- A human induced pluripotent stem cell study investigating the role of haploinsufficiency of *TBX5*, a transcription regulator, in the development of CCD revealed a dose-sensitive requirement of *TBX5* for ventricular myocyte differentiation, highlighting the role of *TBX5* haploinsufficiency in the development

and presents as DiGeorge syndrome and velocardiofacial syndrome. Others include del17q11, which causes William syndrome.⁷³ 5% of CCDs⁶⁹ and include variants in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX2*, *TBX3*, *TBX5*, *GATA4*, and *MEF2*),^{73,75,76} *ZIC3*, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related *NOTCH* signaling genes.⁷⁷

- De novo variants have been reported in ≈8% of patients with CCDs (≈3% in isolated CCDs and ≈28% in those with extracardiac features along with CCDs).⁶⁹ Carriers of de novo variants also have been reported to have worse transplantation-free survival and a longer extubation duration.⁷⁴

- Point variants in single genes are found in 3% to

- Recently, in addition to 14 previously recognized genes associated with CCDs, 7 new genes (*FEZ1*, *MYO16*, *ARID1B*, *NALCN*, *WAC*, *KDM5B*, and *WHSC1*) have been identified as being associated with CCDs.⁸⁴ A recent GWAS in patients of European ancestry with CCDs has identified *MACROD2*, *GOSR2*, *WNT3*, and *MSX1* to have an essential role in embryonic and postnatal cardiac morphogenesis and to contribute to the development of structural cardiac defects.⁸⁵
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.⁷³ GWASs and mechanistic studies have supported a causal role of *WNT5A* in TGA and *MUC4* in bicuspid aortic valve
- Consortia studies have allowed analysis of specific subtypes of CCDs through aggregation across centers. For example, a genome-wide study of congenital heart defects identified 8 candidate genes (*ARF5*, *EIF4E*, *KPNA1*, *MAP4K3*, *MBNL1*, *NCAPG*, *NDFUS1*, and *PSMG3*), 4 of which had not previously been associated with heart development.⁷⁸ Another

disease.^{86,87}

- Complications related to CCDs also may have a genetic component; whole-exome sequence study identified *SOX17* as a novel candidate gene for PAH in patients with CCDs.⁸⁸
- Genetic variants associated with CCDs may also occur within cancer risk genes.⁸⁹

- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,⁷³ but it should be offered to patients with multiple congenital abnormalities or congenital syndromes (including CCD lesions associated with a high prevalence of 22q11 deletion or DiGeorge syndrome), and it can be considered in patients with a family history, in those with developmental delay, and in patients with CCDs and extracardiac manifestations.^{12,90} even lower in nonfamilial disease.^{91,92} Use of whole-exome genetic testing has been shown to improve rates of detection.⁹³
- A Pediatric Cardiac Genomics Consortium has been developed to provide and better understand phenotype and genotype data from large cohorts of patients with CCDs.⁹⁴

years of age), and 1.2% (95% CI, 0.8%–1.7%) for adults (>18 years of age).¹⁰⁰

- Another analysis of mortality after CCD surgery, culled from the US-based multicenter data registry of the Pediatric Cardiac Care Consortium, demonstrated that although standardized mortality ratios continue to decrease, increased mortality in patients with CCDs remains compared with the general

(See Table 17-1 and Charts 17-1 through 17-4)

- In 2017, CCDs were among the top 8 causes of infant mortality in all global regions.¹¹
- In 2022, mortality related to CCDs was 3213 deaths (Table 17-1) in the United States, a 5.2% increase from the number of deaths in 2012 (unpublished NHLBI tabulation using NVSS⁹⁵).
 - CCDs (ICD-10 Q20–Q28) were the most common

Mortality

- In Mexico, 70 741 deaths were attributed to CCDs during the years 2000 to 2015, with the standardized mortality rates increasing from 3.3 to 4 per 100 000 individuals and mortality rates increasing per 100 000 live births.¹⁰²
- Analysis of the NIS database of 20 649 neonates with HLHS showed a 20% decrease in mortality for neonates with HLHS between the time periods of 1998 to 2005 and 2006 to 2014 (95% CI, 25.3%–20.6%; $P=0.001$), despite the later cohort having more comorbidities, including prematurity and chromosomal abnormalities, among others.¹⁰³
- A meta-analysis of outcomes for 848 patients with heterotaxy who underwent a Fontan procedure before May 2018 showed survival rates at 1, 5, and 10 years to be 86% (95% CI, 79%–91%), 80% (95% CI, 71%–87%), and 74% (95% CI, 59%–85%), respectively.¹⁰⁴
- cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99) in 2022; 23.0% of infants who died of a birth defect had a heart defect (*ICD-10* Q20–Q24; unpublished NHLBI tabulation using

- Trends in overall age-adjusted death rates attributable to CCDs showed a decline from 1999 to 2017 with a relative plateau between 2017 and 2022 NVSS⁹⁵).
- In 2022, the age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.0, which is the same as it was in 2012 (unpublished NHLBI tabulation using CDC WONDER⁹⁶).
- (Chart 17-1); this varied by race, ethnicity, and sex
- Death rates attributed to CCDs decrease as gestational age advances to 40 weeks.⁹⁷ In-hospital mortality of infants with a major CCD is independently associated with late PTB (OR, 2.70 [95% CI, 1.69–4.33]) compared with delivery at later gesta-

(Charts 17-2 and 17-3). During this time, there was an overall decline in the age-adjusted death rates attributable to CCDs in NH Black people, NH White people, and Hispanic people (Chart 17-2). Although there was variability by race, death rates generally declined in both males and females (Chart 17-3) and in the groups 1 to 4, 5 to 14, 15 to 24, and ≥ 25 years of age (Chart 17-4) in the United States, although 2017 to 2022 showed a relative plateau

tional ages.⁹⁸

- Analysis of the STS Congenital Heart Surgery Database, a voluntary registry with self-reported data from 116 centers performing CCD surgery (112 based in 40 US states, 3 in Canada, and 1 in Turkey),⁹⁹ showed that of 31 102 analyzable CCD surgeries in 2018, there were 662

in trends.

mortalities among the 25 608 patients included (2.5% [95% CI, 2.3%–2.7%]). For this same time period (2018), the mortality rate was 6.9% (95% CI, 6.2%–7.8%) for neonates, 2.4% (95% CI, 2.1%–2.8%) for infants, 1.1% (95% CI, 0.9%–1.3%) for children (1–18

- CCD-related mortality varies substantially by age, with children 1 to 4 years of age demonstrating higher mortality rates than any age group other than infants from 1999 to 2022 (Chart 17-4).
- The US 2022 age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.2 for NH White males, 1.4 for NH Black males, 0.9 for Hispanic males, 0.6 for NH Asian males, 0.9 for NH White females, 1.2 for NH Black females, 0.8 for Hispanic females, and 0.5 for NH Asian females (Table 17-1). Infant (<1 year of age) mortality rates

were 29.2 for NH White infants, 18.6 for NH Asian Hispanic infants (unpublished using CDC WONDER⁹⁶).

- Prenatal diagnosis can help to rates associated with CCDs, has not been consistently mortality rates among such as HLHS.¹⁰⁵ Even prenatally, greater distance

and cardiac surgical center (>90 miles) has been associated with greater mortality. Time required to drive from the birth center to the cardiac surgical center of <10, 10 to 90, and >90

- The personality type of adults associated with mortality. National Congenital Corvita D (distressed) personality had for all-cause mortality. After adults with CCDs and type D vival rate of 82% versus 87% type D personality
- Institution of an IHM for infants be beneficial for reducing minutes has been associated with 21%, 25.2%, and 39.6% mortality,

Data from the National Pediatric Cardiology Quality Improvement Collaborative have indicated a >40% reduction in interstage 1 mortality, reducing mortality to <2%, in the current era, after changes in practice such as institution of IHM.¹¹² According to a single-

respectively.
com-

- Multiple pregnancies versus singleton pregnancy are associated with higher mortality during the first year of life among infants with critical congenital HD (1.61 [95% CI, 1.042–2.5]).⁵⁸
- Efforts have been made to link data from multiple sources for the purpose of providing risk-adjusted outcome, resource use, health expenditure, and

center retrospective study, institution of an IHM

health disparity–related data for patients <18 years of age with CCDs. The New York Congenital Heart Surgeons Collaborative for Longitudinal Outcomes and Utilization of Resources has linked locally held

pared with a historical control was associated with an average 29% lower predicted probability of interstage death (adjusted probability, -0.29 [95% CI, -0.52 to -0.57]; $P=0.015$).¹¹³ However, the sole benefit of IHM remains a major research gap; no RCTs have assessed the role that IHM plays in improvement in interstage mortality and morbidity, and IHM may be only 1 component of the many factors (eg, improved discharge process, care coordination, nutrition) contributing to improved outcomes.^{112,113}

data from 10 of 11 New York congenital heart centers to Medicaid claims data. In total,

Complications

and 10.0% of children died at 3, 5, and 10 postoperative years, respectively.¹⁰⁶

- For adults with CCDs, both the number of instances of clinic nonattendance (HR, 1.08 [95% CI, 1.05–1.12 per clinic nonattendance];

$P<0.001$) and the ratio of clinic nonattendance to follow-up period (HR, 1.23 [95% CI, 1.04–1.44 per clinic nonattendance per year]; $P=0.013$) are independent predic-

Long-term effects of CCDs include arrhythmias, IE, and HF. Adults with CCDs who survive to 50 years of age have a significant chance of experiencing physical and mental health complications.^{114–116}

- Individuals with CCDs are at increased risk of AF.
In an analysis in Sweden including 21 982 patients with CCDs and 219 816 control patients, the risk of developing AF was 22 times higher (HR, 22.0 [95% CI, 19.3–25.1]) in those with CCDs compared with disease-related outcomes.¹⁰⁷
- Survival and health-related quality of life among individuals with CCDs are affected by genetic, epigenetic, environment, intervention-related, and • According to data from the National Pediatric

control patients without congenital HD.¹¹⁷ By 42 years of age, ≈8% of patients with CCDs had been diagnosed with AF. Macroreentrant atrial tachycardia is very frequent in adults with congenital HD.¹¹⁸ HF rates are 40%, 25%, and 50% among TOF,

Cardiology

Quality

Improvement

Collaborative

coarctation, and

Phase II registry, factors such as gestational age <37 weeks, birth weight <2.5 kg, secondary cardiac lesion, extracardiac anomaly, or genetic syndrome are associated with worse survival.¹⁰⁹ Although the presence of a single high-risk diagnosis is not associated with decreased survival, an incremental increase in the number

of high-risk diagnoses is associated with reduced survival to a first birthday (OR, 0.23 [95% CI, 0.15–0.36]). The presence of 3 to 5 high-risk diagnoses is associated with an even greater odds of mortality (OR, 0.17 [95% CI,

vors, respectively.¹¹⁶

• Arrhythmia is very common and occurs among 35%, 32%, and 60% of TOF, coarctation, and TGA/Fontan-repaired adult survivors, respectively.¹¹⁶ • Adults with CCDs are at risk for reoperation, congestive HF, cerebrovascular events, and subacute bacterial endocarditis. Estimated reoperation rates among adults with TOF, coarctation of the aorta, and TGA and Fontan are 40%, 50%, and 10%, respectively.¹¹⁶ • Chronic hypoxia, neurohormonal derangements, intraglomerular hemodynamic shifts, ischemia, and nephrotoxins place individuals with CCD at 0.10–0.30]).

increased risk for CKD.¹¹⁹ According to data from the Swedish National Patient Register and the Cause of Death Register, the risk of CKD is 6.4 times higher in patients with CCD than control subjects (OR, 6.4 [95% CI, 5.65–7.27]).¹²⁰

- Growth failure, in both weight and length, is common among patients with HLHS.¹²¹ According to a secondary analysis of data from a prospective cohort study of growth physiology compared with healthy infants had lower weight Z scores at 3 months (−1.64 versus −0.22; $P<0.0001$), 6 months (−1.30 versus −0.09; $P<0.0001$), 9 months (−0.76 versus 0.06; $P=0.001$), and 12 months (−0.45 versus 0.20; $P=0.005$).¹²² Analysis of length Z scores demonstrated infants with single-ventricle physiology to be shorter than healthy infants at 3 months (−1.21 versus 0.15; $P<0.0001$), 6 months (−1.02 versus 0.22; $P<0.0001$), 9 months (−0.71 versus 0.28; $P<0.001$), and 12 months (−0.59 versus 0.10; $P=0.013$) of age.

- Children with CCDs may be at risk for adverse neurodevelopmental outcomes, including mild to severe motor impairments among 12.3% to 68.6% (interquartile range, 23.4%–52.2%),¹²³ increased attention-deficit/hyperactivity disorder–related behaviors (mean T score, 57 for inattention and 54 for hyperactivity/impulsivity compared with a normal mean T score of 50; $P<0.0001$ using Connors-3 testing), difficulties in social interaction (mean T score, 53 compared with a normal mean T score of 50; $P=0.035$), combined attention-deficit/hyperactivity

TGA, 10.9 ± 1.7 for TOF, and 11.6 ± 1.6 for aortic arch pathology ($P=0.046$).

Mean fine motor skills score for single-ventricle physiology at 18 months was 9.9 ± 2.5 versus 11.4 ± 1.6 for TGA, 11.6 ± 1.7 for TOF, and 11.9 ± 2.4 for aortic arch pathology ($P=0.002$). Mean gross motor score for single-ventricle physiology at 9 months was 6.8 ± 3.5 versus 9.4 ± 3.0 for TGA, 8.6 ± 2.9 for

disorder–related symptoms and social interaction problems in 23% of children,¹²⁴ and depression or anxiety (OR, 5.23 [95% CI, 3.9%–7.1%]).^{125,126}

- A systematic review and meta-analysis has shown that children with neonatal repair of TGA had normal neurodevelopmental scores at 5 years of age.¹²⁷ Among long-term Dutch survivors of CCDs (median follow-up, 45 years), adults had lower educational level ($P<0.001$), occupational level ($P<0.001$), and employment rate ($P<0.001$) but better health-related quality of life, emotional functioning,¹²⁸ and executive function¹²⁹ compared with normative data from the Dutch population.

- Infants with single-ventricle physiology are more likely to have poorer fine and gross motor skills at 9 and 18 months compared with infants with other CCDs. Using the Dutch version of the Bayley-III shows that infants with single-ventricle physiology compared with infants with other forms of CCD performed significantly ($P\leq0.05$) worse on both fine and gross motor skill assessments at 9 and 18 months.

Mean fine motor score for single-ventricle physiology at 9 months was 9.9 ± 1.6 versus 10.5 ± 1.4 for

7.5±3.7 versus 10.6±3.1 for TGA, 10.2±2.8 for TOF, and 9.6±2.6 for aortic arch pathology (P=0.001).¹³⁰• Adults also may carry a higher burden of neurocognitive dysfunction and mental health complications.

In the United Kingdom, adults with mild to moderate CCDs showed significantly lower performance on neurocognitive testing compared with individuals without CCDs, even when those with prior stroke or CAD were excluded. Among 1020 individuals with adult congenital HD and 497 987 without adult congenital HD, individuals with adult congenital HD had significantly poorer performance on alpha-numeric trail making, a measure of visual attention and cognitive flexibility, spending 6.4 seconds longer on alpha-numeric trail making (95% CI, 3.0–9.9; P=0.002) and 2.5 seconds longer on numeric trail making (95% CI, 0.5–4.6; P=0.034), a measure of visual attention and processing speed.¹³¹

- In patients with HLHS, an older age at Fontan procedure and a history of sepsis were independent predictors of poor neurocognitive outcomes.¹³² According to multivariable linear regression models, sepsis was associated with a lower full-scale intelligence quotient of –9.9 (95% CI, –17.0 to –2.90; P=0.007), a lower performance intelligence quotient of –9.2 (95% CI, –17 to –2.10; P=0.012), and a lower verbal intelligence quotient of –9.2 (95% CI, –17.02 to –1.90; P=0.015). Similarly, a history of Fontan procedure was associated with a lower full-scale intelligence quotient of –6.5 (95% CI, –10.4 to –2.80; P<0.0001), a lower performance intelligence quotient of –6.40 (95% CI, –10.5 to –2.70; P<0.0001), and a lower verbal intelligence quotient of –5.10 (95% CI, –9.00 to –1.10; P=0.013).
- Of 121 patients with adult CCDs in Australia with moderate or complex CCDs, just more than 60% of those with TOF or CoA remained employed, and approximately half had been diagnosed with anxiety or depression.¹¹⁶
- A diagnosis of anxiety is made in ≈5% to 50% of adult CCD survivors with lowest reported rates for individuals with history of coarctation repair and highest among adult survivors after Fontan surgery.¹¹⁶• There are inconclusive data showing an increased risk of serious adverse events from COVID-19 infection in children and adults with CCDs.¹³³

- Roughly one-fourth of patients circulation develop liver hood. The cumulative among patients with Fontan (95% CI, 16.9%–34.4%).¹³⁴
- Independently of the severity of defect, adults with congenital risk for anxiety disorder.¹³⁵ Association class is odds of anxiety and 1.50–4.76).
- Quality of life can also be affected by CCDs. A low to moderate amount of variation in health-related quality of life among children with CCDs can be attributed to variables such as surgical/ICU factors, demographic factors, and health care use factors, with attributable variance ranging from 24% to 29%.¹³⁶ Worse functional class (stage C or D, New York Heart Association class ≥ 2) was associated with more dissatisfaction with health (OR, 3.44 [95% CI, 1.3–10.4]), whereas no differences were seen in the psychological, social relationship, or environmental domains.¹³⁷

Health Care Use: Hospitalizations

- In 2021, the total number of first-listed hospital discharges for CCDs for all ages was 41 785.
- Socioeconomic and sociodemographic factors affect hospitalization rates and length of stay. However, adjustments to length of hospital stay (eg, longer length of stay) may help to mitigate previously identified higher mortality risk for Black infants with CCDs.¹³⁸
- The number of adults with CCD and HF-related admissions increased according to data from the

(interquartile range, \$993–quartile range, \$13–\$1237), tile range, 246–1862); among CCDs, those costs were \$230–\$3640), \$375 \$1083), \$125 (interquartile \$1583 (interquartile range, (interquartile range, \$0–quartile range, \$33–\$892), for all comparisons).¹⁴¹

- Among adolescents and adults
Pediatric Health Information Systems database from 2005 to 2015. A total of 562 admissions occurred at 39 pediatric hospitals, increasing from 4.1% to 6.3% ($P=0.015$) during the study period.¹³⁹ Compared with adults with non-CCD HF-related admissions, adults with CCD and HF-related admissions also demonstrated increased length of stay ≥ 7 days (aOR, 2.5 [95% CI, 2.0–3.1]), incident arrhythmias (aOR, 2.8 [95% CI, 1.7–4.5]), and in-hospital mortality (aOR, 1.9 [95% CI, 1.1–3.1]).¹⁴⁰ Among adults with commercially purchased insurance, those with CCDs had more health care visits and higher expenditures than those without CCDs, even when controlling for baseline characteristics and comorbidities. Among individuals with CCDs, median ambulatory, physician, nonphysician, ED, prescription, and out-of-pocket ambulatory costs were \$3598 (interquartile range, \$1221–\$9454),

within the census tracts with highest area deprivation index (most deprived areas) was associated with a 51% higher odds of inpatient admission, 74% higher odds of ED visit, 41% higher odds of cardiac surgeries, and 45% higher odds of major adverse cardiac events compared with residence within the census tracts with the lowest deprivation index.¹⁴¹

Cost

- Among pediatric hospitalizations (0–20 years of age) in the HCUP 2009 and 2012 Kids' Inpatient Database^{142,143}:
 - Pediatric hospitalizations with CCDs (4.4% of total pediatric hospitalizations) accounted for \$6.6 billion in hospitalization spending (23% of total pediatric hospitalization costs).
 - 26.7% of all CCD costs were attributed to critical CCDs, with the highest costs attributable to HLHS, coarctation of the aorta, and TOF.
 - Median hospital cost was \$51 302 (interquartile range, \$32 088–\$100 058) in children who underwent cardiac surgery, \$21 920 (interquartile range, \$13 068–\$51 609) in children who underwent cardiac catheterization, \$4134 (interquartile range, \$1771–\$10 253) in children who underwent noncardiac surgery, and \$23 062 (interquartile range, \$5529–\$71 887) in children admitted for medical treatments.
 - The mean cost of CCDs was higher in infancy (\$36 601) than in older ages and in those with critical CCDs (\$52 899).
- A Canadian study published in 2017 demonstrated increasing hospitalization costs for children and adults with CCDs, particularly those with complex lesions. Among 59 917 hospitalizations, annual CHD costs increased by 21.6% from CAD: \$99.7 (95% CI, \$89.4–\$110.1) million in 2004 to \$121.2 (95% CI, \$112.8–\$129.6) million in 2013 ($P<0.001$).

Costs were higher for children compared with adults.
The cost increase was greater in adults (4.5%/y; $P<0.001$) than in children (0.7%/y; $P=0.006$).
Adults accounted for 38.2% of costs in 2004 versus \$1120 (interquartile range, \$440–\$2503), 45.8% in 2013 ($P=0.002$). Costs increased most among adults with complex CHD (7.2%/y; \$839 (interquartile range, \$90–\$3413), \$2005 ($P=0.001$).

Adult males accounted for greater increases in costs relative to females ($P<0.001$).

Length of stay was unchanged over time.¹⁴⁴

- A US study evaluating cost and length of stay in neonates with HLHS revealed significant regional differences in cost, length of stay, and mortality.

Adjusted average length of stay was shortest in the West and longest in the South (26.1 days [95% CI, 24.0–35.1] versus 34.9 days [95% CI, the Northeast (\$324 600 [95% CI, \$271 400–\$377 900]) and highest in the West (\$400 500 [95% CI, \$346 700–\$454 300]; $P=0.05$).¹⁴⁵

- A 2021 study in Queensland, Australia, of 2519 patients found that catheter-based and surgical interventions accounted for 90% of the total costs of caring for patients with CCDs.¹⁴⁶
- A Pediatric Heart Network study found an overall

- As with all-age prevalence, there is global variability in birth prevalence by sustainable development index. In 2017, prevalence was estimated to be 25.0 per 1000 in countries with low sustainable development index and 11.8 to 12.6 per 1000 in countries with high-middle or high sustainable development index.¹¹

- A 2019 systematic review including cost reduction for TOF repair of 27% after a clinical practice guideline including early extubation was introduced. A similar cost reduction was not found for patients with aortic coarctation repair.¹⁴⁷
- A cross-sectional survey from the NHIS of US households (2011–2017) found that nearly half (48.9%) of families of children with CCDs had some financial hardship attributable to medical bills. Among 17% of

1.441; patent ductus arteriosus, 1.004; pulmonary stenosis, 0.546; TOF, 0.356; TGA, 0.295; atrioventricular septal defects, 0.290; aortic coarctation, 0.287; HLHS, 0.178; double-outlet RV, 0.106; and truncus arteriosus, 0.078 (among others reviewed).¹⁵¹

• CCDs were responsible for 261 247 deaths globally in 2017 (95% CI, 216 567–308 159), which is a 30% decline from 1990.¹¹ The majority of these deaths (69%) were in infants <1 year of age (180 624 [95% CI, 146 825–214 178]). In large part, CCD mortality tracks socioeconomic development index, with the highest mortality in low and low-middle socioeconomic development index quintiles.¹¹

Based on 204 countries and territories in 2021¹⁵²:

– The prevalence of congenital heart anomalies was 15.77 (95% UI, 14.04–17.39) million cases

families who reported that they could not pay their medical bills (most severe hardship category), there were significantly higher rates of food insecurity and delays in care because of cost.¹⁴⁸

• Cost of CCD care may be affected by center volume.

(Table 17-2).

Data from the Pediatric Health Information Systems database show that of 1024 neonates with truncus arteriosus, of whom 495 (48%) were treated at high-volume centers, costs at the 75th percentile were lower at high-volume versus low-volume cen-

- There were 0.25 (95% UI, 0.21–0.30) million total deaths estimated for congenital heart anomalies worldwide (Table 17-2).
 - Among regions, age-standardized mortality rates of congenital heart anomalies were highest for Oceania, followed by the Caribbean, North Africa and the Middle East, and western sub-Saharan Africa. They were lowest for high-income Asia Pacific, Australasia, and Western Europe (Chart 17-5).
- ters by \$28 456 ($P=0.02$). Patients at high-volume centers had lower median postoperative ventilation days (5 days versus 6 days; $P<0.001$), ICU length of stay (13 days versus 19 days; $P<0.001$), hospital length of stay (23 days versus 28 days; $P=0.02$), and inotropic agent use (3 days versus 4 days;

- The age-standardized prevalence of congenital heart anomalies among regions was highest for high-income Asia Pacific, Central Asia, and Western Europe (Chart 17-6).
- In a 2019 systematic review including 103 632 049 live births globally, the mean prevalence of CCDs ($P=0.004$).^{60,149}
- In a nationally comprehensive cohort of patients with CCD, Black race was associated with greater resource use, with higher odds of ED visits compared with White race (OR, 4.19 [95% CI, 1.35–13.04]; $P=0.001$).¹⁵⁰

Global Burden of CCDs

(See Table 17-2 and Charts 17-5 and 17-6)

- A total of 3.12 (95% UI, 2.40–4.11) million babies were born with CCDs in 2019, representing 2305.2 per 100 000 live births (95% UI, 1772.9–3039.2).¹⁰

globally was 8.2 per 1000. Prevalence of CCDs in Africa was estimated at $\approx 25\%$ of that in other regions, likely attributable to sparse population-level data and low diagnostic access.¹⁵¹

- There are multiple recent estimates on the prevalence of CCDs in China.
 - According to a systematic review and meta-analysis of CCD data from China, birth prevalence of CCDs has increased from 0.2 per 1000 live births (1980–1984) to 4.9 per 1000 live births (2015–2019) with higher rates among males (4.2 per 1000 versus 3.5 per 1000), individuals living in urban compared with rural areas (2.5 per 1000)

versus 4.3 per 1000), and brackets (no data from 4.0 per 1000 in high-income 1000 in upper-middle—reflecting differences in

- In another study from China the overall prevalence of 1000 live births during 2014
- From January to December newborns born in 11 cities

total birth prevalence of CCDs was 5.79 per 1000 births.¹⁵⁵ Birth prevalence was higher in low-income (6.14 per 1000 births) compared

68.4 per 10 000 with live birth per 10 000.¹⁶²

- Although gains in CCD the past 3 decades, effects were found in many tions about health care dren with CCDs.¹⁶³
 - India, China, Pakistan, and est mortality, accounting for resulting from CCDs with high-income (5.58 per 1000 births; $P=0.009$)

- During the past 30 years, favorable mortality reductions were generally found in most high-SDI countries like South Korea (net drift, $-4.0\%/y$ [95% CI, $-4.8\%/y$ to $-3.1\%/y$]) and in many areas.
 - In the Yunnan region of China, differences in CCD prevalence among ethnic groups were found. The overall CCD prevalence was 6.04 cases per 1000 children.¹⁵⁶ The ethnic groups displaying the highest CCD prevalence were the Lisu (15.51 per 1000), Achang (13.18 per 1000), Jingpo (12.32 per 1000), Naxi (9.68 per 1000), and Tibetan (8.57 per 1000).
 - Birth incidence is increasing in the Kingdom of Bahrain, with 9.45 per 1000 live births in 2016 compared with 6.45 per 1000 live births affected in 2000.¹⁵⁷
 - Between 1977 and 2015, a Danish study of 15 900 patients with simple CCDs (ASD, VSD, patent ductus arteriosus) found increasing inci-
- middle-SDI countries like Brazil (-2.7% [95% dence per 100 000 (ASD in adults, 8.8 [95% CI, 7.1–10.5] to 31.8 [95% CI, 29.2–34.5]; ASD in children, 26.6 [95% CI, 20.9–32.3] to 150.8 [95% CI, 126.5–175.0]; VSD in children, 72.1 [95% CI, 60.3–83.9] to 115.4 [95% CI, 109.1–121.6], and patent ductus arteriosus in children, 49.2 [95% CI, 39.8–58.5] to 102.2 [95% CI, 86.7–117.6])).¹⁵⁸• According to a population-based study from Malaysia, CCDs occurred in 1.26 of every 1000 births (2006–2015) with no significant change in

- CI, -3.1% to 2.4%]) and South Africa (95% CI, -2.5% [-3.2% to -1.8%]).
- However, 52 of 129 countries had either increasing trends (net drifts $\geq 0.0\%$) or stagnated reductions ($\geq -0.5\%$) in mortality.

Kawasaki Disease

ICD-9 446.1; ICD-10 M30.3.

KD is an acute inflammatory illness characterized by fever, rash, nonexudative limbal-sparing conjunctivitis, extremity changes, red lips and strawberry tongue, and a swollen lymph node. The most significant consequence of this vasculitis is coronary artery aneurysms, which can result in coronary ischemic events and other cardio-vascular outcomes in the acute period or years later.¹⁶⁴ The cause of KD is unknown but may be an immune response to an acute infectious illness based in part on genetic susceptibilities.^{165,166}

Prevalence

- KD is the most common cause of acquired HD in countries.¹⁶⁷

children in the United States and other high-income

incidence over time.¹⁵⁹

- In Argentina, according to data provided by the national Network of Congenital Anomalies (2009–2018), the prevalence of CCDs was 11.46 (95% CI, 11.02–11.92) per 10 000 births.¹⁶⁰
- Estimated (pooled) prevalence of ASD among CCDs in East Africa is 10.36% (95% CI, 8.05%–12.68%; $I_2=89.5\%$; $P<0.001$).¹⁶¹
- Estimated (pooled) prevalence of VSD among CCDs in East Africa is 29.92% (95% CI,

Incidence

26.12%–33.72%; $I_2=89.2\%$; $P<0.001$), in Ethiopia is 36.04% (95% CI, 29.36%–42.72%), in Djibouti is 37% (95% CI, 18.79%–55.21%), and in Sudan is 32.59% (95% CI, 26.67%–38.59%).¹⁶¹

- A population-based registry analysis of CCD prevalence in French Guiana found a birth prevalence of

- A review of HCUP/Kids' Inpatient Database for KD hospitalizations in children <18 years of age in the United States during 2009 to 2012 revealed 10 486 hospitalizations for KD of 12 678 005 total hospitalizations. The incidence of KD was estimated at 6.35 per 100 000.¹⁶⁸
- The incidence of KD was estimated at 20.8 per 100 000 US children <5 years of age in 2006.¹⁶⁹ This was calculated from 2 databases and limited by reliance on weighted hospitalization data from 38 states.
- Male children have a 1.5-fold higher incidence of KD than female children.¹⁶⁹
- Although KD can occur into adolescence (and rarely adulthood), 76.8% of US children with KD are <5 years of age.¹⁶⁹

- Race-specific incidence rates indicate that KD is most common among Americans of Asian and Pacific Islander descent (30.3 per 100 000 children <5 years of age), occurs with intermediate frequency in NH Black children (17.5 per 100 000 children <5 years of age) and Hispanic children (15.7 per 100 000 children <5 years of age), and is least common in White children (12.0 per 100 000 children <5 years of age).¹⁶⁹ within the United States. States with higher Asian American populations have higher rates of KD; for example, rates are 2.5-fold higher in Hawaii (50.4 per 100 000 children <5 years of age) than in the continental United States.¹⁷⁰ Within Hawaii, the race-specific rates of KD per 100 000 children <5 years of age in 1996 to 2006 were 210.5 for Japanese children, 86.9 for Native Hawaiian children, 83.2 for Chinese children, 64.5 for Filipino children, and 13.7 for White children.¹⁷⁰
- There are seasonal variations in KD that may track other respiratory and enteric viruses¹⁷¹; KD is more common during the winter and early spring months, except in Hawaii, where no clear seasonal trend is seen.^{169,170}
- Incidence of KD may have decreased during SARS-CoV-2 mitigation policies (social distancing and masks), with 1 center reporting a 67% decline ($P=0.01$) comparing April to December 2020 with the same months in the past 8 years,¹⁷² and another study in Korea reporting only 60% of predicted cases (incidence, 18.8 per 100 000) after standard precautions were implemented compared with

associated with coronary artery aneurysm in patients of European descent with KD.¹⁸²

- Various genetic variants have been associated with KD susceptibility or development of coronary artery lesions in KD; however, thus far, these variants have not explained differences in incidence between ancestry groups (eg, Japanese the predicted mean incidence (32.2 per 100 000) based on >50 000 cases between 2010 and 2020.¹⁷³• KD rarely recurs. Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan,¹⁷⁴ and the incidence of first recurrence among children with a history of KD has been reported as 6.5 per 1000 PY in Japan (2007–2010) and 2.6 per 1000 PY in Canada (2004–2014).^{175,176}

Secular Trends

- Although the incidence of KD is rising worldwide, there has been no clear secular trend in the United States, but recent data are lacking. US hospitalizations for KD were 17.5 and 20.8 per 100 000 children <5 years of age in 1997 and 2006, respectively, but the test for linear trend was not significant.¹⁶⁹

Genetics/Family History/Risk Factors

- GWASs have identified loci in *FCGR2A*, *FAM167-BLK*, *CD40*, *IHGV3-66*, HLA class II region, *NAALADL2*, and *ZFHX3* to be associated with KD.^{177–181} Recently, a novel locus (intergenic

$P=0.01$), and Sjögren syndrome (OR, 1.75 [95% CI, 1.03–2.95]; $P=0.04$) may be perinatal factors associated with increased risk of KD.¹⁸⁴

- Certain types of air pollution, both prenatally and during early life, may contribute to the development of KD in children. The strongest risk related to carbon monoxide (parts per million) is during pregnancy (OR, 1.67 [95% CI, 1.23–2.28]; $P=0.001$) and after delivery (1.61 [95% CI, 1.16–2.22]; $P=0.004$).¹⁸⁵

Treatment and Control

- Treatment of acute KD rests on diminishing the inflammatory response with IVIG, which reduces the incidence of coronary artery aneurysms (from 25% to ≈4% for aneurysms defined by absolute dimensions).¹⁶⁷ Aspirin is routinely used for its anti-inflammatory and antiplatelet effects, but it does not reduce the incidence of coronary artery aneurysms.¹⁸⁶
- On the basis of a Cochrane review, adding prednisolone to the standard IVIG regimen could further reduce the incidence of coronary artery abnormalities (RR, 0.29 [95% CI, 0.18–0.46]), but the applicability of these data to non-Asian patients and less severe KD cases is not certain.¹⁸⁷
- Treatment of IVIG resistance is currently not standardized. A multicenter comparative-effectiveness trial including 30 US hospitals and 103 patients (4 weeks–17 years of age) showed that infliximab compared with a second dose of IVIG resulted in shorter fever duration (1.5 ± 1.4 days versus 2.5 ± 2.5 days) and shorter hospitalization (3.2 ± 2.1 days versus 4.5 ± 2.5 days). No difference was found in coronary artery outcomes.¹⁸⁸
- Cyclophosphamide may arrest further coronary artery dilation in those with severe and progressive coronary artery enlargement after KD.¹⁸⁹
- Management of established coronary artery aneurysms in the short and long term is centered on thromboprophylaxis. Successful coronary intervention for late coronary stenosis or thrombosis has been accomplished percutaneously and surgically (eg, CABG).^{190,191}

Complications of KD

In the acute phase (up to ≈6 weeks from fever onset), several important cardiovascular complications can occur. variant rs6017006) cur. has been identified to

- KD shock syndrome, with from myocardial dysfunction and peripheral resistance, occurs in 5% of KD and is associated with arterial dilation, resistance to rarely, long-term myocardial
- It is estimated that even with dose IVIG within the first 10 children develop transient score >2 , 5% develop (Z score ≥ 2.5), and 1% score ≥ 10 or >8 mm).¹⁶⁷ by variability in ascertainment

tive codes or research measurement), size criteria, timing (because the majority of dilated segments and approximately half of aneurysms reduce to normal dimensions over time), and therapeutic regimens in the underlying studies. In US data from 2 centers in 2004 to 2008, maximal coronary artery dimensions reached Z scores ≥ 2.5 in 30% of patients with KD up to 12 weeks from fever onset, including medium (Z score ≥ 5 – <10) and giant aneurysms in $\approx 6\%$ and $\approx 3\%$ of patients with KD, respectively.¹⁹³

IHD death occurred in 2%, in another 2%, and in another 3%, for a total of a rate during 1 to 46 years of events occurred in those with whom the ischemia event—0.63 and 0.36 at 10 and 20 KD onset.²⁰⁰ Findings were study of 76 patients with giant aneurysms diagnosed since 1972 and in a Canadian study of diagnosed in 1990 to 2007 to 15 years.^{190,201}

- A recent study showed that younger age (OR, 0.94 [95% CI, 0.90–0.99]), IVIG nonresponse (OR, 6.70 [95% CI, 1.80–24.50]), and noncoronary cardiac events (OR, 3.20 [95% CI, 1.10–8.70]), in particular in very young children (<6 months), may also increase risk for more severe KD with coronary artery aneurysms (OR, 2.18 [95% CI,

- In a large prospective study across 16 Latin American countries and 64 participating pediatric centers including 1853 patients with a new KD diagnosis, delayed admission (>10 days after symptom onset) occurred in 16%, 25% had incomplete KD, and 11% were IVIG resistant.²⁰² Of 671 who had coronary artery Z scores reported, 21% had coronary artery aneurysms and 4% had giant coronary artery aneurysms. Maximal coronary artery Z score ≥ 2.5 mm at presentation was alone most prognostic of coronary aneurysm at follow-up (AUC, 0.84 [95% CI, 0.80–0.88]).
- A Japanese multicenter cohort study of 1006 individuals identified risk factors for 10-year incidence of coronary events (thrombosis, stenosis, obstruction, acute ischemic events, or coronary intervention).²⁰³ Significant risk factors included giant aneurysm (HR, 8.9 [95% CI, 5.1–15.4]), male sex (HR, 1.25–3.80).¹⁹⁴
 - In Latin America, children <6 months of age were more likely to have delayed diagnoses (OR, 0.17 [95% CI, 0.08–0.35]) and less obvious clinical features (oral changes: OR, 0.26 [95% CI, 0.12–0.58]; cervical lymphadenopathy: OR, 0.28 [95% CI, 0.14–0.58]; extremity changes: OR, 0.45 [95% CI, 0.23–0.88]; complete KD: OR, 0.24 [95% CI, 0.12–0.48]).

(HR, 2.8 [95% CI, 1.7–4.8]), and resistance to IVIG therapy (HR, 2.2 [95% CI, 1.4–3.6]).

- In 2022, US mortality attributable to KD was 14 patients for all-cause mortality and 11 deaths for underlying mortality (unpublished NHLBI tabulation using CDC WONDER₉₆).

0.13–0.47]) and were at greater risk of developing coronary artery aneurysm (OR, 11.25 [95% CI, 3.87–36.25]), even after controlling for day of treat- *Health Care Use*

- In 2021, there were 3400 principal and 5145 all-listed diagnoses hospital discharges for KD
ment initiation.¹⁹⁵ (HCUP,²⁰⁴ unpublished NHLBI tabulation).
- Peak KD-associated mortality occurs during the acute phase but is rare, estimated at 0% to 0.17%
in older US data and 0.03% in data from
Japan.^{196–198} Mortality is related to thrombosis or
rupture of rapidly expanding
aneurysms or, less commonly,
shock or macrophage activation
syndrome with multiorgan

- A Canadian study found that children with KD compared with control subjects had higher rates of hospitalization (adjusted rate ratio, 2.07 [95% CI, 2.00–2.15]), outpatient visits (adjusted rate ratio, 1.30 [95% CI, 1.28–1.33]), and ED visits (adjusted rate ratio, 1.22 [95% CI, 1.18–1.26]) throughout failure.^{198,199} chil- follow-up.²⁰⁵ Within 1 year after discharge, 717 small, 4.1% medium, and 2.5% giant aneurysms. Among those with persistent aneurysms beyond 1 month,
- Prognosis is predicted largely by coronary artery size 1 month from illness onset. In a Taiwanese study of 1073 patients with KD from 1980 to 2012, coronary artery aneurysms were present in 18.3% beyond 1 month, including 11.6%

dren with KD (15.6%) were rehospitalized, 4587 (99.8%) had ≥ 1 outpatient physician visits, and 1695 (45.5%) had ≥ 1 ED visits.

- Patients with KD also had higher composite health care costs after discharge (eg, median cost within 1 year [Canadian dollars], \$2466 [KD cases] versus \$234 [comparators]).²⁰⁵

Global Burden of KD

- The annual incidence of KD is highest in Japan, at 264 per 100 000 children <5 years of age in 2014, followed by South Korea at 134.4 per 100 000 children <5 years of age in 2014 and Taiwan at 82.7 per 100 000 in children <5 years of age.²⁰⁶
- In Japan, the cumulative incidence of KD at 10 years of age has been calculated with different methodology with complete capture of cases through the national health insurance program, Taiwan recorded a cumulative incidence of 2.8% by 5 years of age in 2014.²⁰⁸
- The incidence of KD is lower in Canada, at 19.6 per 100 000 children <5 years of age for the period of 2004 to 2014, and in European countries such as Italy with 14.7 per 100 000 children <5 years of age in 2008 to 2013, Spain with 8 per 100 000 children <5 years of age in 2004 to 2014, Germany with 7.2 per 100 000 children <5 years of age in 2011 to 2012, and the

pandemic. The CDC reported that early in the COVID-19 pandemic, MIS-C occurred in ≈1 of every 3000 to 4000 children and adolescents with SARS-CoV-2 infection, but the incidence has become more rare, decreasing from 2020 to 2023. A multicenter, international, cross-sectional study collected the MIS-C incidence from the participant United Kingdom and Ireland with 4.6 per 100 000 children <5 years of age in 2014 to 2015.^{176,209–213}

Multisystem Inflammatory Syndrome in Children

MIS-C is a clinical syndrome characterized by fever, inflammation, and multiorgan dysfunction that most commonly manifests late in the course of SARS-CoV-2 infection.²¹⁴ MIS-C has overlapping signs and symptoms of KD and toxic shock syndrome. Case definitions of MIS-C

tion of 17 906 432 children, a significant decrease of MIS-C/COVID-19 cases was found globally ($P<0.001$).

- A meta-analysis showed that the pooled OR for MIS-C in vaccinated children compared with unvaccinated children was 0.4 (95% CI, 0.03–0.06).²¹⁹ A meta-analysis of patient characteristics in MIS-C shows that more males (55.8% [95% CI, 50.3%–61.2%]) are affected, most patients (79.1% [95% CI, 70.8–85.5]) require ICU admission, nearly one-third of patients (29.2% [95% CI, 19.9%–40.5%]) require mechanical ventilation, and a small number (7.6% [95% CI, 4.1%–13.8%]) require extracorporeal membrane oxygenation.²²⁰
 - Risk of MIS-C may vary with ethnicity, with apparently higher risk among those of African descent.^{221,222} A potential association has been found in 2 studies between severe vitamin D deficiency and severe disease in children presenting with MIS-C.^{223,224} There is also an association with obesity and the severity of MIS-C. In Poland, among 306 children with MIS-C, children with obesity had a higher rate of incomplete recovery (OR, 4.2 [95% CI, 1.4–12.1]).²²⁵
- by the CDC and WHO require fever, elevated markers of inflammation, evidence of recent SARS-CoV-2 infection or exposure, multisystem organ involvement, and exclusion of alternative diagnoses. The first case reports of MIS-C (which has gone by many names) came from the United States and Europe in April 2020,²¹⁵ with dozens of case series now reported from around the world.
- MIS-C most commonly occurs 4 to 6 weeks after a population peak of SARS-CoV-2 infection.²¹⁶
 - Since May 2020, the CDC has been tracking reports of MIS-C. As of June 2, 2024, 9684 cases and 79 attributable deaths (0.81%) have been reported.
- Median age of cases was 9 years of age; 56% of cases that have ethnicity information available have occurred in children who are Hispanic or Latino or Black (2398 cases); 98% tested positive for SARS-CoV-2 (reverse transcriptase–polymerase chain reaction, serology, or antigen test); and 60% of reported patients were male.²¹⁷
- Some data suggest that the risks of MIS-C have changed over the course of the SARS-CoV-2

- In England during the Alpha wave, MIS-C occurred in 0.038% (interquartile range, 0.037%–0.041%) of pediatric SARS-CoV-2 infections; during the Delta wave, MIS-C occurred in 0.026% (interquartile range, 0.025%–0.029%).^{.226}
- Among 903 cases of MIS-C in Brazil, the RR of 9.87; $P<0.001$) times higher in adolescents from 4 years of age. In addition, residency in the North indicators, was a risk factor for death (RR, 3.72 [95% CI, 1.29–10.74]; $P=0.008$).^{.227}
- Multiple follow-up studies have been published on the cardiac outcomes of children who had MIS-C. In a single-site study, residual cardiac disease among patients with MIS-C 6 months after presentation was 10.3%.^{.228} A similar longitudinal study showed MR persisted in 7.5% at 6 months and that coronary artery dilatation persisted in 5.2% at 6 months.^{.229}

Table 17-1. CCDs in the United States

Population group	Estimated prevalence, 2010, all ages	Mortality, 2022, all ages*
Both sexes	2.4 million	3213
Males	...	1758 (54.7%)†
Females	...	1455 (45.3%)†
NH White males	...	1078
NH White females	...	844
NH Black males	...	277
NH Black females	...	257
Hispanic males	...	306
Hispanic females	...	265
NH Asian males	...	49‡
NH Asian females	...	41‡

CCD indicates congenital cardiovascular defect; ellipses (...), data not available; and NH, non-Hispanic.

*Mortality for Hispanic people, NH American Indian or Alaska Native people, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown under-reporting on death certificates of American Indian or Alaska Native decedents, Asian decedents, Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Gilboa et al.¹³ Mortality (for underlying cause of CCDs): unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System¹⁹⁵ and CDC WONDER.⁹⁶ These data represent underlying cause of death only.

Table 17-2. Global Mortality and Prevalence of Congenital Heart Anomalies, by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	0.25 (0.21 to 0.30)	15.77 (14.04 to 17.39)	0.14 (0.11 to 0.18)	7.72 (6.86 to 8.52)	0.11 (0.09 to 0.14)	8.05 (7.15 to 8.90)
Percent change (%) in total	-52.58 (-63.16 to -20.09)	33.83 (31.88 to 35.67)	-54.29 (-65.96 to -17.31)	31.54 (29.65 to 33.47)	-50.25 (-61.52 to -1.19)	36.10 (34.01 to 38.21)
Percent change (%) in total	-30.29 (-40.27 to -13.40)	10.46 (9.47 to 11.35)	-31.21 (-42.31 to -8.58)	9.40 (8.34 to 10.45)	-29.08 (-38.64 to -8.13)	11.50 (10.48 to 12.48)
Rate per 100 000, age	3.86 (3.19 to 4.70)	210.70 (187.92 to 232.48)	4.18 (3.31 to 5.42)	204.17 (181.75 to 225.77)	3.51 (2.74 to 4.29)	217.20 (193.26 to 240.16)
Percent change (%) in rate, age	-54.63 (-64.72 to -24.20)	0.56 (-0.27 to 1.42)	-56.02 (-67.23 to -21.08)	-0.17 (-1.03 to 0.71)	-52.70 (-63.42 to -6.51)	1.32 (0.36 to 2.31)
Percent change (%) in rate, age	-28.61 (-39.03 to -11.13)	0.81 (-0.01 to 1.49)	-29.30 (-40.85 to -6.03)	0.17 (-0.76 to 0.95)	-27.67 (-37.42 to -6.14)	1.46 (0.64 to 2.31)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁵²

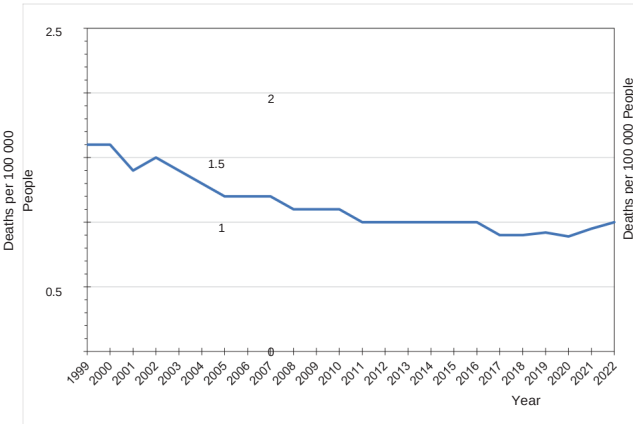


Chart 17-1. Trends in age-adjusted death rates attributable to CCDs, United States, 1999 to 2022.

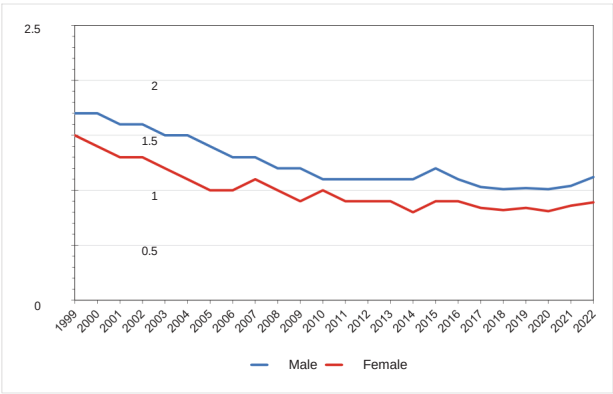
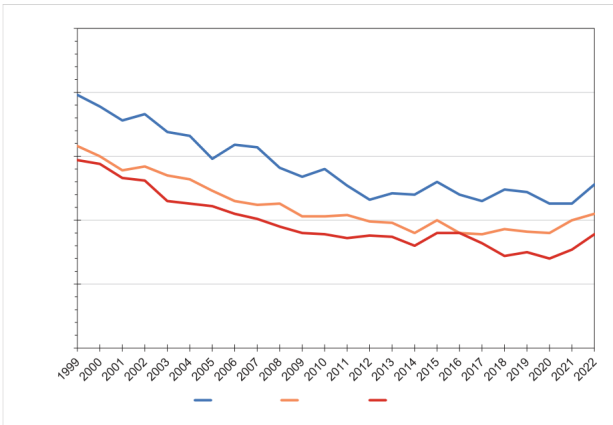


Chart 17-3. Trends in age-adjusted death rates

CCD indicates congenital cardiovascular defect.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.⁹⁶



CCDs, by sex, United States, 1999 to 2022.

CCD indicates congenital cardiovascular defect.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.⁹⁶

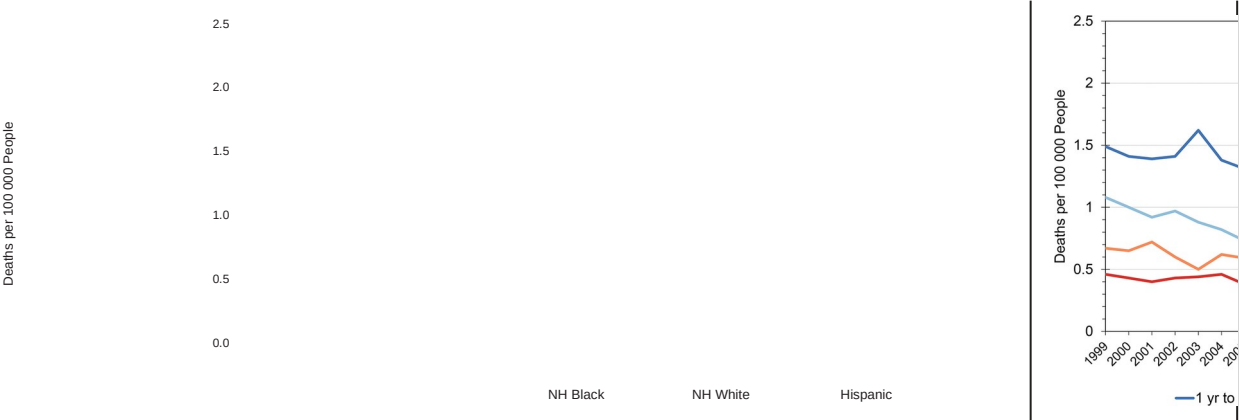


Chart 17-2. Trends in age-adjusted death rates attributable to CCDs, by race and ethnicity, United States, 1999 to 2022.

CCD indicates congenital cardiovascular defect; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.⁹⁶

CCD indicates congenital cardiovascular defect.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.⁹⁶

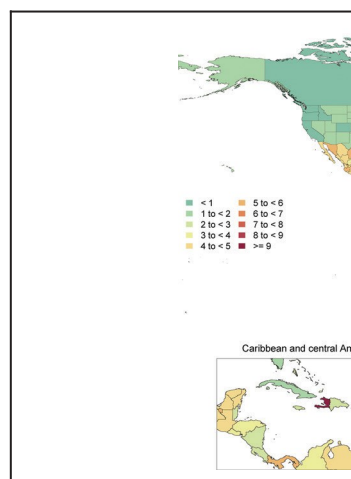


Chart 17-5. Age-standardized global mortality rates of congenital heart anomalies per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁵²

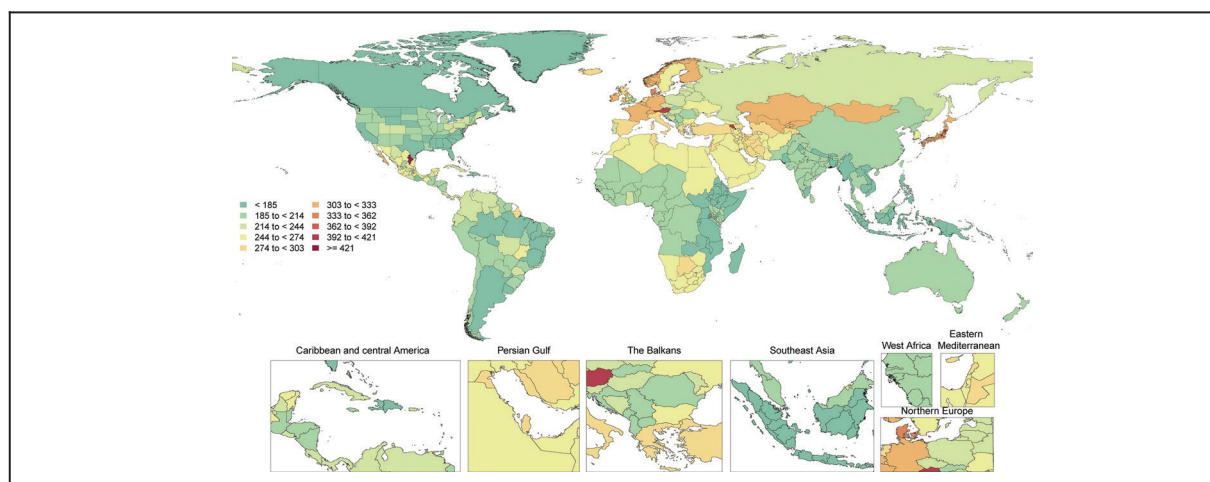


Chart 17-6. Age-standardized global prevalence rates of congenital heart anomalies per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁵²

REFERENCES

1.	C.	Addor	MC.	Carbonell	CC.	Dias	CM.	1
	Echevarria-Gonzalez-de-Garibay LJ, Gatt M, Khoshnood B, Klungsoyr	K, Randall K, Stoianova S, et al. Prevalence of						6
	congenital heart de-	fects in Europe, 2008-2015: a registry-based study. <i>Birth Defects</i>						.
	doi: 10.1002/bdr2.2117							B
2.	Chimah OU, Emeagui KN, Ajaegbu OC, Anazor CV, Ossai CA, Fagbemi AJ,					Emeagui OD. Congenital		o
	malformations: prevalence and characteristics of	newborns admitted into Federal Medical Center, Asaba. <i>Health Sci Rep.</i>						y
	2022;5:e599. doi: 10.1002/hsr2.599							d
3.	Cocomello L, Taylor K, Caputo M, Cornish RP, Lawlor DA. Health and well-					being in surviving congenital heart		R
	disease patients: an umbrella review							,
	with synthesis of best evidence. <i>Front Cardiovasc Med.</i>							
	2022;9:870474. doi: 10.3389/fcvm.2022.870474							
4.	Mellion K, Uzark K, Cassedy A, Drotar D, Wernovsky G, Newburger							
	JW, Mahony L, Mussatto K, Cohen M, Limbers C, et al; Pediatric							
	Cardiac Quality of Life Inventory Testing Study Consortium. Health-							
	related quality of life outcomes in children and adolescents with							
	congenital heart disease. <i>J Pediatr.</i> 2014;164:781–788.e1. doi:							
	10.1016/j.jpeds.2013.11.066							
5.	Vasserman M, Myers K, Brooks BL, Fay-McClymont TB, McColm L, Mish					S, Becker		
	N, MacAllister WS. Patterns of WISC-V performance in chil-					dren with congenital		
	heart disease. <i>Pediatr Cardiol.</i> 2024;45:483–490. doi: 10.1007/s00246-023-03367-8							
6.	Mamasoula C, Pennington L, Adesanya AM, Rankin J. A systematic re-					view and		
	meta-analysis of school and cognitive function domains of					health-related quality		
	of life measures for children and young adults					with congenital heart disease.		
	<i>Birth Defects Res.</i> 2024;116:e2275. doi:							

20. Sullivan PM, Dervan LA, Reiger S, Buddhé S, Schwartz SM. Risk of congenital heart defects in the offspring of smoking mothers: a population-based study. *J Pediatr*. 2015;166:978–984.e2. doi: 10.1016/j.jpeds.2014.11.042
21. Liu Y, Zhang H, Li J, Liang C, Zhao Y, Chen F, Wang D, Pei L. Geographical variations in maternal lifestyles during pregnancy associated with congenital heart defects among live births in Shaanxi province, Northwestern China. *Sci Rep*. 2020;10:12958. doi: 10.1038/s41598-020-69788-0
22. Deng C, Pu J, Deng Y, Xie L, Yu L, Liu L, Guo X, Sandin S, Liu H, Dai L. Association between maternal smoke exposure and congenital heart defects from a case-control study in China. *Sci Rep*. 2022;12:14973. doi: 10.1038/s41598-022-18909-y
23. Bolin EH, Gokun Y, Romitti PA, Tinker SC, Summers AD, Roberson PK, Hobbs CA, Malik S, Botto LD, Nembhard WN; National Birth Defects Prevention Study. Maternal smoking and congenital heart defects, National Birth Defects Prevention Study, 1997-2011. *J Pediatr*. 2022;240:79–86. doi: 10.1016/j.jpeds.2021.09.005
24. Mateja WA, Nelson DB, Kroelinger CD, Ruzek S, Segal J. The association between maternal alcohol use and smoking in early pregnancy and congenital cardiac defects. *J Womens Health (Larchmt)*. 2012;21:26–34. doi: 10.1089/jwh.2010.2582
7. Sood E, Newburger JW, Anixt JS, Cassidy AR, Jackson JL, Jonas RA, Lisanti AJ, Lopez KN, Peyvandi S, Marino BS; on behalf of the American Heart Association Council on Lifelong Congenital Heart Disease and Heart Health in the Young the Council on Cardiovascular and Stroke Nursing. Neurodevelopmental outcomes for individuals with congenital heart disease: updates in neuroprotection, risk-stratification, evaluation, and management: a scientific statement from the American Heart Association. *Circulation*. 2024;149:e997–e1022. doi: 10.1161/CIR.0000000000001211
8. Aleksonis HA, King TZ. Relationships among structural neuroimaging and neurocognitive outcomes in adolescents and young adults with congenital heart disease: a systematic review. *Neuropsychol Rev*. 2022;33:432–458. doi: 10.1007/s11065-022-09547-2
9. Holcomb RM, Ündar A. Are outcomes in congenital cardiac surgery better than ever? *J Card Surg*. 2022;37:656–663. doi: 10.1111/jocs.16225
10. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: up-date from the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76:2982–3021.
11. GBD Congenital Heart Disease Collaborators. Global, regional, and nation-al burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Child Adolesc Health*. 2020;4:185–200. doi: 10.1016/S2352-4642(19)30402-X
12. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, et al. ACC/ AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). *Circulation*. 2008;118:e714–e833. doi: 10.1161/circulationaha.108.190690
13. Gilboa SM, Devine OJ, Kucik JE, Oster ME, Riehle-Colarusso T, Nembhard WN, Xu P, Correa A, Jenkins K, Marelli AJ. Congenital heart defects in the United States: estimating the magnitude of the affected population in 2010. *Circulation*. 2016;134:101–109. doi: 10.1161/CIRCULATIONAHA.115.019307
14. Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, Lupo PJ, Riehle-Colarusso T, Cho SJ, Aggarwal D, et al; National Birth Defects Prevention Network. National population-based estimates for major birth defects, 2010-2014. *Birth Defects Res*. 2019;111:1420–1435. doi: 10.1002/bdr2.2275

25. Butler M. An exploratory analysis of maternal health variables increasing the severity of congenital heart disease in infants. *J Perinat Neonatal Nurs.* 2022;36:344–352. doi: 10.1097/jpn.0000000000000640
26. Hedermann G, Hedley PL, Thagaard IN, Krebs L, Ekelund CK, Sorensen TIA, Christiansen M. Maternal obesity and metabolic disorders associate with congenital heart defects in the offspring: a systematic review. *PLoS One.* 2021;16:e0252343. doi: 10.1371/journal.pone.0252343
27. Cai GJ, Sun XX, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. *Am J Obstet Gynecol.* 2014;211:91–117. doi: 10.1016/j.ajog.2014.03.028
28. Persson M, Razaz N, Edstedt Bonamy AK, Villamor E, Cnattingius S. Maternal overweight and obesity and risk of congenital heart defects. *J Am Coll Cardiol.* 2019;73:44–53. doi: 10.1016/j.jacc.2018.10.050
29. Nie X, Liu X, Wang C, Wu Z, Sun Z, Su J, Yan R, Peng Y, Yang Y, Wang C, et al. Assessment of evidence on reported non-genetic risk factors of congenital heart defects: the updated umbrella review. *BMC Pregnancy Childbirth.* 2022;22:371. doi: 10.1186/s12884-022-04600-7
30. Huida J, Ojala T, Ilvesvuo J, Surcel HM, Priest JR, Helle E. Maternal first trimester metabolic profile in pregnancies with transposition of the great arteries. *Birth Defects Res.* 2022;115:517–524. doi: 10.1002/bdr2.2139
31. Simeone RM, Devine OJ, Marcinkavage JA, Gilboa SM, Razzaghi H, Bardenheier BH, Sharma AJ, Honein MA. Diabetes and congenital heart defects: a systematic review, meta-analysis, and modeling project. *Am J Prev Med.* 2015;48:195–204. doi: 10.1016/j.amepre.2014.09.002
32. He R, Hornberger LK, Kaur A, Crawford S, Boehme C, McBrien A, Eckersley L. Risk of major congenital heart disease in pregestational maternal diabetes is modified by hemoglobin A1c. *Ultrasound Obstet Gynecol.* 2024;63:378–384. doi: 10.1002/uog.27456
33. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, Elixson M, Warnes CA, Webb CL; on behalf of the American Heart Association Council on Cardiovascular Disease in the Young. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young. *Circulation.* 2007;115:2995–3014. doi: 10.1161/CIRCULATIONAHA.106.183216
34. Mires S, Caputo M, Overton T, Skerrett C. Maternal micronutrient deficiency and congenital heart disease risk: a systematic review of observational studies. *Birth Defects Res.* 2022;114:1079–1091. doi: 10.1002/bdr2.2072
35. Wang T, Li Q, Chen L, Ni B, Sheng X, Huang P, Zhang S, Qin J. Maternal viral infection in early pregnancy and risk of congenital heart disease. *J Am Coll in offspring: a prospective cohort study in central China. Clin Epidemiol. Cardiol.* 2002;39:1890–1900. doi: 10.1016/s0735-1097(02)01886-7
- 2022;14:71–82. doi: 10.2147/CLEP.S338870

36. Fazekas-Pongor V, Csaky-Szunyogh M, Penzes M. Congenital heart diseases and sure in a Hungarian case-control study in (Kvato). 2021;61:55–62. doi:
37. Wilson PD, Loffredo CA, Correa-Villasenor tion for cardiac malformations. *Am J* 10.1093/oxfordjournals.aje.a009666
38. Havama-Terada M, Aochi Y, Ikehara S, H. Paternal occupational exposures and in the Japan Environment and Children's 2023;28:12. doi: 10.1265/ehnm.22-00202
39. Mahle WT, Martin GR, Beekman RH 3rd. *Cardiology and Cardiac Surgery Executive Health and Human Services recommendation for pulse oximetry screening for critical congenital heart disease. Pediatrics.* 2012;129:190–192. doi: 10.1542/peds.2011-3211
40. Glidewell J, Grosse SD, Riehle-Colarusso T, Pinto N, Hudson J, Daskalov R, Gaviglio A, Darby E, Singh S, Sontag M. Actions in support of new- born screening for critical congenital heart disease– United States, 2011–2018. *MMWR Morb Mortal Wkly Rep.* 2019;68:107–111. doi: 10.15585/mmwr.mm6805a3
41. Glidewell J, Olney RS, Hinton C, Pawelski J, Sontag M, Wood T, Kucik JE, Daskalov R, Hudson J; Centers for Disease Control and Prevention (CDC). State legislation, regulations, and hospital guidelines for newborn screening for critical congenital heart defects–United States, 2011–2014. *MMWR Morb Mortal Wkly Rep.* 2015;64:625–630.
42. de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlm C, Inganas L, Eriksson M, Segerdahl N, Agren A, Ekman-Joelsson BM, et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. *BMJ.* 2009;338:a3037. doi: 10.1136/bmj.a3037 43.
- Meberg A, Brugmann-Pieper S, Due R Jr, Eskedal L, Fagerli I, Farstad T, Froisland DH, Sannes CH, Johansen OJ, Keljalic J, et al. First day of life pulse oximetry screening to detect congenital heart defects. *J Pediatr.* congenital heart disease. *BMC* 10.1186/s12884-020-03512-8
54. Miao O, Dunn S, Wen SW, Loudheed J. Associations of congenital heart rural-urban maternal residence: a cohort study in Ontario, Canada. *BMC* 10.1186/s12887-022-03498-6
55. Hu CY, Huang K, Fan Y, Yang XJ, Jiana ZX, Zhang XJ. Maternal air defects in offspring: a systematic 2020;253:126668. doi:
56. Siffel C, Riehle-Colarusso T, Oster ME. hyponlastic left heart syndrome 2008;152:761–765. doi: 10.1016/j.jpeds.2007.12.043
44. Riede FT, Worner C, Dahnert I, Mockel A, Kostelka M, Schneider P. Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine: results from a prospective multicenter study. *Eur J Pediatr.* 2010;169:975–981. doi: 10.1007/s00431-010-1160-4
45. Sharma M, Brown AW, Powell NM, Rajaram N, Tong L, Mourani PM, Schootman M. Racial and skin color mediated disparities in pulse oximetry in infants and young children. *Paediatr Respir Rev.* 2024;50:62–72. doi: 10.1016/j.prrv.2023.12.006
46. Ailes EC, Gilboa SM, Honein MA, Oster ME. Estimated number of in-fants detected and missed by critical congenital heart defect screening. *Pediatrics.* 2015;135:1000–1008. doi: 10.1542/peds.2014-3662
47. Plana MN, Zamora J, Suresh G, Fernandez-Pineda L, Thangaratnam S, Ewer AK. Pulse oximetry screening for critical congenital heart

10.1542/peds.2014-1427

57. Cherestal B, Erickson LA, Noel-MacDonnell JR, Shirali G, Graue Hancock HS, Aly D, Files M, Clauss S, Jayaram N. Association between remote monitoring and interstage morbidity and death in patients with single-ventricle heart disease across socioeconomic groups. *J Am Heart Assoc.* 2023;12:e031069. doi: 10.1161/JAHA.123.031069

58. Tran R, Forman R, Mossialos E, Nasir K, Kulkarni A. Social determinants of disparities in mortality outcomes in congenital heart disease: a systematic review and meta-analysis. *Front Cardiovasc Med.* 2022;9:829902. doi: 10.3389/fcvm.2022.829902

59. Anderson BR, Fieldston ES, Newburger JW, Bacha EA, Glied SA. Disparities in outcomes and resource use after hospitalization for cardiac surgery by neighborhood income. *Pediatrics.* 2018;141:e20172432. doi: 10.1542/peds.2017-2432

60. Tillman AR, Colborn KL, Scott KA, Davidson AJ, Khanna A, Kao D, McKenzie L, Ong T, Rausch CM, Duca LM, et al. Associations between socioeconomic context and congenital heart disease related outcomes in adolescents and adults. *Am J Cardiol.* 2021;139:105–115. doi: 10.1016/j.amjcard.2020.10.040

61. Lopez KN, Baker-Smith C, Flores G, Gurvitz M, Karamlou T, Nunez Gallegos F, Pasquali S, Patel A, Peterson JK, Salemi JL, et al; on behalf of the American Heart Association Congenital Cardiac Defects Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Epidemiology and Prevention; and Council on Lifestyle and Cardiometabolic Health. Addressing social determinants of health and mitigating health disparities across the lifespan in congenital heart disease: a scientific statement from the American Heart Association [published correction appears in *J Am Heart Assoc.* 2022;11:e020758]. *J Am Heart Assoc.* 2022;11:e025358. doi: 10.1161/jaha.122.025358

62. Krishnan A, Jacobs MB, Morris SA, Peyvandi S, Bhat AH, Chelliah A, Chiu JS, Cuneo BF, Freire G, Hornberger LK, et al; Fetal Heart Society. Impact of socioeconomic status, race and ethnicity, and geography on prenatal detection of hypoplastic left heart syndrome and transposition of the great arteries. *Circulation.* 2021;143:2049–2060. doi: 10.1161/CIRCULATIONAHA.120.053062

10.1002/14651858.CD011912.pub2	49. Jawin V, Ang HL, Omar A, Thong MK. Beyond critical congenital heart disease: newborn screening using pulse oximetry for neonatal sepsis and respiratory diseases in a middle-income country. <i>PLoS One.</i> 2015;10:e0137580. doi: 10.1371/journal.pone.0137580
48. Abouk R, Grosse SD, Ailes EC, Oster ME. Association of US state implementation of newborn screening policies for critical congenital heart disease with early infant cardiac deaths. <i>JAMA.</i> 2017;318:2111–2118. doi: 10.1001/jama.2017.17627	63. Zaidi AH, Saleeb SF, <i>Cochrane Database Syst Rev.</i> 2018;3:CD011912. doi: 10.1002/14651858.CD011912.pub2

- de Ferranti SD. Social determinants of health including child opportunity index leading to gaps in care for patients with significant congenital heart disease. *J Am Heart Assoc.* 2024;13:e028883. doi: 10.1161/JAHA.122.028883
64. Judge A, Kramer M, Downing KF, Andrews J, Oster ME, Benavides A, Nembhard WN, Farr SL. Neighborhood social deprivation and healthcare utilization, disability, and comorbidities among young adults with congenital heart defects: congenital heart survey to recognize outcomes, needs, and well-being 2016-2019. *Birth Defects Res.* 2023;115:1608–1618. doi: 10.1002/bdr2.2239
50. Liberman RF, Heinke D, Lin AE, Nestoridi E, Jalali M, Markenson GR, Sekhvat S, Yazdy MM. Trends in delayed diagnosis of critical congenital heart defects in an era of enhanced screening, 2004-2018. *J Pediatr.* 2023;257:113366. doi: 10.1016/j.jpeds.2023.02.012
51. Davey B, Sinha R, Lee JH, Gauthier M, Flores G. Social determinants of health and outcomes for children and adults with congenital heart disease: a systematic review. *Pediatr Res.* 2021;89:275–294. doi: 10.1038/s41390-020-01196-6
52. Peyvandi S, Baer RJ, Chambers CD, Norton ME, Rajagopal S, Ryckman KK, Moon-Grady A, Jelliffe-Pawlowski LL, Steurer MA. Environmental and socioeconomic factors influence the live-born incidence of congenital heart disease: a population-based study in California. *J Am Heart Assoc.* 2020;9:e015255. doi: 10.1161/JAHA.119.015255
53. Miao Q, Dunn S, Wen SW, Loughheed J, Reszel J, Lavin Venegas C, Walker M. Neighbourhood maternal socioeconomic status indicators and risk of

65. Pierpont ME, Brueckner M, Chung WK, Garg V, Lacro RV, McGuire AL, Mital S, Priest JR, Pu WT, Roberts A, et al; on behalf of the American Heart Association Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Genomic and Precision Medicine. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2018;138:e713]. *Circulation*. 2018;138:e653–e711. doi: 10.1161/CIR.0000000000000606
66. Wang X, Li P, Chen S, Xi L, Guo Y, Guo A, Sun K. Influence of genes and the environment in familial congenital heart defects. *Mol Med Rep*. 2014;9:695–700. doi: 10.3892/mmr.2013.1847
67. Pettit KE, Merchant M, Machin GA, Tacy TA, Norton ME. Congenital heart defects in a large, unselected cohort of monochorionic twins. *J Perinatol*. 2013;33:457–461. doi: 10.1038/jp.2012.145

68. Nora JJ, Dodd PF, McNamara DG, Hattwick MA, Leachman RD, Cooley DA. Risk to offspring of parents with congenital heart defects. *JAMA*. 1969;209:2052–2053.
69. Jin SC, Homsy J, Zaidi S, Lu Q, Morton S, DePalma SR, Zeng X, Qi H, Chang W, Sierant MC, et al. Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. *Nat Genet*. 2017;49:1593–1601. doi: 10.1038/ng.3970
70. Hartman RJ, Rasmussen SA, Botto LD, Riehle-Colarusso T, Martin CL, Cragan JD, Shin M, Correa A. The contribution of chromosomal abnormalities to congenital heart defects: a population-based study. *Pediatr Cardiol*. 2011;32:1147–1157. doi: 10.1007/s00246-011-0034-5
71. Korbelt JO, Tirosh-Wagner T, Urban AE, Chen XN, Kasowski M, Dai L. Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. *Proc Natl Acad Sci U S A*. 2009;106:12031–12036. doi: 10.1073/pnas.0813248106
86. Skoric-Milosavljevic D, Tadros R, Bosada FM, Tessadori F, van Weerd JH, Woudstra OI, Tjong FVY, Lahrouchi N, Bajolle F, Cordell HJ, et al. Common genetic variants contribute to risk of transposition of the great arteries. *Circ Res*. 2022;130:166–180. doi: 10.1161/CIRCRESAHA.120.317107
87. Gehlen J, Stundl A, Debiec R, Fontana F, Krane M, Sharipova D, Nelson CP, Kassou B, Giel AS, Sinning JM, et al. Elucidation of the genetic causes of bicuspid aortic valve disease. *Cardiovasc Res*. 2023;119:857–866. doi: 10.1093/cvr/cvac099
72. Soemedi R, Wilson IJ, Bentham J, Darlay R, Topf A, Zelenika D, Cosgrove C, Setchfield K, Thornborough C, Granados-Riveron J, et al. Contribution of global rare copy-number variants to the risk of sporadic

- AC, Jin SC, Gurvitz M, Brueckner M, Chung WK, et al. Association of damaging variants in genes with increased cancer risk among patients with congenital heart disease. *JAMA Cardiol.* 2021;6:457–462. doi: 10.1001/jamacardio.2020.4947
90. Nees SN, Chung WK. The genetics of isolated congenital heart disease. *Am J Hum Genet.* 2012;91:489–501. doi: 10.1016/j.ajhg.2012.08.003
73. Zaidi S, Brueckner M. Genetics and genomics of congenital heart disease. *Circ Res.* 2017;120:923–940. doi: 10.1161/CIRCRESAHA.116.309140
74. Boskovski MT, Homsy J, Nathan M, Sleeper LA, Morton S, Manheimer KB, Tai A, Gorham J, Lewis M, Swartz M, et al. De novo damaging variants, clinical phenotypes, and post-operative outcomes in congenital heart disease. *Circ Genom Precis Med.* 2020;13:e002836. doi: 10.1161/CIRCGEN.119.002836
91. Blue GM, Kirk EP, Giannoulatou E, Dunwoodie SL, Ho JW, Hilton DC, et al. Identification of *TBX2* and *TBX3* variants in patients with conotruncal heart de-

- White SM, Sholler GF, Harvey RP, Winlaw DS. Targeted next-generation sequencing identifies pathogenic variants in familial congenital heart disease. *J Am Coll Cardiol*. 2014;64:2498–2506. doi: 10.1016/j.jacc.2014.09.048 92. Jia Y, Louw JJ, Breckpot J, Callewaert B, Barrea C, Sznajder Y, Gewillig M, Souche E, Dehaspe L, Vermeesch JR, et al. The diagnostic value of next generation sequencing in familial nonsyndromic congenital heart defects. *Am J Med Genet A*. 2015;167:1822–1829. doi: 10.1002/ajmg.a.37108 93. Szot JO, Cuny H, Blue GM, Humphreys DT, Ip E, Harrison K, Sholler GF, Giannoulatos E, Leo P, Duncan EL, et al. A screening approach to identify clinically actionable variants by target sequencing. *Hum Genomics*. 2018;12:44. doi: 10.1186/s40246-018-0176-0
76. Garg V, Kathiriyai IS, Barnes R, Schluterman MK, King IN, Butler CA, Rothrock CR, Eapen RS, Hirayama-Yamada K, Joo K, et al. *GATA4* mutations cause human congenital heart defects and reveal an interaction with *TBX5*. *Nature*. 2003;424:443–447. doi: 10.1038/nature01827
77. Preuss C, Capredon M, Wunnemann F, Chetaille P, Prince A, Godard B, Leclerc S, Sobreira N, Ling H, Awadalla P, et al; MIBAVA Leducq Consortium. Family based whole exome sequencing reveals the multifaceted role of notch signaling in congenital heart disease. *PLoS Genet*. 2016;12:e1006335. doi: 10.1371/journal.pgen.1006335
78. Sewda A, Agopian AJ, Goldmuntz E, Hakonarson H, Morrow BE, Taylor D, Mitchell LE; Pediatric Cardiac Genomics Consortium. Gene-based genome-wide association studies and meta-analyses of conotruncal heart defects. *PLoS One*. 2019;14:e0219926. doi: 10.1371/journal.pone.0219926 79. Page DJ, Miossec MJ, Williams SG, Monaghan RM, Fotiou E, Cordell HJ, Sutcliffe L, Topf A, Bourgey M, Bourque G, et al. Whole exome sequencing reveals the major genetic contributors to nonsyndromic tetralogy of Fallot. *Circ Res*. 2019;124:553–563. doi: 10.1161/CIRCRESAHA.118.313250 80. Agopian AJ, Goldmuntz E, Hakonarson H, Sewda A, Taylor D, Mitchell LE; Pediatric Cardiac Genomics Consortium. Genome-wide association studies and meta-analyses for congenital heart defects. *Circ Cardiovasc Genet*. 2017;10:e001449. doi: 10.1161/CIRCGENETICS.116.001449
81. Richter F, Morton SU, Kim SW, Kitaygorodsky A, Wasson LK, Chen KM, Zhou J, Qi H, Patel N, DePalma SR, et al. Genomic analyses implicate noncoding de novo variants in congenital heart disease. *Nat Genet*. 2020;52:769–777. doi: 10.1038/s41588-020-0652-z
82. Xiao F, Zhang X, Morton SU, Kim SW, Fan Y, Gorham JM, Zhang H, Berkson PJ, Mazumdar N, Cao Y, et al. Functional dissection of human cardiac enhancers and noncoding de novo variants in congenital heart disease. *Nat Genet*. 2024;56:420–430. doi: 10.1038/s41588-024-01669-y

- ease in exome data. *Circ Genom Precis Med*. 2018;11:e001978. doi: 10.1161/CIRCGEN.117.001978
94. Hoang TT, Goldmuntz E, Roberts AE, Chung WK, Kline JK, Deanfield JE, Giardini A, Aleman A, Gelb BD, Mac Neal M, et al. The Congenital Heart Disease Genetic Network Study: cohort description. *PLoS One*. 2018;13:e0191319. doi: 10.1371/journal.pone.0191319
95. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
96. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.
97. Cnota JF, Gupta R, Michelfelder EC, Ittenbach RF. Congenital heart disease infant death rates decrease as gestational age advances from 34 to 40 weeks. *J Pediatr*. 2011;159:761–765. doi: 10.1016/j.jpeds.2011.04.020
98. Swenson AW, Dechert RE, Schumacher RE, Attar MA. The effect of late preterm birth on mortality of infants with major congenital heart defects. *J Perinatol*. 2012;32:51–54. doi: 10.1038/jp.2011.50
99. Shahian DM, Jacobs JP, Edwards FH, Brennan JM, Dokholyan RS, Prager RL, Wright CD, Peterson ED, McDonald DE, Grover FL. The Society of Thoracic Surgeons national database. *Heart*. 2013;99:1494–1501. doi: 10.1136/heartjnl-2012-303456
100. Society of Thoracic Surgeons. The Society of Thoracic Surgeons (STS) national database: congenital heart surgery database participants, spring 2017 harvest. Accessed April 1, 2024. /
101. Spector LG, Menk JS, Knight JH, McCracken C, Thomas AS, Vinocur JM, Oster ME, St Louis JD, Moller JH, Kochilas L. Trends in long-term mortality after congenital heart surgery. *J Am Coll Cardiol*. 2018;71:2434–2446. doi: 10.1016/j.jacc.2018.03.491
83. Kathirya IS, Rao KS, Iacono G, Devine WP, Blair AP, Hota SK, Lai MH, Garay BI, Thomas R, Gong HZ, et al. Modeling human *TBX5* haploinsufficiency predicts regulatory networks for congenital heart disease. *Dev Cell*. 2021;56:292–309.e9. doi: 10.1016/j.devcel.2020.11.020

102. Sanchez-Barriga JJ. Mortality trends from congenital malformations of the heart and the great vessels in children and adults in the seven socio-economic regions of Mexico, 2000-2015. *Congenit Heart Dis.* 2018;13:690–699. doi: 10.1111/chd.12631
84. Audain E, Wilsdon A, Breckpot J, Izarzugaza JMG, Fitzgerald TW, Kahlert AK, Sifrim A, Wunnemann F, Perez-Riverol Y, Abdul-Khaliq H, et al. Integrative analysis of genomic variants reveals new associations of candidate haploinsufficient genes with congenital heart disease. *PLoS Genet.* 2021;17:e1009679. doi: 10.1371/journal.pgen.1009679
85. Lahm H, Jia M, Dressen M, Wirth F, Puluca N, Gilsbach R, Keavney BD, Cleuziou J, Beck N, Bondareva O, et al. Congenital heart disease risk loci identified by genome-wide association study in European patients. *J Clin Invest.* 2021;131:141837. doi: 10.1172/JCI141837

103. Metcalf MK, Rychik J. Outcomes in hypoplastic left heart syndrome. *Pediatr Clin North Am*. 2020;67:945–962. doi: 10.1016/j.pcl.2020.06.008
104. Marathe SP, Cao JY, Celermajer D, Ayer J, Sholler GF, d'Udekem Y, Winlaw DS. Outcomes of the Fontan operation for patients with heterotaxy: a meta-analysis of 848 patients. *Ann Thorac Surg*. 2020;110:307–315. doi: 10.1016/j.athoracsur.2019.11.027
105. Morris SA, Ethen MK, Penny DJ, Canfield MA, Minard CG, Fixler DE, Nembhard WN. Prenatal diagnosis, birth location, surgical center, and

- neonatal mortality in infants with
2014;129:285–292. doi:
106. Anderson BR, Dragan K, Crook S, Woo JL, JW, Jacobs M, Bacha EA, Vincent R, et al: Heart Surgery Collaborative for Resources (CHS-COLOUR). Improving and equity in the care of patients with *Cardiol*. 2021;78:1703–1713. doi:
 107. Kempny A, Diller GP, Dimopoulos K, Li W, Babu-Narayan S, Swan L, Wort SJ. of outpatient clinic attendance amongst heart disease and outcome. *Int J Cardiol*. 10.1016/j.ijcard.2015.10.081
 108. Diller GP, Arvanitaki A, Opatowsky AR, Jenkins K, Moons P, Kempny A, Tandon A, Redington A, Khairy P, Mital S, et al. Lifespan perspective on congenital heart disease research: JACC state-of-the-
 122. Irving SY, Ravishankar C, Miller M, B. Anthropometry based growth and complex congenital heart disease. 10.1177/10547738221075720
 123. Bolduc M-E, Dionne E, Gagnon I, M. Motor impairment in children with review. *Pediatrics*. 2020;146:1–16.
 124. Werninger I, Ehrler M, Wehrle FM, Valsangiacomo Buechel ER, Latal B. 10-year-old children with congenital factors. *Front Pediatr*. 2020;8:604918.
 125. Gonzalez VJ, Kimbro RT, Cutitta KE, Lopez KN. Mental health disorders in art review. *J Am Coll Cardiol*. 2021;77:2219–2235. doi: 10.1016/j.jacc.2021.03.012

- ease. *Pediatrics*. 2021;147:e20201693. doi: 10.1542/peds.2020-1693 126. Nematollahi M, Bagherian B, Sharifi Z, Keshavarz F, Mehdipour-Rabori R. Self-care status in children with congenital heart disease: a mixed-method study. *J Child Adolesc Psychiatr Nurs*. 2020;33:77–84. doi: 10.1111/jcap.12265
109. Backes ER, Afonso NS, Guffey D, Tweddell JS, Tabbutt S, Rudd NA, O'Harrow G, Molossi S, Hoffman GM, Hill G, et al. Cumulative comorbid conditions influence mortality risk after staged palliation for hypoplastic left heart syndrome and variants. *J Thorac Cardiovasc Surg*. 2023;165:287–298.e4. doi: 10.1016/j.jtcvs.2022.01.056
110. Kauw D, Schoormans D, Sieswerda GT, Van Melle JP, Vliegen HW, Van Dijk APJ, Hulsbergen-Zwarts MS, Post MC, Ansink TJ, Mulder BJM, et al. Type D personality associated with increased risk for mortality in adults with congenital heart disease. *J Cardiovasc Nurs*. 2022;37:192–196. doi: 10.1097/JCN.0000000000000747
111. Meakins LT, Knox P, Legge L, Penner M, Wiebe P, Mackie AS. Interstage mortality among infants with hypoplastic left heart syndrome: outcomes of a multicenter home monitoring program. *Prog Pediatr Cardiol*. 2023;68:101610. doi: 10.1016/j.ppedcard.2022.101610
112. Rudd NA, Ghanayem NS, Hill GD, Lambert LM, Mussatto KA, Nieves JA, Robinson S, Shirali G, Steltzer MM, Uzark K, et al; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Interstage home monitoring for infants with single ventricle heart disease: education and management: a scientific statement from the American Heart Association. *J Am Heart Assoc*. 2020;9:e014548. doi: 10.1177/2164275020954441

127. Soares C, Vieira RJ, Costa S, Moita R, Andrade M, Guimaraes H. Neurodevelopment outcomes in the first 5 years of the life of children with rioid: systematic review and meta-analysis. *Cardiol Young*. 2023;33:2471–2480. doi: 10.1017/S104795112300375X
128. Pelosi C, Kauling RM, Cuypers J, van den Bosch AE, Helbing WA, Utens E, Legerstee JS, Roos-Hesselink JW. Daily life and psychosocial functioning of adults with congenital heart disease: a 40-53 years af- ter surgery follow-up study. *Clin Res Cardiol*. 2023;112:880–890. doi: 10.1007/s00392-022-02132-w
129. Pelosi C, Kauling RM, Cuypers J, Utens E, van den Bosch AE, Kardys I, Bogers A, Helbing WA, Roos-Hesselink JW, Legerstee JS. Executive functioning of patients with congenital heart disease: 45 years after surgery. *Clin Res Cardiol*. 2023;112:1417–1426. doi: 10.1007/s00392-023-02187-3
130. Sprong MCA, van Brussel M, de Vries LS, van der Net J, Nijman J, Breur JMPJ, Slieker MG. Longitudinal motor-developmental outcomes in in- fants with a critical congenital heart defect. *Children*. 2022;9:570. doi: 10.3390/children9040570
131. Perrotta ML, Saha P, Zawadzki R, Beidelman M, Ingelsson E, Lui GK, Priest JR. Adults with mild-to-moderate congenital heart disease demonstrate measurable neurocognitive deficits. *J Am Heart Assoc*. 2020;9:e015379. doi: 10.1161/JAHA.119.014548
113. Gardner MM, Mercer-Rosa L, Faerber J, DiLorenzo MP, Bates KE, Stagg A, Natarajan SS, Szwaast A, Fuller S, Mascio CE, et al. Association of a home monitoring program with interstage and stage 2 outcomes. *J Am Heart Assoc*. 2019;8:e010783. doi: 10.1161/JAHA.118.010783
114. Cahill TJ, Jewell PD, Denne L, Franklin RC, Frigiola A, Orchard E, Prendergast BD. Contemporary epidemiology of infective endocarditis in patients with congenital heart disease: a UK prospective study. *Am Heart J*. 2019;215:70–77. doi: 10.1016/j.ahj.2019.05.014
115. Van De Bruaene A, Hickey EJ, Kovacs AH, Crean AM, Wald RM, Silversides CK, Redington AN, Ross HJ, Alba AC, Billia F, et al. Phenotype, manage-ment and predictors of outcome in a large cohort of adult congenital heart disease patients with heart failure. *Int J Cardiol*. 2018;252:80–87. doi: 10.1016/j.ijcard.2017.10.086
116. Rehan R, Kotchetkova I, Cordina R, Celermajer D. Adult congenital heart disease survivors at age 50 years: medical and psychosocial status. *Heart Lung Circ*. 2021;30:261–266. doi: 10.1016/j.hlc.2020.05.114
117. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Gilljam T, Hansson PO, Skoglund K, Fedchenko M, Dellborg M. Atrial fibrillation burden in young patients with congenital heart disease. *Circulation*. 2018;137:928–937. doi: 10.1161/CIRCULATIONAHA.117.029590
118. Capestro A, Soura E, Compagnucci P, Casella M, Marzullo R, Dello Russo A. Atrial Flutters in adults with congenital heart disease. *Card Electrophysiol Clin*. 2022;14:501–515. doi: 10.1016/j.ccep.2022.05.008
119. El Sayegh S, Ephrem G, Wish JB, Moe S, Lim K. Kidney disease and con-genital heart disease: partnership for life. *Front Physiol*. 2022;13:970389.

132. Atallah J, Garcia Guerra G, Joffe AR, Bond GY, Islam S, Ricci MF, AlAklabi M, Rebeyka IM, Robertson CMT. Survival, neurocognitive, and functional out-comes after completion of staged surgical palliation in a cohort of patients with hypoplastic left heart syndrome. *J Am Heart Assoc.* 2020;9:e013632. doi: 10.1161/jaha.119.013632
133. Haiduc AA, Ogunjimi M, Shammus R, Mahmood S, Kutty R, Lotto A, Guerrero R, Harky A, Dhannapuneni R. COVID-19 and congenital heart disease: an insight of pathophysiology and associated risks. *Cardiol Young.* 2021;31:233–240. doi: 10.1017/S1047951120003741
134. Asbeutah AAA, Jefferies JL. Meta-analysis of the incidence of liver cirrhosis among patients with a Fontan circulation. *Am J Cardiol.* 2022;177:166–167. doi: 10.1016/j.amjcard.2022.05.009
135. Lebherz C, Frick M, Panse J, Wienstroer P, Brehmer K, Kerst G, Marx N, Mathiak K, Hövels-Gürich H. Anxiety and depression in adults with congenital heart disease. *Front Pediatr.* 2022;10:906385. doi: 10.3389/fped.2022.906385
136. Marino BS, Cassidy A, Brown KL, Franklin R, Gaynor JW, Cvetkovic M, Laker S, Levinson K, MacGloin H, Mahony L, et al. Long-term quality of life in congenital heart disease surgical survivors: multicenter retrospective study of surgical and ICU explanatory factors. *Pediatr Crit Care Med.* 2023;24:391–398. doi: 10.1097/PCC.0000000000003190
137. Martínez-Quintana E, Estupiñán-León H, Rojas-Brito A-B, Déniz-Déniz L, Barreto-Martín A, Rodríguez-González F. Quality of life in congenital heart disease patients according to their anatomical and physiological classification. *Congenit Heart Dis.* 2023;18:197–206. doi: 10.3389/fphys.2022.970389
120. Gillesen M, Fedchenko M, Giang KW, Dimopoulos K, Eriksson P, Dellborg M, Mandalenakis Z. Chronic kidney disease in patients with congenital heart disease: a nationwide, register-based cohort study. *Eur Heart J Open.* 2022;2:oeac055. doi: 10.1093/ehjopen/oeac055
121. Ntiloudi D, Rammos S, Giannakoulas G. Growth failure in patients with hypoplastic left heart syndrome: an ongoing challenge. *Int J Cardiol.* 2022;364:50–51. doi: 10.1016/j.ijcard.2022.06.011

138. Karamlou T, Hawke JL, Zafar F, Kafle M, Tweddell JS, Najm HK, Frebis JR, Bryant RG 3rd. Widening our focus: characterizing socioeconomic and racial disparities in congenital heart disease. *Ann Thorac Surg*. 2022;113:157–165. doi: 10.1016/j.athoracsur.2021.04.008
139. Chan J, Collins RT 2nd, Hall M, John A. Resource utilization among adult congenital heart failure admissions in pediatric hospitals. *Am J Cardiol*. 2019;123:839–846. doi: 10.1016/j.amjcard.2018.11.033

140. Agarwal A, Dudley CW, Nah G, Hayward R, Tseng ZH. Clinical outcomes during admissions for heart failure among adults with congenital heart disease. *J Am Heart Assoc.* 2019;8:e012595. doi: 10.1161/JAHA.119.012595
141. Agarwal A, Vittinghoff E, Myers JJ, Dudley RA, Khan A, John A, Marcus GM. Ambulatory health care service use and costs among commercially insured US adults with congenital heart disease. *JAMA Network Open.* 2020;3:e2018752. doi: 10.1001/jamanetworkopen.2020.18752
142. Faraoni D, Nasr VG, DiNardo JA. Overall hospital cost estimates in children with congenital heart disease: analysis of the 2012 Kid's Inpatient Database. *Pediatr Cardiol.* 2016;37:37–43. doi: 10.1007/s00246-015-1235-0
143. Simeone RM, Oster ME, Cassell CH, Armour BS, Grav DT, Honein
144. Mackie AS, Tran DT, Marelli AJ, Kaul P. Cost of congenital heart disease hospitalizations in Canada: a population-based study. *Can J Cardiol.* 2017;33:792–798. doi: 10.1016/j.cjca.2017.01.024
145. Essaid L, Strassle PD, Jernigan EG, Nelson JS. Regional differences in cost and length of stay in neonates with hypoplastic left heart syndrome. *Pediatr Cardiol.* 2018;39:1229–1235. doi: 10.1007/s00246-018-1887-7
146. Strange GA, Veerappan S, Alphonso N, Refeld S, Simon S, Justo R. Prevalence and cost of managing paediatric cardiac disease in Queensland. *Heart Lung Circ.* 2021;30:254–260. doi: 10.1016/j.hlc.2020.06.002
147. McHugh KE, Mahle WT, Hall MA, Scheurer MA, Moga MA, Friedman J, Nicolson SC, Amula V, Cooper DS, Schamberger M, et al; Pediatric Heart Network Investigators. Hospital costs related to early extubation after infant cardiac surgery. *Ann Thorac Surg.* 2019;107:1421–1426. doi: 10.1016/j.athoracsur.2018.10.019
160. Groisman B, Barbero P, Liascovich R, Brun P, Bidondo MP. Detection of critical congenital heart disease among newborns in Argentina through the National Surveillance System of Congenital Heart Disease (RENAC). *Arch Argent Pediatr.* 2022;120:6–13. doi: 10.5546/aap.2022.eng.6
161. Zikarg YT, Yirdaw CT, Aragie TG. Prevalence of congenital septal defects among congenital heart defect patients in East Africa: a systematic review and meta-analysis. *PLoS One.* 2021;16:e0250006. doi: 10.1371/journal.pone.0250006
162. Lucron H, Brard M, d'Orazio J, Long L, Lambert V, Zedong-Assountsa S, Le Harivel de
148. Ludomirsky AB, Bucholz EM, Newburger JW. Association of financial hardship because of medical bills with adverse outcomes among families of children with congenital heart disease. *JAMA Cardiol.* 2021;6:713–717. doi: 10.1001/jamacardio.2020.6449
149. Johnson JT, Scholtens DM, Kuang A, Feng XY, Eltayeb OM, Post LA, Marino BS. Does value vary by center surgical volume for neonates with truncus arteriosus? A multicenter study. *Ann Thorac Surg.* 2021;112:170–177. doi: 10.1016/j.athoracsur.2020.05.178
150. Reddy KP, Jones AL, Naim MY, Mercer-Rosa L. Association of race and ethnicity with resource utilisation among children with CHD: an evaluation of the National Health Interview Survey, 2010–2018. *Cardiol Young.* 2023;33:1471–1473. doi: 10.1017/S1047951123000033
151. Liu Y, Chen S, Zuhlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol.* 2019;48:455–463. doi: 10.1093/ije/dyz009
152. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation.* University of Washington. Accessed July 1, 2024.

- Martin GR, Wilner LB, et al. Global, regional, and national time trends in mortality for congenital heart disease, 1990–2019: an age-period-cohort analysis for the Global Burden of Disease 2019 study. *eClinicalMedicine*. 2022;43:101249. doi: 10.1016/j.eclinm.2021.101249
164. Gordon JB, Daniels LB, Kahn AM, Jimenez-Fernandez S, Vejar M, Numano F, Burns JC. The spectrum of cardiovascular lesions requiring intervention in adults after Kawasaki disease. *JACC Cardiovasc Interv*. 2016;9:687–696. doi: 10.1016/j.jcin.2015.12.011
165. Xie X, Shi X, Liu M. The roles of genetic factors in kawasaki disease: a systematic review and meta-analysis of genetic association studies. *Pediatr Cardiol*. 2018;39:207–225. doi: 10.1007/s00246-017-1760-0
166. Nakamura Y. Kawasaki disease: epidemiology and the lessons from it. *Int J Rheum Dis*. 2018;21:16–19. doi: 10.1111/1756-185X.13211
167. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, et al; on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association [published correction appears in *Circulation*. 2019;140:e181–e84]. *Circulation*. 2017;135:e927–e999. doi: 10.1161/CIR.0000000000000484
168. Ghimire LV, Chou FS, Mahotra NB, Sharma SP. An update on the epidemiology, length of stay, and cost of Kawasaki disease hospitalisation in the United States. *Cardiol Young*. 2019;29:828–832. doi: 10.1017/S1047951119000982
169. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997–2007. *Pediatr Infect Dis J*. 2010;29:483–488. doi: 10.1097/INF.0b013e3181cf8705
170. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, Forbes S, Schonberger LB, Melish M. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Med J*. 2010;69:194–197.
153. Zhao L, Chen L, Yang T, Wang T, Zhang S, Chen L, Ye Z, Luo L, Qin J, Birth J, Forbes S, Schonberger LB, Melish M. Racial/ethnic differences in the prevalence of congenital heart disease in China, 1980–2019: a systematic review and meta-analysis of 617 studies. *Eur J Epidemiol*. 2020;35:631–642. doi: 10.1007/s10654-020-00653-0
154. Yan H, Zhai B, Feng R, Wang P, Zhang Y, Wang Y, Hou Y, Zhou Y. S, Zhou L, et al. Prevalence and risk factors for congenital heart defects among children in the multi-ethnic Yunnan region of China. *Transl Pediatr*. 2022;11:813–824. doi: 10.21037/tp-21-371
- Prevalence of congenital heart disease in Chinese children with different birth weights and its relationship to the neonatal birth weight. *Front Pediatr*. 2022;10:828300. doi: 10.3389/fped.2022.828300
155. Pan F, Li J, Lou H, Li J, Jin Y, Wu T, Pan L, An J, Xu J, Cheng W, et al. Geographical and socioeconomic factors influence the birth prevalence of congenital heart disease: a population-based cross-sectional study in eastern China. *Curr Probl Cardiol*. 2022;47:101341. doi: 10.1016/j.cpcardiol.2022.101341
156. Cao Y, Huang R, Kong R, Li H, Zhang H, Li Y, Liang L, Xiong D, Han 157. Agarwal A, Al Amer SR, Kalis NN. Epidemiology of congenital heart disease in the Kingdom of Bahrain. *Bahrain Med Bull*. 2020;42:192–195.
158. El-Chouli M, Mohr GH, Bang CN, Malmberg M, Ahlehoff O, Torp-Pedersen C, Gerds TA, Idorn L, Raunsø J, Gislason G. Time trends in simple congenital heart disease over 39 years: a Danish nationwide study. *J Am Heart Assoc*. 2021;10:e020375. doi: 10.1161/JAHA.120.020375
159. Bah MNM, Sopian MH, Alias EY. Birth prevalence and late diagnosis of critical congenital heart disease: a population-based study from a middle-income country. *Ann of Pediatr Cardiol*. 2020;13:320–326. doi: 10.4103/apc.APC_35_20

171. Lim JH, Kim YK, Min SH, Kim SW, Lee YH, Lee JM. Seasonal trends of viral prevalence and incidence of Kawasaki disease: a Korea public health data analysis. *J Clin Med*. 2021;10:3301. doi: 10.3390/jcm10153301
172. Shulman S, Geevarghese B, Kim K-Y, Rowley A. The impact of social distancing for COVID-19 upon diagnosis of Kawasaki disease. *Pediatr Infect Dis Soc*. 2021;10:742–744. doi: 10.1093/jpids/piab013
173. Kang JM, Kim YE, Huh K, Hong J, Kim DW, Kim MY, Jung SY, Kim JH, Jung J, Ahn JG. Reduction in Kawasaki disease after nonpharmaceutical interventions in the COVID-19 era: a nationwide observational study in Korea. *Circulation*. 2021;143:2508–2510. doi: 10.1161/CIRCULATIONAHA.121.054785
174. Maddox RA, Holman RC, Uehara R, Callinan LS, Guest JL, Schonberger LB, Nakamura Y, Yashiro M, Belay ED. Recurrent Kawasaki disease: USA and Japan. *Pediatr Int*. 2015;57:1116–1120. doi: 10.1111/ped.12733
175. Sudo D, Nakamura Y. Nationwide surveys show that the incidence of recurrent Kawasaki disease in Japan has hardly changed over the last 30 years. *Acta Paediatr*. 2017;106:796–800. doi: 10.1111/apa.13773
176. Manlhiot C, O'Shea S, Bernknopf B, LaBelle M, Chahal N, Dillenburg RF, Lai LS, Bock D, Lew B, Masood S, et al. Epidemiology of Kawasaki disease in Canada 2004 to 2014: comparison of surveillance using administrative data vs periodic medical record review. *Can J Cardiol*. 2018;34:303–309. doi: 10.1016/j.cjca.2017.12.009
177. Lee YC, Kuo HC, Chang JS, Chang LY, Huang LM, Chen MR, Liang CD, Chi H, Huang FY, Lee ML, et al; Taiwan Pediatric ID Alliance. Two new

- susceptibility loci for Kawasaki disease association analysis. *Nat Genet.*
178. Burrner D, Davila S, Breunis WB, Ng SB, Li VJ, Thalamuthu A, Odam M, et al; Consortium. A genome-wide association tionally related susceptibility loci for 2009;5:e1000319. doi:
 179. Khor CC, Davila S, Breunis WB, Lee YC, Tan DE, Sim KS, Wang JJ, et al; Hong Genetics Consortium, Korean Kawasaki Taiwan Kawasaki Disease Genetics Alliance, Japan Kawasaki Disease Genome Disease Genetics Consortium, International Consortium, U. S. Kawasaki Disease Genetics Consortium and Blue Mountains Eye Study. Genome-wide association study identifies *FCGR2A* as a susceptibility locus for Kawasaki disease. *Nat Genet.* 2011;43:1241–1246. doi: 10.1038/ng.981
 180. Onouchi Y, Ozaki K, Burns JC, Shimizu C, Terai M, Hamada H, Honda
 193. Ogata S, Tremoulet AH, Sato Y, Ueda Silverstein L, Baker AL, Tanaka N, et children with Kawasaki disease in the *Cardiol.* 2013;168:3825–3828. doi:
 194. Fabi M, Andreozzi L, Frabboni I, Dormi Tchana B, Francavilla R, Sforzati M, vonder age, and IVIG aneurysms in Italian children with 2021;40:1507–1514. doi:
 195. Moreno E, Garcia SD, Bainto E, Ulloa-Gutierrez R, Garrido-Garcia LM, REKAMLATINA-2 Study Group of Kawasaki disease in Latin T, Suzuki H, Suenaga T, Takeuchi T, et al; Japan Kawasaki Disease Genome Consortium and U. S. Kawasaki Disease Genetics Consortium. A genome-

- of age: a multinational multicenter study of the REKAMLATINA Network. *Front Pediatr.* 2020;8:384. doi: 10.3389/fped.2020.00384
196. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics.* 2003;112:495–501. doi: 10.1542/peds.112.3.495
197. Chang RK. Hospitalizations for Kawasaki disease among children in the United States, 1988-1997. *Pediatrics.* 2002;109:e87. doi: 10.1542/peds.109.6.e87
- wide association study identifies three new risk loci for Kawasaki disease. *Nat Genet.* 2012;44:517–521. doi: 10.1038/ng.2220
181. Johnson TA, Mashimo Y, Wu JY, Yoon D, Hata A, Kubo M, Takahashi A, Tsunoda T, Ozaki K, Tanaka T, et al; Korean Kawasaki Disease Genetics

198. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, Kojo T, Aoyama Y, Kotani K, Yanagawa H. Epidemiological observations of Kawasaki disease in Japan, 2013–2014. *Pediatr Int*. 2018;60:581–587. doi: 10.1111/ped.13544
- Consortium, Taiwan Kawasaki Disease Genetics Consortium, Taiwan Pediatric ID Alliance, Japan Kawasaki Disease Genome Consortium. Association of an *IGHV3-66* gene variant with Kawasaki disease. *J Hum Genet*. 2021;66:475–489. doi: 10.1038/s10038-020-00864-z
182. Hoggart C, Shimizu C, Galassini R, Wright VJ, Shailes H, Bellos E, Herberg JA, Pollard AJ, O'Connor D, Choi SW, et al; International Kawasaki Disease Genetics Consortium, U. K. Kawasaki Disease Genetics Consortium, and EUCLIDS Consortium. Identification of novel locus associated with coronary artery aneurysms and validation of loci for susceptibility to Kawasaki disease. *Eur J Hum Genet*. 2021;29:1734–1744. doi: 10.1038/s41431-021-00838-5
183. Onouchi Y. The genetics of Kawasaki disease. *Int J Rheum Dis*. 2018;21:26–30. doi: 10.1111/1756-185X.13218
184. Chang CL, Lin MC, Lin CH, Ko TM. Maternal and perinatal factors associated with Kawasaki disease among offspring in Taiwan. *JAMA Netw Open*. 2021;4:e213233. doi: 10.1001/jamanetworkopen.2021.3233
185. Kuo NC, Lin CH, Lin MC. Prenatal and early life exposure to air pollution and the incidence of Kawasaki disease. *Sci Rep*. 2022;12:3415. doi: 10.1038/s41598-022-07081-y
186. Huang YH, Hsin YC, Wang LJ, Feng WL, Guo MMH, Chang LS, Tu YK, Kuo HC. Treatment of Kawasaki disease: a network meta-analysis of four dosage regimens of aspirin combined with recommended intravenous immunoglobulin. *Front Pharmacol*. 2021;12:725126. doi: 10.3389/fphar.2021.725126
187. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev*.

199. Garcia-Pavon S, Yamazaki-Nakashimada MA, Baez M, Borjas-Aguilar KL, Murata C. Kawasaki disease complicated with macrophage activation syn-drome: a systematic review. *J Pediatr Hematol Oncol*. 2017;39:445–451. doi: 10.1097/MPH.0000000000000872
200. Lin MT, Sun LC, Wu ET, Wang JK, Lue HC, Wu MH. Acute and late coronary outcomes in 1073 patients with Kawasaki disease with and without intra-venous gamma-immunoglobulin therapy. *Arch Dis Child*. 2015;100:542– 547. doi: 10.1136/archdischild-2014-306427
201. Manlhiot C, Millar K, Golding F, McCrindle BW. Improved classifica- tion of coronary artery abnormalities based only on coronary artery z- scores after Kawasaki disease. *Pediatr Cardiol*. 2010;31:242–249. doi: 10.1007/s00246-009-9599-7
202. Narayan HK, Lizcano A, Lam-Hine T, Ulloa-Gutierrez R, Bainto EV, Garrido-Garcia LM, Estripeaut D, Del Aguila O, Gomez V, Faugier-Fuentes E, et al; Kawasaki Disease RNSG. Clinical presentation and outcomes of Kawasaki disease in children from Latin America: a multicenter observation- al study from the REKAMLATINA Network. *J Pediatr*. 2023;263:113346. doi: 10.1016/j.jpeds.2023.02.001
203. Miura M, Kobayashi T, Kaneko T, Ayusawa M, Fukazawa R, Fukushima N, Fuse S, Hamaoka K, Hirono K, Kato T, et al; The Z-Score Project 2nd Stage Study Group. Association of severity of coronary artery aneurysms in patients with Kawasaki disease and risk of later coronary events. *JAMA Pediatr*. 2018;172:e180030. doi: 10.1001/jamapediatrics.2018.0030
204. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024. 2017;1:CD011188. doi: 10.1002/14651858.CD011188.pub2
188. Burns JC, Roberts SC, Tremoulet AH, He F, Printz BF, Ashouri N, Jain SS, Michalik DE, Sharma K, Truong DT, et al; KIDCARE Multicenter Study Group. Infliximab versus second intravenous immunoglobulin for treat-ment of resistant Kawasaki disease in the USA (KIDCARE): a randomised, multicentre comparative effectiveness trial. *Lancet Child Adolesc Health*.

205. Robinson C, Chanchlani R, Gayowsky A, Darling E, Seow H, Batthish M. Health care utilization and costs following Kawasaki disease. *Paediatr Child Health*. 2022;27:160–168. doi: 10.1093/pch/pxab092
206. Elakabawi K, Lin J, Jiao F, Guo N, Yuan Z. Kawasaki disease: global burden and genetic background. *Cardiol Res*. 2020;11:9–14. doi: 10.14740/cr993
189. Halyabar O, Friedman KG, Sundel RP, Baker AL, Chang MH, Gould PW, Newburger JW, Son MBF. Cyclophosphamide use in treatment of refractory Kawasaki disease with coronary artery aneurysms. *Pediatr Rheumatol Online J*. 2021;19:31. doi: 10.1186/s12969-021-00526-0
190. Suda K, Iemura M, Nishiono H, Teramachi Y, Koteda Y, Kishimoto S, Kudo Y, Itoh S, Ishii H, Ueno T, et al. Long-term prognosis of patients with Kawasaki disease complicated by giant coronary aneurysms: a single-institution experience. *Circulation*. 2011;123:1836–1842. doi: 10.1161/CIRCULATIONAHA.110.978213
191. Dionne A, Bakloul M, Manhiot C, McCrindle BW, Hosking M, Houde C, Pepelassis D, Dahdah N. Coronary artery bypass grafting and percutaneous coronary intervention after Kawasaki disease: the Pediatric Canadian Series. *Pediatr Cardiol*. 2017;38:36–43. doi: 10.1007/s00246-016-1480-x
192. Taddio A, Rossi ED, Monasta L, Pastore S, Tommasini A, Lepore L, Bronzetti G, Marrani E, Mottollese BD, Simonini G, et al. Describing Kawasaki shock syndrome: results from a retrospective study and literature review. *Clin Rheumatol*. 2017;36:223–228. doi: 10.1007/s10067-016-3316-8

207. Nakamura Y, Yashiro M, Yamashita M, Aoyama N, Otaki U, Ozeki Y, Sano T, Kojo T, Ae R, Aoyama Y, et al. Cumulative incidence of Kawasaki disease in Japan. *Pediatr Int*. 2018;60:19–22. doi: 10.1111/ped.13450

208. Wu MH, Lin MT, Chen HC, Kao FY, Huang SK. Postnatal risk of acquiring Kawasaki disease: a nationwide birth cohort database study. *J Pediatr*. 2017;180:80–86.e2. doi: 10.1016/j.jpeds.2016.09.052

209. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child*. 2015;100:1084–1088. doi: 10.1136/archdischild-2014-307536

210. Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of Kawasaki disease in Italy: surveillance from national hospitalization records. *Eur J Pediatr*. 2017;176:1061–1065. doi: 10.1007/s00431-017-2947-3

211. Sanchez-Manubens J, Anton J, Bou R, Iglesias E, Calzada-Hernandez J, Rodó X, Morguí J-A; el Grupo de Trabajo en Enfermedad de Kawasaki en Cataluña. Kawasaki disease is more prevalent in rural areas of Catalonia (Spain) [in Spanish]. *An Pediatr (Barc)*. 2017;87:226–231. doi: 10.1016/j.anpedi.2016.12.009

212. Jakob A, Whelan J, Kordecki M, Berner R, Stiller B, Arnold R, von Kries R, Neumann E, Roubinis N, Robert M, et al. Kawasaki disease in Germany: a prospective, population-based study adjusted for underreporting. *Pediatr Infect Dis J*. 2016;35:129–134. doi: 10.1097/inf.0000000000000953
213. Tulloh RMR, Mayon-White R, Harnden A, Ramanan AV, Tizard EJ, Shingadia D, Michie CA, Lynn RM, Levin M, Franklin OD, et al. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. *Arch Dis Child*. 2018;104:640–646. doi: 10.1136/archdischild-2018-315087
214. Dionne A, Son MBF, Randolph AG. An update on multisystem inflammatory syndrome in children related to SARS-CoV-2. *Pediatr Infect Dis J*. 2022;41:e6–e9. doi: 10.1097/inf.0000000000003393
- 2020;395:1607–1608. doi: 10.1016/S0140-6736(20)31094-1
216. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, Newburger JW, Kleinman LC, Heidemann SM, Martin AA, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383:334–346. doi: 10.1056/NEJMoa2021680
217. Centers for Disease Control and Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. 2023. Accessed May 23, 2024.
218. Buonsenso D, Perramon A, Català M, Torres JP, Camacho-Moreno
221. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, Debray A, Basmaci R, Salvador E, Biscardi S, et al. Kawasaki-like multi-system inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094. doi: 10.1136/bmj.m2094
222. Toubiana J, Cohen JF, Brice J, Poirault C, Bajolle F, Curtis W, Moulin F, Matczak S, Leruez M, Casanova JL, et al. Distinctive features of Kawasaki disease following SARS-CoV-2 infection: a controlled study in Paris, France. *J Clin Immunol*. 2021;41:526–535. doi: 10.1007/s10875-020-00941-0
223. Torpoco Rivera D, Misra A, Sanil Y, Sabzghabaei N, Safa R. Garcia RU. 2020;383:334–346. doi: 10.1056/NEJMoa2021680

224. Hadžić-Kečalović A, Čosićkić A, Pašić A, Selimović A, Sabitović D, Kardašević M, Mršić D. Vitamin D assessment in patients with multisystem inflammatory syndrome and SARS-CoV-2 infection. *Cent Eur J Paediatr*. 2022;18:91–99. doi: 10.5457/p2005-114.321
225. Gawlik AM, Berdej-Szczot E, Chmiel I, Lorek M, Antosz A, Firek-Pędras M, Szydłowski L, Ludwikowska KM, Okarska-Napierała M, Dudek N, et al. A tendency to worse course of multisystem inflammatory syndrome in children with obesity: MultiOrgan Inflammatory Syndromes COVID-19 related study. *Front Endocrinol*. 2022;13:934373. doi: 10.3389/fendo.2022.934373
226. Ptak K, Szymonska I, Olchawa-Czech A, Kukla K, Cisowska M, Kwinta P. G, Rojas-Solano M, Ulloa-Gutierrez R, Camacho-Badilla K, Comparison
- Pérez-Corrales C, Cotugno N, et al. Multisystem inflammatory syndrome in children in Western countries? Decreasing incidence as the pandemic progresses? An observational multicenter international cross-sectional study. *Pediatr Infect Dis J*. 2022;41:989–993. doi: 10.1097/inf.0000000000003713
219. Hamad Saied M, van der Griend L, van Straalen JW, Wulfraat NM, Vastert S, Jansen MHA. The protective effect of COVID-19 vaccines on developing multisystem inflammatory syndrome in children (MIS-C): a systematic literature review and meta-analysis. *Pediatr Rheumatol Online J*.

- dren during different pandemic waves. *Eur J Pediatr*. 2023;182:1647–1656. doi: 10.1007/s00431-022-04790-4
227. Barros LAF, Oliveira VDS, Morais WJ, Dias LA, Almeida JP, Soares MB, Aquino EC, Pinto RM. Pediatric inflammatory multisystemic syndrome in Brazil: sociodemographic characteristics and risk factors to death. *J Pediatr (Rio J)*. 2023;99:31–37. doi: 10.1016/j.jped.2022.04.003
228. Ghodsi AR, Malek A, Siroosbakht S, Aminian A, Dormanesh B, Azarfar A, Zoshk MY. Cardiac outcome of children with SARS-CoV-2 related multisystem inflammatory syndrome. *Indian Pediatr*. 2023;60:381–384. doi: 10.1186/s12969-023-00848-1
220. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, Klein JD, Bhutta ZA. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*. 2020;20:e276–e288. doi: 10.1016/S1473-3099(20)30651-4

229. Yasuhara J, Masuda K, Watanabe K, Shirasu T, Takagi H, Sumitomo N, Lee S, Kuno T. Longitudinal cardiac outcomes of multisystem inflammatory syn-drome in children: a systematic review and meta-analysis. *Pediatr Cardiol*. 2023;44:892–907. doi: 10.1007/s00246-022-03052-2

18. DISORDERS OF HEART RHYTHM

See Table 18-1 and Charts 18-1
through 18-16

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Arrhythmias (Disorders of

2022, United States: Underlying cause mortality—57
725. Any-mention mortality—659 234.

2021, United States: Hospital discharges—604 679.

Bradyarrhythmias

Swedish population-based

The age- and sex-
degree heart block in a
Chinese adults (N=15 181
CI, 0.03%–0.04%).⁶

- In an analysis of standard
264 324 Brazilian primary
lence of complete
ranging from 0.02% in
of age to 0.3% in people

*ICD-9 426.0, 426.1, 427.81; ICD-10 I44.0
to I44.3, I49.5*

2022, United States: Underlying cause
mortality—1700. Any-mention mortality—
10 251.

2021, United States: Hospital
discharges—98 230.

larger Brazilian cohort (N=1 557 901), the prevalence of complete atrioventricular block was far less (0.04%).⁴

- In a post hoc analysis of the LOOP randomized trial, high-grade atrioventricular block was identified in 115 of 6004 trial participants, all of whom were ≥70 years of age and had hypertension, diabetes, HF, or prior stroke.⁹
- Atrioventricular block of varying degrees is reported in 8.6% of patients hospitalized with acute COVID-19 infection.¹⁰ The prevalence appears higher in Asia (22.7%) than in Europe (8.1%) and North America (7.0%).

Disorders of Atrioventricular Conduction

Prevalence and Incidence

Prolonged PR Interval

- The prevalence of PR-interval prolongation ranged between 1.9% (sex-pooled 95% CI, 1.3%–3.0%) and 3.7% (95% CI, 3.1%–4.3%) in studies (N=1081–10 785) conducted in different European countries.^{1–3}

Second-Degree Atrioventricular Block

- Mobitz II second-degree atrioventricular block is rare in healthy individuals (<0.003%),⁴ whereas Mobitz I (Wenckebach) is observed in 1% to 2% of healthy individuals <20 years of age, especially during sleep.⁵ In a population-based sample of Chinese adults (N=15 181 402), the age- and sex-standardized prevalence of second-degree atrioventricular block was reported as 0.18% (95% CI, 0.17%–0.18%)

but was not further classified as Mobitz I or II.⁶

Third-Degree or Complete Heart Block

- The prevalence of complete (third-degree) atrioventricular block is low. The prevalence was 0.11% in a

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Risk Factors

- Sex and race and ethnicity may impart varying risk.
In individuals from MESA (N=1252) without recognized CVD or CVD risk factors, PR-interval reference ranges in individuals ≥65 years of age were reported as 176 milliseconds (32 milliseconds) in males and 162 milliseconds (22 milliseconds) in females of White race; 178 milliseconds (31 milliseconds) in males and 160 milliseconds (19 milliseconds) in females of Black race; and 162 milliseconds (17 milliseconds) in males and 163 milliseconds (18 milliseconds) in females of Hispanic ethnicity.¹¹
- Although a prolonged PR interval and Mobitz type I second-degree atrioventricular block can occur in healthy people, especially during sleep, presence of Mobitz II second- or third-degree atrioventricular block may indicate underlying HD, including CHD, and HF.⁵
- Long sinus pauses and atrioventricular block can occur during sleep apnea, which may be reversible with treatment of the condition.¹² In a meta-analysis of 10 studies (N=1077), the estimated prevalence of daytime atrioventricular nodal disease in individuals with sleep apnea was 6.07% (95% CI, 2.53%–13.87%) and nighttime prevalence (11 studies, N=2177) was 9.94% (95% CI, 3.96%–22.82%).¹²• In multivariable-adjusted analysis including adjustment for competing risk, a full sibling with a history of complete atrioventricular block is associated with a 3-fold increased risk of the condition (HR, 2.91 [95% CI, 2.43–3.49]). In contrast, the risk is 1.5-fold

increased in those with a half-sibling with the condition (HR, 1.51 [95% CI, 0.56–4.10]).⁷

• In a Finnish population-based cohort, risk factors for complete atrioventricular block were older age (HR per 5-year increment, 1.34 [95% CI, 1.16–1.54]), male sex (HR, 2.04 [95% CI, 1.19–3.45]), history of MI (HR, 3.54 [95% CI, 1.33–9.42]), and history of HF (HR, 3.33 [95% CI, 1.10–10.09]).¹³ fasting glucose (HR per 20-mg/dL increase, 1.22 [95% CI, 1.06–1.49]).

Risk Factors

• The causes of SND can be classified as intrinsic (secondary to pathological conditions involving the sinus node, particularly degenerative fibrosis of sinus nodal tissue) or extrinsic (caused by depression of sinus node function by external factors such as drugs or autonomic influences).¹⁸

higher BMI, height, prevalent hypertension, lower heart rate, right bundle-branch block, NT-proBNP, cystatin

Complications

- In the LOOP study, which enrolled individuals 70 to 90 years of age without AF, a PR interval with a duration <120 or >200 milliseconds was associated with an HR of 1.46 (95% CI, 1.14–1.86) for the development of AF.¹⁴
- In a population-based Finnish cohort, a PR interval with duration >220 milliseconds was associated with 3-fold increased risk of SCD (HR, 3.23 [95% CI, 1.88–5.54]), which was attenuated with inclusion of additional electrocardiographic variables (HR, 2.10 [95% CI, 1.20–3.68]).¹⁵
- In a large, prospective, regional French registry of 6662 patients with STEMI presenting from 2006 to 2013, high-degree atrioventricular block was noted in 3.5% of individuals. In 64% of those with high-grade atrioventricular block, this level of conduction disease was present on admission. After multivariable adjustment, high-degree atrioventricular block on admission or occurring during the first 24 hours

C, and history of a major cardiovascular

of hospitalization was not associated with in-hospital mortality (OR, 0.99 [95% CI, 0.60–1.66]).¹⁶

Sinus Node Dysfunction

Prevalence and Incidence

- In a post hoc analysis of the LOOP randomized trial, SND was identified in 270 of 6004 trial participants, all of whom were ≥70 years of age and had hypertension, diabetes, HF, or prior stroke.⁹
- Bradycardia (including SND) has been reported in 12.8% of patients hospitalized with acute COVID-19 infection. The occurrence of bradycardia appears to be higher in Asia (20.5%) than in Europe (10.7%) and North or South America (13.6% and 8.0%, respectively).¹⁰
- A survey of 3846 patients hospitalized with acute COVID-19 infection at 2 London institutions revealed only 6 patients requiring permanent pacemaker implantation (4 implantations were indicated for Mobitz II or complete heart block, and 2 were for SND). All implantations were in males, whose mean age was 82.7 years.¹⁷

Family History and Genetics

- Bradycardia and atrioventricular block have a heritable component. Data from the Danish Civil Registry, including 4 648 204 individuals of whom 26 880 patients received a first-time pacemaker because of atrioventricular block, showed that the adjusted rate ratio for atrioventricular block was 2-fold higher than the general population if an individual had a first-degree relative who received a pacemaker for atrioventricular block (RR, 2.1 [95% CI, 1.8–2.5]).²⁰
- Monogenic cardiomyopathies are associated with bradycardia. For example, *LMNA* cardiomyopathy is associated with atrioventricular block. Rare coding variants in genes affecting ion channels (eg, *HCN4*,²¹ *SCN5A*,²² *RYR2*,²³ *KCNJ3*,²⁴ and *KCNJ5*²⁵) and variants in *ANK2*²⁶ and *TRPM4*²⁷ have been associated with SND in families and sporadic cases with severe forms of disease.
- An examination of the diagnostic yield of targeted genetic screening with a panel of 102 genes associated with inherited cardiac diseases among young patients (<50 years of age) who received a pacemaker for atrioventricular block of unknown cause showed that 5% of the 226 patients included in the study harbored a pathogenic/likely pathogenic variant in genes associated with atrioventricular block.²⁸

Complications

- A large (N=1 692 157) observational study in France demonstrated a higher incidence of stroke in individuals with SND compared with those with other cardiac conditions (HR, 1.27 [95% CI, 1.19–1.35]). In contrast, the study observed that individuals with SND had a lower incidence of stroke compared with those with AF (HR, 0.77 [95% CI, 0.73–0.82]).²⁹

SVT (Excluding AF and Atrial Flutter)

ICD-9 427.0; ICD-10 I47.1

2022, United States: Underlying cause mortality—251. Any-mention mortality—2539.

2021, United States: Hospital discharges—37 065.

Prevalence, Incidence, and Risk

- Analysis of health claims data Commercial Research 2016 identified the prevalence of SVT (including AF/atrial flutter) as 418.0–440.1 per 100 000 and 227.2 (95% CI, 218.9–236.5) per 100 000. Analysis conducted in an electronic health system from 2010 to 2015 found the prevalence of SVT as 140.2 (95% CI, 130.0–150.4) per 100 000 individuals and the prevalence of SVT was more common in females than males.³²
- An analysis of the nationally representative National Emergency Medical Services (NEMS) 2016 to 2018 (N=20.6 million) (excluding AF/atrial flutter) found ED visits in females and 1.5% in males.³³
- A global registry of acute COVID-19 infection had SVTs in 9.7% of patients.³⁴

ter.¹⁰ The prevalence of SVT was reported as higher in Asia (18.2%) than in Europe (10.3%) and North and South America (8.4% and 12.0%, respectively).

Family History and Genetics

- Although general SVT does not appear to have a strong heritable component, atrioventricular nodal reentry tachycardia has shown familial clustering.³⁵ A study of 298 patients with atrioventricular nodal reentry tachycardia and 10 family members with atrioventricular nodal reentry tachycardia identified 229 coding variants in 60 genes. Variants were present predominantly in the ion channel genes such as sodium (*SCN1A*, *SCN2B*, *SCN3A*, *SCN4A*, *SCN5A*, *SCN8A*, *SCN9A*, and *SCN10A*) and calcium (*RYR2*, *RYR3*, *CACNB2*, *ATP2A2*, *CACNA1C*, *CACNA1D*, *CACNA1I*, and *CACNA1G*) handling genes and *HCN1-4*, which has been associated with sinoatrial nodal dysfunction.³⁴
- A European ancestry-based GWAS meta-

analysis found moderate evidence of genetic right ventricular

Complications

- Among 2 350 328 pregnancies in the national insurance database 2012, 769 females had SVT during pregnancy. Compared with the general population, pregnancy was associated with a higher risk of maternal outcomes (severe preeclampsia, preterm labor, fetal stress, and stillbirth) and poor fetal outcomes (low birth weight, small for gestational age, and neonatal intensive care unit admission).³⁶
- In a Swedish study of 214 patients with paroxysmal SVT, 16.2±14.6 years versus 10.2±14.6 years, patients were more likely to report not being consulted for their symptoms and were more symptomatic than males.³⁸

analysis for atrioventricular nodal reentry tachycardia, including 2011 individuals with atrioventricular nodal reentry tachycardia and 316 815 control subjects, identified loci within or near cardiomyocyte genes (*TTN*, *MYH6*, *NKX2-5*) as associated with atrioventricular nodal reentry tachycardia.³⁵

- Patients with arrhythmogenic right ventricular cardiomyopathy can often present with ventricular arrhythmias. The Clinical Genome Resource Gene Curation Expert Panel appraised the 26 genes reportedly associated with arrhythmogenic right ventricular cardiomyopathy and found that only 6 genes (*PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, and *TMEM43*) had strong evidence and 2 genes (*DES* and *PLN*) had

Types of SVT

- Individuals with SVT (N=2260) in a registry in Singapore from 2010 to 2018 had a mean age of 45±18 years. The most common SVT was atrioventricular nodal reentry (57%) followed by atrioventricular reentry (37%) and atrial tachycardia (6%). Generalizability may be limited because all individuals included in the registry underwent catheter ablation.³⁹
- In children, atrioventricular reentrant tachycardia has been identified as the most common SVT mechanism (66%–68% of SVT cases), and the remainder of the patients had predominantly atrioventricular nodal reentrant tachycardia (24%–32%).^{40,41}

WPW Syndrome

Prevalence

- WPW syndrome refers to the presence of ventricular preexcitation on the ECG combined with a related arrhythmia (SVT). A WPW electrocardiographic pattern (ventricular preexcitation) was observed in 44 of 34 965 adults in a population-based Chinese cohort. In males, the prevalence was 0.14% in those 20 to 44 years of age, 0.04% in those 45 to 59 years of age, and 0.02% in those ≥60 years of age. In females, the prevalence was 0.12%, 0.04%, and 0.05% in these age groups, respectively.⁴² In an electrocardiographic study of 32 837 Japanese students, ventricular preexcitation was reported in 0.07%, 0.07%, and 0.17% of elementary, junior high, and high school students, respectively.⁴³

Complications

- WPW syndrome deserves special attention because of the associated risk of sudden death. Sudden

death is generally attributed to rapid heart rates in AF conducting down an accessory pathway and leading to VF.⁴⁴

- A cohort study from Intermountain Healthcare with ≈8 years of follow-up reported that rates of cardiac arrest were low and similar between patients with WPW and referents without WPW. In follow-up, WPW was associated with a significantly higher risk of AF (HR, 1.55 [95% CI, 1.29–1.87]); 7.0% of the 3.8% of those without WPW.⁴⁵

- Asymptomatic adults with ventricular preexcitation

prescription-based data and determined as 1.8% (95% CI, 1.6%–1.9%) in males and 1.0% (95% CI, 1.3%–1.5%) in females. In those age ≥70 years, the prevalence increased to 11.9% (95% CI, 10.3%–13.6%) and 10.1% (95% CI, 8.6%–11.8%), respectively.⁵⁰

- In an integrated regional health care system, the incidence of AF increased

observed in all subgroups by sex and age. The study did not report data on AF incidence by race or ethnicity.⁵¹ appear to be at no increased risk of sudden death compared with the general population.⁴⁴ Although there are rare exceptions, the majority of patients who experience cardiac arrest in association with WPW have had symptomatic SVT.

- An administrative health claims analysis quantified the prevalence of WPW syndrome in children (1–

18 years of age) as 0.03% (8733/26 684 581) over a median follow-up 1.6 years (interquartile range, 0.7–2.9 years).⁴⁶ Of those without CHD or cardio-myopathy, the incidence of a life-threatening event (defined as VF or cardiac arrest) was 0.8 events per

- Investigators from MESA identified clinically detected AF after 14.4 years of follow-up as 11.3% in NH White people, 7.8% in Hispanic people, 6.6% in NH Black people, and 9.9% in those of Chinese origin. In contrast, in these same individuals, the proportion with AF detected with 14-day electrocardiographic monitoring was 7.1% in NH White people, 6.9% in Hispanic people, 6.4% in NH Black people, and 5.2% in those of Chinese origin (Chart 18-1).⁵²• An analysis of Medicare data identified the annual prevalence of AF among American Indian and Alaska Native beneficiaries from 2015 to 2019 as

- A multicenter international survey of 1589 individuals ≤ 21 years of age (mean, 13 years of age) with preexcitation identified that 15% had nonpersistent (intermittent) preexcitation.⁴⁷ Two percent of the study population experienced SCA. Patients with nonpersistent preexcitation were significantly less likely to exhibit high-risk conduction properties of the accessory pathway at electrophysiological study. A total of 29 patients (2%) experienced SCA, and 3 of these individuals had nonpersistent preexcitation. Thus, 1.2% of 244 pediatric patients with nonpersistent preexcitation experienced SCA.

ICD-9 427.3; ICD-10 I48

2022, United States: Underlying cause mortality—28 936. Any-mention mortality—233 966.

2021, United States: Hospital discharges—442 909.

Prevalence

(See Chart 18-1)

- Prevalence of AF in the United States is estimated to increase from ≈ 5.2 million in 2010 to 12.1 million in 2030.⁴⁸ An analysis of 5 medical claims datasets used data from 2012 to 2017 to estimate the prevalence of AF in 2015 in the United States as 6.6 million individuals.⁴⁹

- The prevalence of AF in Greenland in 2022 was estimated from electronic health records and

AF and Atrial Flutter

stable, being 9.4% in 2015 and 9.3% in 2019.⁵³ In a population-based analysis conducted in South Korea, the prevalence of AF increased from 0.73% in 2006 to 1.53% in 2015 and is estimated to reach 5.35% in 2050 and 5.81% in 2060.⁵⁴

- Although the prevalence of undiagnosed AF is unknown, investigators used data from 2015 derived from 5 US medical claims datasets to estimate that 591 000 of ≈5.6 million cases, ie, 11%, were undiagnosed.^{49,55}

Incidence

- Comparison of AF incidence across studies is challenged by differing methods with regard to population studied, restriction by age or comorbidity, and statistical approaches to population-based standardization.
- A secondary analysis of a trial conducting screening for AF in at-risk older adults determined that the incidence of AF among 14 960 individuals was 23.7 per 1000 PY (95% CI, 21.0–26.7).⁵⁶ AF incidence increased with age (14.2 per 1000 PY at 65–69 years of age to 50.8 per 1000 PY at ≥85 years of age).
- In a population-based analysis conducted in South Korea, the incidence of AF between 2006 and 2015 remained flat at 1.77 new cases per 1000 PY during this 10-year observation period.⁵⁴
- A population-based study in England determined that incident AF increased from 247 per 100 000 PY in 1998 to 322 per 100 000 PY in 2017 in

age- and sex-standardized of 1.30 (95% CI, 1.27–1.33).⁵⁷ California State HCUP the incidence of AF in the state of California was people and higher than in ple. and Hispanic people.⁵⁸

*Lifetime Risk and Cumulative Risk
(See Chart 18-2)*

- In the ARIC study, the lifetime mated as 36% (95% CI, 32%–21% (95% CI, 13%–24%) in 22% (95% CI, 16%–25%) in
 - In a population-based study the lifetime risk of AF was (95% CI, 16.7%–14.2%) in CI, 14.4%–14.9%) in
 - The lifetime risk for AF in ancestry has been estimated
- In the BiomarCaRE Consortium including 4 community-based European studies, the incidence of AF began to increase after 50 years of age in males and 60 years of age in

- Analysis of a national health Korea from 2006 to 2015 lence of AF increased 2.10-remained flat (1.8 per 1000 2-year risks of all-cause CI, 0.68–0.93]) and ischemic [95% CI, 0.88–0.93]) after AF
- COVID-19 and AF: A reported a 47% reduction in diagnoses during the period 1, 2020, compared with the (562 versus 1053).⁶⁴ An tudinal prescription claims, institutional claims data from 2020 of individuals receiving (N=1 439 145) identified ED visits, inpatient sions for ischemic stroke or the declaration of the COVID

Risk Factors

females with a cumulative incidence of ≈30% by 90 years of

- The highest PAF for AF was for hypertension followed by BMI, smoking, cardiac disease, and diabetes in ARIC. A large health claims analysis conducted in Japan of individuals 20 to 75 years of age (N=2 597 441, spanning 2005–2020) com-

age.⁶¹

- In an FHS report based on participants with DNA collected after 1980, the lifetime risk of AF after 55 years of age was 37.1% when accounting for both clinical and genetic risk.⁶² A subsequent analysis conducted in the FHS reported that individuals with optimal cardiovascular risk profiles had a lifetime AF risk of 23.4% (95% CI, 12.8%–34.5%), those with a borderline risk profile had a lifetime AF risk of 33.4% (95% CI, 27.9%–38.9%), and those with an elevated risk profile had a lifetime AF risk of 38.4% (95% CI, 35.5%–41.4%; Chart 18-2).⁶³

Secular Trends

- In an integrated health care system, standardized AF incidence rates increased from 4.74 (95% CI, 4.58–4.90) cases per 1000 PY in 2006 to 6.82 (95% CI, 6.65–7.00) cases per 1000 PY in

pared the effect of age on AF risk over 3.3±2.5 2018. The foremost increase in incidence was in those ≥85 years of age.⁵¹ From 2006 to 2018, individuals with AF were more likely to have high BMI (1351/3389 [39.9%] in 2006–2008 versus 4504/9214 [48.9%] in 2015–2018), hypertension (2764 [81.6%] in 2006–2008 versus 7937 [86.1%] in 2015–2018), and ischemic stroke (328 [9.7%] in 2006–2008 versus 1455 [15.8%] in 2015–2018) but less likely to have CAD (1533 [45.2%] in 2006–2008 versus 3810 [41.4%] in 2015–2018). Incidence rates of AF increased in all diagnostic settings and priority pairings.

years of follow-up. In younger individuals (20–49 years of age), the modifiable risk factors of obesity, WC, hypertension, and diabetes were associated with greater risk than in those 50 to 59 or 60 to 75 years of age. For example, in multivariable-adjusted analysis, diabetes in individuals 20 to 49 years was associated with an HR of 1.35 (95% CI, 1.18–1.55) for incident AF compared with 1.10 (95% CI, 1.01–1.21) and 0.93 (95% CI, 0.84–1.03) in those 50 to 59 and 60 to 75 years of age, respectively.⁶⁶

- An analysis in the FHS related electrocardiographic age (determined by deep neural networking to estimate chronological age from the electrocardiogram) every 10-year increase of electrocardiographic age was associated with 23% increase in AF risk (HR, 1.23 [95% CI, 1.17–1.29]).

BP and Hypertension

- In a single-center study (N=47 772), SBP >140 mm Hg was associated with increased risk of AF in Black individuals (HR, 1.14 [95% CI, 1.03–1.27]) and Hispanic individuals (HR, 1.18 [95% CI, 1.06–1.31]) but not NH White individuals (HR, 0.92 [95% CI, 0.83–1.02]) over 3.3 mean years of follow-up.⁶⁸

The PAR (percent) for SBP >140 mm Hg and the development of AF was 4.9 (95% CI, 1.3–8.2), 4.6 (95% CI, 1.8–7.2), and –3.0 (95% CI, –7.0 to 0.5), respectively. • Among 9 797 418 individuals enrolled in the Korean National Health Insurance Service and followed up

from 2009 to 2017, a graded association between hypertension and AF was identified. In reference to nonhypertension, the HR was 1.15 for prehypertension, 1.39 for hypertension without medication, 1.85 for hypertension treated <5 years, and 2.34 for hypertension treated ≥5 years. Each 5-mm Hg increase in SBP and DBP was associated with an increased risk of 4.3% and 4.6%, respectively, of incident AF.⁶⁹ In a meta-analysis of the relationship between hypertension and AF, the summary RR was 1.50 (95% CI, 1.42–1.58; $I^2=98.1\%$; $n=56$ studies) for people with hypertension compared with those without

AF (HR, 1.13 [95% CI, 1.04–1.23] per 5% weight gain). Nonsurgical loss of 5% body weight was not significantly related to AF risk (HR, 1.04 [95% CI, 0.94–1.16]).⁷⁵

- Genetic associations of obesity have been related to risk of AF. A genetic mendelian randomization study conducted in a consortium of 7 cohorts of European ancestry identified hypertension (1 080 611 cases, 30 539 230 participants).⁷⁰ In 37 studies, a 20-mm Hg increase in SBP was associated with 1.18 (95% CI, 1.16–1.21) and a 10-mm Hg increase in

increased risk of incident AF.⁷⁶ A mendelian ran-domization study summarized data from 6 GWASs to relate SNPs associated with adult and childhood obesity, waist-to-hip ratio, childhood BMI, and birth weight to AF.⁷⁷ The analysis concluded that 1-SD increases in adult obesity, childhood BMI, and birth weight were associated with 13%, 18%, and 26%

DBP with a 1.07 (95% CI, 1.03–1.11) increased higher risks of AF.
 risk of AF. The dose-response curve between
 SBP and AF was linear.

devel- oped in 6.3% of those who had obesity and
 3.1% of those without obesity. Individuals with
 obesity had an RR of 1.51 for developing AF (95%
 CI, 1.35– 1.68) compared with those without
 obesity.⁷¹

BMI and Obesity

• In a meta-analysis of 16 studies involving >580
 000 individuals, of whom ≈91 000 had obesity, AF

• The association of weight loss and bariatric surgery
 on AF and its subtypes has been studied in obser-

Smoking

• A meta-analysis of 29 studies identified that current smoking was associated with an RR of 1.32 (95% CI, 1.12–1.56) for AF, former smoking with an RR of 1.09 (95% CI, 1.00–1.18), and ever-smoking with an RR of 1.21 (95% CI, 1.12–1.31) compared with the referent of never having smoked. There appeared to be a dose-response relationship such that the RR per 10 cigarettes/d was 1.14 (95% CI, 1.10–1.20) and the RR per 10 pack-years was 1.16 (95% CI, 1.09–1.25).⁷⁸

ventional studies and clinical trials.⁷² In a limited-sized cohort (N=220) of morbidly obese individuals, reversal of AF type occurred in 92 individuals (71%) who underwent gastric bypass

Diabetes and HbA1c

compared with 36 (56%) who underwent sleeve gastrectomy and 13 (50%) who received gastric banding.

- In a meta-analysis of 8 prospective studies (N=102 006), elevated HbA1c was associated with an increased risk of AF when analyzed continuously (RR, 1.11 [95% CI, 1.06–1.16]) or categorically (RR, 1.09 [95% CI, 1.00–1.18]).⁷⁹

• In a large, prospective Norwegian cohort

• In a meta-

(N=43 602), individuals with BMI 25.0 to 29.9 or ≥ 30 kg/m² had increased risk of AF over a mean 8.1-year follow-up (HR, 1.18 [95% CI, 1.03–1.35]

and HR, 1.59 [95% CI, 1.37–1.84], respectively) than those with BMI <25.0 kg/m².⁷³ High levels of PA slightly attenuated the association of obesity

ing a large outlier study), the RR of diabetes for 1.22–1.35]) and for prediabetes was 1.20 (4 stud-

- A meta-analysis of 4 studies determined that individuals with type 1 diabetes had a higher risk of AF.
- A meta-analysis of 29 studies related anthropometric components to incident AF. A 5–kg/m² increment in BMI was associated with an

incident AF was 1.28 (31 cohort studies [95% CI, 1.03–1.39]).⁸⁰

Individuals with type 1 diabetes had a higher risk of AF (HR, 1.30 [95% CI, 1.15–1.47]) than referents (RR of 1.28 (95% CI, 1.20–1.38) in relation to AF. The risk was nonlinear ($P<0.0001$) with stronger associations

without type 1 diabetes.⁸¹ Subgroup analyses determined that females had an increased AF risk (HR, 1.50 [95% CI, 1.26–1.79]) compared with males and those <65 years of age had increased risk (HR, 1.45 [95% CI, 1.21–1.74]) compared with those observed at higher BMIs, but a BMI of 22 to 24 kg/m² was still associated with excess risk compared with a BMI of 20 kg/m². WC, waist-hip ratio, fat mass, and weight gain also were associated with

- >65 years of age.
increased risk of AF.⁷⁴
- In a meta-analysis of 10 studies (N=108 996), weight gain was associated with increased risk of

- A machine-learning meta-analysis of 29 studies (N=8 037 756) reported similar risks of incident AF in individuals with type 1 and type 2 diabetes. In a meta-analysis, diabetes was associated with an RR of 1.11 (95% CI, 1.01–1.22) for incident AF in males and an RR of 1.38 (95% CI, 1.19–1.60) in females.⁸²

Activity and Exercise
(See Chart 18-3)

- A meta-analysis of 15 studies identified an inverse nonlinear PA and AF risk.⁸³ Results indicating the decreased risk of AF indicating up to 50 METs of task-limited for higher levels of PA.
- An analysis in the Korea National Service (N=66 692) classified

cise status before and after with those who continued not to exercise, those who maintained exercise were significantly less likely to have ischemic stroke (HR, 0.86 [95% CI, 0.77–0.96]), HF (HR, 0.92 [95% CI, 0.88–0.96]),

Miscellaneous Risk Factors

- Other consistently reported include clinical and subclinical ism.⁹⁰ CKD.⁹¹ and moderate or consumption.⁹²
 - Concerning heavy alcohol study (N=100) correlated AF as identified by mobile concluded that ingestion of beverage was associated (95% CI, 1.38–3.17) and or mortality (HR, 0.61 [95% CI, 0.55–0.67]; Chart

with an OR of 3.58 (95% CI, 1.63–7.89) relative to the absence of alcohol use.⁹³ In an n-of-1 clinical trial (N=446), those identifying alcohol as a trigger for AF (n=43) reported 1.8-fold increased odds of AF with alcohol exposure (OR, 1.77 [95%

18-3]).⁸⁴

- A meta-analysis of 9 observational studies concluded that endurance athletes had an increased risk of AF compared with referents not engaging in comparable exertional activity (OR, 2.34 [95%

CI, 1.20–2.69]).⁹⁴

CI, 1.04–5.28]). The investigators reported substantial

– In a meta-analysis of 9 observational studies (N=5436), moderate to high alcohol use was associated with increased risk of AF recurrence after catheter ablation (OR, 1.45 [95% CI, 1.06–1.99]) compared with no or little alcohol use.⁹⁵

heterogeneity in the data and identified the highest risks observed among males and individuals <60 years of age.⁸⁵ A second meta-analysis of 11 studies (N=1 901 833) concluded that cross-country skiing was not associated with increased risk of AF (RR, 0.93 [95% CI, 0.80–1.07]), noting

• Sleep disorders:

significant heterogeneity across studies ($I^2=94.0\%$).⁸⁶

• A meta-analysis of 23 observational studies included

– Meta-analyses have consistently reported the association between the sleep apnea–hypopnea syndrome and a 1.4-fold increased risk of AF. After adjustment for confounders, 2 meta-analyses, both of 8 studies, reported that sleep apnea–hypopnea is associated with an RR of 1.40 (95% CI, 1.12–1.74)⁹⁶ and 1.38 (95% CI, 1.24–1.54)⁹⁷

1 930 725 individuals, in whom there were 45 839 cases of AF. The most physically active had an RR of 0.99 (95% CI, 0.93–1.05) compared with the least active. This association was modified by sex: The most physically active males had an increased risk (RR, 1.20 [95% CI, 1.02–1.42]) and the most physically active females had a decreased risk (RR, 0.91 [95% CI, 0.84–0.99]) for AF.⁸⁷

for AF.

or HFpEF) was not differentially associated with the incidence of AF, but prevalent AF was marginally more strongly associated ($P=0.06$) with multivariable-adjusted incidence of HFpEF (HR, 2.34 [95% CI, 1.48–3.70]) than with HFrEF (HR, 1.32 [95%

HD as a Risk Factor

- Among participants in the FHS, type of HF (HFrEF

- A meta-analysis of sleep quality reported associations between insomnia (N=3 studies) and increased odds of AF (OR, 1.30 [95% CI, 1.26–1.35]) and frequent awakening (N=2 studies) and AF (OR, 1.36 [95% CI, 1.13–1.63]).⁹⁸
- A meta-analysis of 6 studies identified a significant association between short sleep duration (defined as ≤ 6 h/night in 5 studies and ≤ 5 h/night in 1 study) and AF (RR, 1.06 [95% CI, 1.02–1.11]).⁹⁹ Further mendelian randomization analysis relating genetic loci associated to short sleep duration did not determine a relation to AF risk (OR, 0.98 [95% CI, 0.88–1.09]).
- In a prospective, urban-dwelling Japanese cohort (N=6898), short sleep (≤ 6 hours) and irregular sleep (eg, night-shift work) were associated with
 - Individuals with congenital HD are at increased risk of AF. In an analysis in Sweden including 21 982 individuals with congenital HD and 219 816 with-out congenital HD, risk of developing AF was 22 times higher (HR, 22.0 [95% CI, 19.3–25.1]) in those with congenital HD compared with referents without congenital HD.⁸⁹ By 42 years of age, $\approx 8\%$ of patients with congenital HD had been diagnosed

increased risks of AF (HR, 1.34 [95% CI, 1.01–
tively) compared with moderate sleep (7 hours) in
median of 14.5 years of follow-up.¹⁰⁰

- Air pollution

(See Charts 18-4 and 18-5):

- A systematic review and meta-analysis of 18
with AF.

1.77] and HR, 1.63 [95% CI, 1.16–2.30], respec-
multivariable-adjusted analyses over a

studies reported short-term and
long-term

associations of air pollution with AF.¹⁰¹ For every 10- $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} and PM₁₀ (particulates with aerodynamic diameter <10 μm) concentration, the ORs for AF were 1.01 (95% CI, 1.00–1.02) and 1.03 (95% CI, 1.01–1.05), respectively. The corresponding ORs for long-term exposure were 1.07 (95% CI, 1.04–1.10) for PM_{2.5} and 1.03 (95% CI, 1.03–1.04) for PM₁₀. SO₂ and NO₂ also were associated with AF in the short term: ORs for 10-ppb CI, 1.01–1.04), respectively.

• Psychosocial factors:

- Among close to 1 million individuals seeking care through the Veterans Health Administration between 2001 and 2014, a diagnosis of post-traumatic stress disorder was associated with a 13% increased risk of AF after multivariable adjustment (HR, 1.13 [95% CI, 1.02–1.24]).¹⁰⁶
- In the MESA study, higher burden of depression was associated with a 13% increased risk of AF after adjustment for other factors.
- A nationwide, time-stratified case-crossover study using air pollution data from 322 cities in

Epidemiological Studies Depression Scale were compared with those with a score <2. Anger, anxiety, and chronic stress were not associated with

China observed an increased incidence of symptomatic AF and SVT in the 24 hours after higher pollutant exposure (Chart 18-4).¹⁰² The change in the odds of onset of symptomatic

AF risk.¹⁰⁷

AF associated with a 10- $\mu\text{g}/\text{m}^3$ (1 mg/m^3 for CO) increase

- Similarly, in the ARIC study, higher levels of vital exhaustion were associated with increased AF risk (HR, 1.20 [95% CI, 1.06–1.35]). Neither anger nor social isolation was associated with the risk of AF.¹⁰⁸
 - The association of caffeine ingestion and AF has been variable. In the Spanish PREDIMED study, ingestion of 1 to 7 cups of coffee weekly was asso-
- in air pollutant concentrations during lag 0 to 24 hours was 0.6% (95% CI, 0.2%–1.1%) for PM_{2.5}, 1.6% (95% CI, 0.8%–2.4%) for NO₂, and 5.7% (95% CI, 1.8%–9.8%) for CO.

- A meta-analysis of 3 prospective studies evaluating the association between job strain (defined as high demands and low control in the occupational setting) and AF risk reported an HR of 1.37 (95% CI, 1.13–1.67) for those with job strain compared with those without job strain.¹⁰⁹

ciated with • AF frequently occurs secondary to other comorbidities.

tion.¹⁰³ However, a higher level of caffeine ingestion (>1 cup of coffee/d) was not associated with AF risk (HR, 0.79 [95% CI, 0.49–1.28]) compared with no or rare coffee ingestion.

- A follow-up examination of the REGARDS study (n=8977) did not identify an association between Mediterranean diet score (OR, 1.03 [95% CI, 0.95–1.11] per SD) or plant-based dietary pattern (OR, 1.03 [95% CI, 0.94–1.12] per SD) and AF.¹⁰⁴ In addition, less healthy eating was not associated with incident AF during an average 9.4-year follow-up.
- An analysis of the UK Biobank (N=201 856) combined dietary recall of fruit juice and soft drink consumption with the

PRS for AF developed in the cohort (Chart 18-5).¹⁰⁵ Over a median of 9.9-years follow-up, consumption of >2 L/wk of SSBs and ASBs was associated with increased risk of AF in multivariable-adjusted analyses including demographic, social, clinical, and genetic risk factors (HR, 1.10 [95% CI, 1.01–1.20], 1.20 [95% CI, 1.10–1.31], respectively) compared with nonconsumption of SSBs or ASBs. Consumption of >2 L/wk of fruit juice was not associated with increased risk of AF (HR, 1.05 [95% CI, 0.96–1.14]) compared with nonconsumption. However, consumption of ≤1 L/wk of fruit juice was associated with reduced risk of AF (HR, 0.92 [95% CI, 0.87–0.97]) compared with nonconsumption.

- Among 11 239 patients undergoing isolated CABG at 5 sites in the United States between 2002 and 2010, the risk-adjusted incidence of AF was 33.1%, which did not vary significantly over the observation period.¹¹⁰
- A secondary analysis of the PARAGON-HF trial (N=4776) identified that 1552 had AF at trial enrollment. Those with AF at enrollment had 1.3-fold increased risk (RR, 1.31 [95% CI, 1.11–1.54]) of HF hospitalization, the primary outcome of the trial, compared with those without AF.¹¹¹– A meta-analysis of 13 studies (N=52 959) reported that new-onset AF has been observed in 10.9% (95% CI, 7.2%–15.3%) of patients undergoing noncardiac general surgery.¹¹²
- A meta-analysis of 13 studies (N=225 841) determined that new-onset AF during sepsis was associated with ≈2-fold increase in in-hospital mortality (OR, 2.09 [95% CI, 1.53–2.86]), postdischarge mortality (OR, 2.44 [95% CI, 1.81–3.29]), and stroke (OR, 1.88 [95% CI, 1.13–3.14]). The incidence of AF varied with severity of sepsis, from 1.9% in mild sepsis to 46% in septic shock.¹¹³
- AF is a common occurrence in hospitalized patients with acute COVID-19 infection. A meta-analysis of 14 studies (N=17 435) reported an incident atrial arrhythmia (AF, atrial flutter, or atrial

tachycardia) in 8.2% (95% of patients hospitalized with international registry of COVID-19 reported that AF mon arrhythmia in COVID of 827 events (61.5%).¹⁰ A studies (N=13 124) during COVID-related ciated with increased in- 1.86 [95% CI, 1.54–

significant heterogeneity ($I^2=72\%$).

- Limited literature has investigated the associations between cancer and its treatment with risk of AF. A random-effects meta-analysis of 19 anticancer drugs used as monotherapy included 191 clinical trials (47.1% randomized) of 16 anticancer drugs used in 26 604 individuals.¹¹⁶ Summary annualized AF incidence rates ranged from 0.26 (95% CI, 0.11–0.63) to 4.92 (95% CI, 2.91–8.31) per 100 PY in those receiving chemotherapy and 0.25 per 100 PY (95% CI, 0.10–0.65) in those in the placebo arms. A meta-analysis of 8 studies (N=2580) reported that ibrutinib was associated with AF (RR, 4.69 [95% CI, 2.17–7.64]).¹¹⁷ A meta-analysis of 6 studies (N=533 514)

undergo catheter ablation coding.¹²² The analysis may sification and underreporting 3 650 995 hospitalizations for time frame with only 1.2% having health-related social ICD coding. consequently prevalence of health-related

- Further analysis of Canada. of individuals with evaluating the association between new-onset AF and risk of cancer reported a pooled RR of 1.24 (95% CI, 1.10–1.39).¹¹⁸ The association was restricted to the first 90 days after AF diagnosis (RR, 3.44 [95% CI, 2.29–5.57]) with no association after that time.

Social Determinants of AF and Health Equity

See Chart 18-6

- Study of social determinants and AF remains

dence in the fifth quintile of neighborhood-based material deprivation was associated with decreased 1-year likelihood of primary care visits (HR, 0.91 [95% CI, 0.89–0.92]), cardiology visits (HR, 0.84 [95% CI, 0.82–0.86]), receipt of echocardiography (HR, 0.97 [95% CI, 0.96–0.99]), or ambulatory electrocardiographic monitoring (HR, 0.89 [95% CI, 0.87–0.91]). The authors concluded that universal health care systems may still have substantial disparities in health care access.¹²¹

- An analysis of an administrative claims study of individuals with prevalent AF (N=336 736) identified that those with household income <\$40 000/y had increased risks for HF (HR, 1.17, [95% CI, 1.05–1.30]) and MI (HR, 1.18 [95% CI, 0.98–1.41]) compared with those with household income ≥\$100 000/y.¹²³

- A claims-based analysis (N=28 779) related social measures derived at the 3-digit US zip code level to 180- and 360-day adherence to oral anticoagulation from 2016 to 2020 (Chart 18-6).¹²⁴ The analysis determined that geospatially derived, community-based estimate of health literacy, summarized as a social risk score, was associated with decreased anticoagulation persistence at 180 days limited.¹¹⁹ (OR, 0.80 [95% CI, 0.76–0.83]), where

persistence

- In an analysis of a large regional health care system, individuals (N=28 858) living in intermediate-poverty neighborhoods (as defined by census tract-level variables) had higher adjusted odds of

5-year incident AF (OR, 1.23 [95% CI, 1.01–1.48]) compared with those residing in lower-poverty

was calculated as the number of days for which an individual had claims for an oral anticoagulant pre-scription. The analysis further reported that health literacy was associated with decreased likelihood of a proportion of days covered of ≥ 0.80 (OR, 0.81 [95% CI, 0.76–0.87]). The analysis is limited by use

neighborhoods.¹²⁰

- An administrative data analysis of individuals with AF in Ontario, Canada, determined that residence in the fifth quintile of neighborhood-based material deprivation was associated with increased 1-year risk of death (HR, 1.16 [95% CI, 1.13–1.20]), stroke (HR, 1.16 [95% CI, 1.07–1.27]), bleeding (HR, 1.16 [95% CI, 1.13–1.25]), and HF (HR, 1.14 [95% CI, 1.11–1.18]) compared with residence in

of the 3-digit zip code.

the first quartile.¹²¹

- An analysis of the Nationwide Readmission Database using data from 2010 to 2019 determined that individuals categorized as having health-related social needs according to ICD coding were less likely to

- In an analysis in the community-based ARIC study, AF incidence decreased with progressively increased categories of income and education.⁵⁹ The risk of AF in White males with annual income $\geq$ \$50 000 was an RR of 0.76 (95% CI, 0.65–0.88) and in White females of 0.70 (95% CI, 0.59–0.83) compared with those with annual income $<$ \$25 000. Income was not associated with AF risk in Black males; in Black females with annual income $\geq$ \$25 000, the risk was an RR of 0.73 (95% CI, 0.56–0.96) compared with those with annual income $<$ \$25 000. Similar estimates were observed with educational attainment.

- In a limited-sized cohort (N=339) followed up for a median of 2.6 years (range, 0–3.4 years), individuals in the lowest income category ($\leq \$19\,999/\text{y}$) had 2.0-fold greater hospitalization risk (OR, 2.11 [95% CI, 1.08–4.09]) compared with those in the highest income category ($\geq \$100\,000/\text{y}$).¹²⁵
- A Danish population-based study of individuals with incident AF who underwent catheter ablation (N=9728) examined social [95% CI, 1.02–1.17], income (HR, 1.14 [95% CI, 1.06–1.22]), and living alone (HR, 1.07 [95% CI, 1.00–1.13]) were associated with AF recurrence during a median 1.4-year follow-up (quartile 1–3, 0.4–6.3 years) after ablation. These associations were no longer significant after adjustment for comorbid conditions and treatment with antiarrhythmic medications.
- A meta-analysis of 5 studies (N=132 431) determined that individuals of Black race were less
 - A similar analysis in the MESA cohort reported a 27% lower risk of AF over a median follow-up of 11.2 years (interquartile range, 10.6–11.7 years) in participants with optimal CVH (HR, 0.73 [95% CI, 0.59–0.91]) compared with those with inadequate scores without substantive differences by race and likely to receive oral anticoagulation than those of White race (OR, 0.86 [95% CI, 0.75–0.98]).¹²⁷ Heterogeneity of the pooled estimate was high ($I^2=85\%$) with further analysis suggesting that the heterogeneity was attributable to type of anticoagulant (ie, warfarin or DOAC); differences by race were not observed in studies reporting warfarin use, whereas individuals of Black race were less likely compared with those of White race in studies reporting DOAC use.

onset AF include advancing age, European ancestry, body size (greater height and BMI), electrocardiographic features (LVH, LA enlargement), diabetes, BP (SBP and hypertension treatment), and presence of CVD (CHD, HF, valvular HD). In contrast, the HARMS₂-AF score had an AUC of 0.782 (95% CI, 0.775–0.789) in the UK Biobank for 5-year risk prediction of AF and validation in FHS with an AUC of 0.757 (95% CI, 0.735–0.779).¹³⁵

- A CHARGE-AF risk prediction model for AF has been validated in a US multiancestry patient cohort,¹³⁶ in MESA,¹³⁷ in a UK cohort (EPIC Norfolk),¹³⁸ in a post-CABG cohort,¹³⁹ and in a large nationwide primary care database in the Netherlands.¹⁴⁰
- A study evaluating electronic health records in a machine-learning models to predict 6-month incident AF.¹⁴¹ The resulting model had a similar C statistic (0.800) compared with a model using basic regression and established clinical risk factors for AF (C statistic, 0.794).

Risk Prediction of AF

- Investigation of AHA's Life's Essential 8 in relation to AF remains limited. Several studies have examined CVH as determined by Life's Simple 7 in relation to AF:
 - In the REGARDS study, better CVH, as classified by Life's Simple 7, was associated with decreased risk of AF similarly between sexes and in White people and Black people.
- Individuals with optimal CVH (score, 10–14 points) had an adjusted 32% lower risk of AF (OR, 0.68 [95% CI, 0.47–0.99]).¹²⁸
 - The ARIC study observed that cohort participants with average (HR, 0.59 [95% CI, 0.51–0.67]) and optimal (HR, 0.38 [95% CI, 0.32–0.44]) CVH had a lower risk of incident AF. For every 1-point higher Life's Simple 7 score, the risk of AF was 12% lower (HR, 0.88 [95% CI, 0.86–0.89]).¹²⁹
 - In 2363 participants of the ARIC study who underwent continuous electrocardiographic monitoring for 14 days, Life's Simple 7 score was associ-

Borderline Risk Factors

• Data from the FHS examining lifetime risk of AF identified that the prevalence of AF risk factors increased gradually with age. At an index age of 55 years, lifetime AF risk was 37.0% (95% CI, 34.3%–39.6%).⁶³ Lifetime AF risk was 23.4% (95% CI, 12.8%–34.5%) for those with an optimal risk profile, 33.4% (95% CI, 27.9%–38.9%) in those with a borderline risk profile, and 38.4% (95% CI, 35.5%–41.4%) in those with an elevated risk profile. At index ages of 65 and 75 years, the gradient of AF lifetime risk was similar.

Subclinical Atrial Tachyarrhythmias, Unrecognized AF, and Screening for AF

Device-Detected AF

• Cardiac implantable electronic devices (eg, pacemakers and defibrillators) have increased clinician awareness of the frequency of subclinical AF and atrial high-rate episodes in people without a documented history of AF. Documented history of AF. ated with reduced risk of continuous AF (HR, 0.87 [95% CI, 0.79–0.95] per 1-point increase in Life's Simple 7 score) but not with risk of inter-mittent AF (HR, 0.92 [95% CI, 0.83–1.02]).¹³⁰

- A meta-analysis reported that atrial high-rate epi-sodes detected by implanted cardiac devices were associated with $\approx$ 2-fold increased thromboembolic

stroke risk (RR, 2.13 [95% CI, 1.46–3.21]) in studies excluding patients with rhythmias (n=7 studies) and across all studies (N=10 participants: RR, 1.92 [95% CI, 1.46–2.52]).

- A meta-analysis of 9 studies mined that individuals with stroke burden as detected by ECG had an HR of 1.20 (95% CI, 1.04–1.38) for systemic embolism

atrial high-rate episodes.¹⁴³ In contrast, those with a high burden of atrial high-rate episodes had an HR of 2.52 (95% CI, 1.46–4.37) relative to those without atrial high-rate episodes.

Community Screening for Undiagnosed AF (See Charts 18-7 and 18-8)

- The incidence of detecting previously undiagnosed AF by screening depends on the underlying risk of AF in the population studied, the intensity and duration of screening, and the method used to detect AF.¹⁴⁴ Methods vary in their sensitivity and specificity in the detection of undiagnosed AF, increasing from pulse palpation to devices such as hand-held single-lead ECGs, modified BP devices, and plethysmographs.¹⁴⁵
- The prevalence of undiagnosed AF in the community is unknown. Using Medicare and commercial claims data, investigators have estimated that in 2009 ≈0.7 million (13.1%) of the ≈5.3 million AF cases in the United States were undiagnosed. Of the undiagnosed AF cases, investigators estimated that 698 900 were undiagnosed, including 535 400 (95% CI, 331 900–804 400) in individuals ≥65 years of age and 163 500 (95% CI, 17 700–400 000) in individuals 18 to 64 years of age.¹⁴⁶
- A multicenter study conducted in France enrolled individuals (N=336) with palpitations and CHADS₂-

coupled with an automated oscillometric AF screening over a 6-month period.¹⁴⁹ AF was detected in 434 (5.3%) in the screening cohort and 2 of 422 (0.5%) in the control cohort. The number needed to screen (NNS) was 21. By 6 months, AF was more frequently prescribed in the screening cohort (18/434 [4.1%] versus 4/422 [0.9%]).

VASc scores ≥2 in males and ≥3 in females to 14-day electrocardiographic monitoring.¹⁴⁷ AF was detected in 14% of the cohort with detection occurring in the first 24 hours of monitoring in 23.4% in whom the arrhythmia was ascertained.

- A single-center study examined the duration of monitoring for AF detection after ischemic stroke or TIA in 379 individuals at a median of 63 years of age (interquartile range, 55–73 years).¹⁴⁸ There were 10 cases of AF detected, with 7 in the first 48 hours of monitoring (IR, 1.85% [95% CI, 0.74%–3.81%]; number needed to screen, 54) and 3 additional cases with duration of monitoring from 48 hours to 14 days (IR, 0.83% [95% CI, 0.17%–2.42%]; number needed to screen, 121).
- A multicenter, open-label, randomized trial of individuals ≥75 years of age with hypertension compared a 2-week continuous electrocardiographic patch

- A multicenter clinical trial randomized individuals with at least 1 stroke risk factor and without prevalent AF in a 1:3 ratio to receive long-term rhythm monitoring with an implanted loop recorder (n=1501) or usual care (n=4503).¹⁵⁰ Over a median follow-up of 64.5 months (interquartile range, 59.3–69.8 months), those randomized to monitoring were 3-fold more likely to be diagnosed with AF (HR, 3.17 [95% CI, 2.81–3.59]).
- A multicenter, parallel-group RCT conducted in Sweden evaluated the effect of intermittent ECGs for 14 days as an intervention for AF detection on a composite outcome of stroke, systemic embolism, bleeding, and mortality compared with usual care. After a median follow-up of 6.9 years (interquartile range, 6.5–7.2 years), there were significantly fewer primary end-point events in the intervention group (n=13 979; 5.45 events per 100 years [95% CI, 5.52–5.61]) than in the control group (n=13 996; 5.68 events per 100 years [95% CI, 5.52–5.85]). The intervention was associated with an ≈4% reduced risk for the composite outcome (HR, 0.96 [95% CI, 0.92–1.00]).¹⁵¹ Post hoc analysis concluded that this screening approach was cost-effective; screening of 1000 older adults resulted in 10.6 (95% CI, –22.5 to 1.4) fewer strokes.¹⁵²
- An artificial intelligence algorithm analyzed 494 042 ECGs, all in sinus rhythm, obtained from 142 310 patients with and without paroxysmal AF.¹⁵³ The model had an accuracy of 78.1% (95% CI, 77.6%–78.5%), area under the receiver-operating characteristic curve of 0.87 (95% CI, 0.86–0.87), and area under the precision recall curve of 0.48 (95% CI, 0.46–0.50). In a cohort with an AF prevalence of 3%, the area under the precision recall curve decreased to 0.21 (95% CI, 0.18–0.24). In a cohort with AF prevalence of 30%, this figure increased to 0.76 (95% CI, 0.75–0.78).
- A cluster randomized trial examined point-of-care screening with a single-lead ECG in 16 primary care clinics.¹⁵⁴ Of 30 715 individuals enrolled, 1.72% of 15 393 individuals randomized to screening were diagnosed with AF compared with 1.59% of 15 322 individuals randomized to the control arm at 1-year follow-up (risk difference, 0.13% [95% CI, –0.16% to 0.42%]; Chart 18-7).

-
- Screening for AF has been evaluated as cost-effective.
 - A meta-analysis of 26 studies determined that population-based (n=13), opportunistic (n=4), targeted (n=6), and mixed-methods screening (n=3) were superior to no screening. However, only 5 studies were categorized as moderate usefulness for policy, and none of the included studies advocated a policy direction on implementation.
 - In Canada's single-payer health care environment, screening for AF with a single-lead ECG was determined to improve health outcomes and cost savings.¹⁵⁶ A model identified that screening 2 929 301 individuals identified 127 670 cases of AF and estimated avoidance of 12 236 strokes with a gain of 59 577 QALYs (0.02 per patient) over the lifetime of screened individuals.
 - 83 for ≥65 years of age, 926 for 60 to 64 years of age, and 1089 for <60 years of age.¹⁵⁹
 - Another systematic review included 25 published studies from 2000 to 2015 involving 88 786 participants. The investigators reported that the incidence of newly detected AF was 1.5% (95% CI, 1.1%–1.8%) and was higher
 - A post hoc analysis of the STROKESTOP study (N=27 975, all ≥75 years of age, invited to participate in AF screening performed with a handheld ECG for 30 seconds twice daily for 14 days or control) calculated 77 gained life-years and 65 gained QALYs per 1000 individuals invited to the screening group and incremental costs estimated as €1.77 million (\$1.92 million using the average 2023 exchange rate) lower in the screening

- CI, 1.5%–2.8%]) versus single-time-point (1.2% [95% CI, 0.8%–1.6%]) rhythm assessments.¹⁶⁰
- A meta-analysis of 9 RCTs (N=85 209) examining systematic screening, opportunistic screen- ing, and no screening determined that any AF screening (systematic or opportunistic) was associated with higher detection of AF (1.8% versus 1.3%; RR, 2.10 [95% CI, 1.20–3.65]) than no screening.¹⁶¹
 - Wearable, commercially available technology:
 - In the largest study to date, investigators recruited 419 297 Apple Watch owners to participate in a monitoring study to detect possible AF. The median follow-up was 117 days, during which 0.52% (n=2161) received irregular pulse warnings; 450 participants returned an electro- cardiographic patch (on average 13 days after notification) that detected AF in 34%.¹⁶²
 - Systematic reviews of screening:
 - A systematic review by the US Preventive Services Task Force of asymptomatic adults at least 65 years of age included 17 studies (135 300 individuals). Compared with no screening, systematic screening with ECG detected more new cases of AF (over 1 year, absolute increase from 0.6% [95% CI, 0.1%–0.9%] to

- To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications. The minimum duration of AF episodes required to increase risk for stroke is unknown. However, longer episode duration is associated with increased thrombo-embolic risk (Chart 18-8); the threshold varies depending on the presence of other stroke risk factors.¹⁶³
 - 2.8% [95% CI, 0.9%–4.7%]). However, the systematic ECGs did not detect more cases than pulse palpation. Furthermore, none of the studies compared systematic screening and usual care, and none examined health outcomes.¹⁵⁷
- The US Preventive Services Task Force has concluded that evidence for screening for AF in individuals ≥ 50 years of age remains lacking.¹⁵⁸
- A systematic review of 19 studies from 2007 to 2018 identified 24 single-time-point screening

studies; 141 220 participants were included, of whom 1539 had newly detected AF. The detection rate adjusted for age and sex was 1.44% (95% CI, 1.13%–1.82%) in those ≥ 65 years of age and 0.41% in individuals < 65 years of age. The study included low-, middle-, and high-income countries but did not identify geographic region variation in detection rates. The authors estimated that the number needed to screen to identify 1 treatable new AF case varied by age:

Family History and Genetics

- AF is found to be a common presentation in certain monogenic genetic cardiomyopathies, for example, in individuals with *PRKAG2*- or *TTN*-related cardiomyopathy.^{164,165}
- A prospective observational cohort study has noted that among individuals of predominantly European ancestry with early-onset AF (<66 years of age), the prevalence of disease-associated pathogenic/likely pathogenic variants in cardiomyopathy- and arrhythmia-associated genes was 10.1%.¹⁶⁶ The prevalence of the pathogenic/likely pathogenic variants was highest among patients with an AF diagnosed before 30 years of age (≈17%) and was lowest among those diagnosed with AF after 60 years of age (≈7%). Similarly, a study of 227 probands with early AF of African and Hispanic descent showed that 7.0% of the study population

improve risk prediction for AF over models that include only clinical factors.¹³⁴ A study of 229 incident AF cases and >10 000 controls found that the net classification index for an AF GRS for incident AF was 10.0% (95% CI, 4.2%–15.7%) with slightly higher classification ability in early-onset AF cases (net reclassification index, 14.8% [95% CI, 3.8%–25.7%]) and in late-onset cases (net reclassification index, 10.4% [95% CI, 4.1%–16.7%]).¹⁷⁸ In contrast, a study of 5 cohorts with 18 191 individuals found that a GRS associated with incident AF added only marginally to clinical risk prediction.¹⁶⁹

- Many common genetic variants have been identified as associated with AF. A GWAS that included >65 000 patients with AF reported 97 AF-associated loci, including the most consistent genetic locus *PITX2*, 67 of which were novel in combined-ancestry analyses.¹⁷⁰ Another GWAS of >1 000 000 individuals identified 111 independent genes associated with AF, many of which are near deleterious variants that cause more serious heart defects or near genes important for striated muscle function and integrity.¹⁷¹

- Whole-exome/genome sequencing studies have identified rare variants in additional genes associated with AF, including *MYL4*,¹⁷² and loss-of-function variants in *SCN4B* and *KCNA5*, a conserved gene that encodes the voltage-gated Kv1.5 potassium channel.^{173,174} Loss-of-function variants in the titin gene have been associated with early-onset

(maximum change in C statistic from clinical score alone, 0.009–0.017).¹⁷⁹

- A multiancestry meta-analysis of GWASs for AF including >1 000 000 individuals led to the discovery of 35 new loci. *IL6R* has been identified as a putative causal gene for AF on the basis of transcriptome-wide association analysis indicating the role of the immune response in the pathogenesis of AF. A GRS developed from the multiancestry GWAS meta-analysis predicted the risk of cardiovascular and stroke mortality. A 1-SD increase in GRS was associated with increased odds of cardioembolic stroke (OR, 1.36 [95% CI, 1.13–1.63]) in individuals without diagnosed AF.¹⁸⁰
- GWASs also have been conducted with variations in electrocardiographic traits used as a phenotype (ie, QRS duration and area) and have identified novel genetic variants associated with these traits

AF.^{175,176}

that also are associated with cardiac conduction,

- Combinations of these genetic variants for AF are predictive of the lifetime risk of AF. Investigators in the FHS examined the lifetime risk of AF at 55 years of age using both clinical risk score and GRS (derived from thousands of variants associated with AF in the UK Biobank). Individuals within the low-est tertile of clinical risk score and GRS had a life-time risk of AF of 22.3% (95% CI, 15.4%–29.1%), whereas those in the highest tertile of clinical risk score and GRS had a lifetime risk of 48.2% (95%

arrhythmias, and other cardiovascular end points.¹⁸¹ A GWAS meta-analysis of PR interval in 293 051 multi-ancestry individuals found 202 genomic loci associated with PR interval, with enrichment of cardiac muscle development/contractile and cyto-skeletal genes.¹⁸² A GRS of PR interval-associated variants was found to be associated with a higher risk of atrioventricular block (OR per SE of GRS, 1.11; $P=7\times10^{-8}$) and pacemaker implantation (OR, 1.06; $P=1.5\times10^{-4}$) and reduced risk of AF (OR, 0.95; $P=4.3\times10^{-8}$).⁶²

- Proteomic studies have identified proteins identified with incident AF. For example, in the ARIC study, 4668 participants were followed up for 5.7 ± 1.7 years, during which 585 developed AF. After

- In a study of 19 709 participants from ARIC, MESA, and CHS, mitochondrial DNA copy number, a marker of mitochondrial dysfunction, was associated with incident AF with participants with the lowest

quintile of mitochondrial DNA copy number having an overall 13% increased risk (95% CI, 1%–27%) of AF compared with those in the highest quintile in adjusted models.¹⁸³

- A UK Biobank–based analysis including 1546 cases and 41 593 controls examining the contribution of rare and common genetic variants to AF risk revealed that 0.44% of individuals carried rare loss-of-function high-proportion spliced-in variants in the *TTN* gene.¹⁸⁴ Carriers of *TTN* variants had higher odds of AF (OR, 6.15; $P=3.26\times10^{-14}$).¹⁸⁴

Among *TTN* variant carriers, 14% had AF compared with 9.3% of individuals in the top 0.44% of the AF PRS.¹⁸⁴

- A multiancestry study using data from the All of Us Research Program, including 38 154 individuals of African ancestry and 105 904 individuals of European ancestry, demonstrated that carrying a high-proportion spliced-in *TTN* truncating variant was associated with a similar increase in the risk of AF in individuals of European (aHR, 1.96 [95% CI, 1.58–2.43]) and African (aHR, 2.42 [95% CI, 1.52–3.85]) ancestry.¹⁸⁵

- An integrative approach combining genomic, epigenomic, and transcriptomic data led to the identification of 1931 potential AF genes with multiple genes implicated in the development and regulation of cardiac muscle tissue.¹⁸⁶ The integration of multiomics approach yielded a heritability estimate of 18.9% (95% CI, 18.2%–19.5%).

- Functional studies incorporating pluripotent stem cell–derived cardiomyocytes and murine gene-knockout studies demonstrated that the *ZFHX3* gene, a transcription factor encoding gene at the 16q22 locus, is causative in the

reduced progressively with any level of weekly PA. Limitations of the analysis include underrepresentation of studies with individuals exercising 70 METs of task-hours/wk and absence of follow-up of PA assessment.

Secondary Prevention of AF:

Observational Data

- Data support the importance of risk factor modification for secondary prevention of AF recurrence and improved symptoms.

- Individuals with overweight and obesity with symptomatic AF who opted to participate in weight loss and aggressive risk factor management

interventions ($n=208$; mean follow-up, 47 months) had fewer hospitalizations (0.74 ± 1.3

versus 1.05 ± 1.60), cardioversions (0.89 ± 1.50 versus

1.51 ± 2.30), and ablation procedures (0.60 ± 0.69 versus 0.72 ± 0.86) than

their counterparts who declined enrollment ($n=147$; mean follow-up, 49 months). Participation in risk factor management

was associated with a predicted 10-year cost savings of \$12 094 per patient.¹⁹⁰

- Randomized data supporting the role of CPAP in primary prevention of AF in individuals with SDB are limited, and most attention has focused on secondary prevention.^{191,192} In a small, parallel-arm randomized clinical trial ($n=109$),

Prevention: Observational Data

Primary Prevention of AF: Observational Data

- An observational prospective Swedish study revealed that individuals having bariatric surgery had a 29% lower (HR, 0.71 [95% CI, 0.60–0.83]; $P<0.001$) risk of developing AF in a median 19-year follow-up than matched referents.¹⁸⁸ A registry-based study that matched individuals with obesity and

diabetes

not having

AF (HR,

concomitant HF and

0.46]) after bariatric

follow-up.¹⁸⁹

undergoing bariatric surgery to those

surgery reported a 41% reduced risk of

0.59 [95% CI, 0.44–0.78]) and

AF (HR, 0.23 [95% CI, 0.12–

surgery during a mean 4.5-year

- A meta-analysis of 14 studies ($N=1\,812\,422$)

examined the association of PA with risk of AF

in females.⁸³ The analysis identified that AF risk

Prevention: Randomized Data

Primary Prevention of AF: Randomized Data

- An analysis of SPRINT participants without AF at trial initiation (n=8022) determined that those randomized to the intensive BP-lowering arm (SBP <120 mm Hg) had decreased AF risk (HR, 0.74 [95% CI, 0.56–0.98]) over a median 3.8-year follow-up compared with those randomized to the standard BP-lowering arm (SBP <140 mm Hg).¹⁹⁴
- A meta-analysis of individuals with HF enrolled in 6 placebo-controlled trials of SGLT-2 inhibitors (N=9467) reported that those randomized to the SGLT-2 arm had reduced risk of incident AF (RR, 0.62 [95% CI, 0.44–0.87]).¹⁹⁵
- A meta-analysis of 14 studies (N=2883) observed that pretreatment with statins reduced the risk of post-operative AF (OR, 0.71 [95% CI, 0.60–0.85]) after

cardiothoracic surgery.¹⁹⁶ Studies excluding studies demonstrate that initiation of cardiac surgery was associated with reduced risk of AF in cardiac surgery (OR, 0.87 [95% CI, 0.53–1.43]).¹⁹⁷

- A meta-analysis of 8 studies demonstrated that colchicine with reduced risk of AF in cardiac surgery (RR, 0.70 [95% CI, 0.53–0.93]).¹⁹⁸

(2006–2009) and self-report (2010). Of 12 517 individuals 14.5% were unaware of their limited health literacy. In limited health literacy was awareness of AF diagnosis (OR, 0.94–0.98).²⁰³

Treatment and Control Anticoagulation Undertreatment

Secondary Prevention of AF: Randomized Data See Chart 18-9

- An Australian multisite, open-label, controlled trial randomized 140 adults who consumed ≥ 10 drinks of alcohol per week with a history of AF and in sinus rhythm at baseline either to abstain from alcohol or to continue their usual alcohol consumption.¹⁹⁸ AF recurred in 53% of the abstinence group and 73% of the control group. Compared with the control group, the abstinence group had a significantly longer duration without AF recurrence (HR, 0.55 [95% CI, 0.36–0.84]; $P=0.005$) and significantly lower AF burden (median percent time in AF, 0.5% versus 1.2%; $P=0.01$).
- An open-label, parallel-group RCT randomized individuals with PAF and AHI ≥ 15 to 5 months of treatment with CPAP ($n=55$) or control ($n=54$).¹⁹² The adjusted between-group difference in AF burden as measured by loop recorder was -0.63 (95% CI, -2.55 to 1.30).
- RCTs have determined that colchicine does not reduce likelihood of AF recurrence after catheter ablation or noncardiac surgery.^{199,200}
- Small trials have examined the effects of exercise and PA in individuals with AF. A multicenter, randomized, open-label trial randomized individuals with AF after cardioversion to

intensified pharmacological therapies and cardiac rehabilitation ($n=119$) or conventional therapy ($n=126$).²⁰¹ At the 1-year follow-up, 75% of intervention participants were in sinus rhythm (determined by 7-day Holter monitoring) compared with 63% of conventional therapy participants (OR, 1.77 [95% CI, 1.02–3.05]). In a second trial, individuals randomized to receive an exercise and PA intervention for 6 months achieved significant improvement in AF symptoms (mean difference, -2.0 [95% CI, -3.7 to -0.3]) at 6 months.²⁰² The study conducted rhythm monitoring for 4 days at baseline and 6 and 12 months in all participants and reported that randomization to the intervention arm was associated with reduced risk of AF (HR, 0.50 [95% CI, 0.33–0.78]; Chart 18-9).

Awareness

- A study from Kaiser Permanente in California examined the relationship between AF diagnosis

- The GWTG-Stroke program conducted a retrospective analysis consisting of 1622 hospitals and 94 474 patients with AIS in the setting of known AF from 2012 to 2015. In that analysis, 79 008 patients (83.6%) were not receiving therapeutic anticoagulation: 13.5% had a subtherapeutic international normalized ratio; 39.9% were receiving antiplatelet treatment only; and 30.3% were not receiving any antithrombotic therapy. In adjusted analyses, compared with patients receiving no antithrombotic medications, patients receiving antecedent therapeutic warfarin, non-vitamin K antagonist oral anticoagulant drugs, or antiplatelet therapy had lower odds of moderate or severe stroke (aOR, 0.56 [95% CI, 0.51–0.60], 0.65 [95% CI, 0.61–0.71], and 0.88 [95% CI, 0.84–0.92], respectively) and lower in-hospital mortality.²⁰⁴
- Treatment for subclinical AF (ie, AF duration 6 minutes–24 hours as detected by pacemaker or defibrillator) was evaluated in a double-blind RCT (N=4012) comparing the effectiveness of apixaban with aspirin.²⁰⁵ After a mean follow-up of 3.5±1.8 years, apixaban was associated with 37% decreased risk of stroke or systemic embolism (HR, 0.63 [95% CI, 0.45–0.88]).
- In the NCDR PINNACLE registry of outpatients with AF:
 - Fewer than half of high-risk patients, defined as those with a CHA₂DS₂-VASc score ≥4, received an oral anticoagulant prescription.²⁰⁶
 - Between 2008 and 2014, in individuals with a CHA₂DS₂-VASc score >1, direct anticoagulant use increased from 0% to 24.8%, and use of warfarin decreased from 52.4% to 34.8%.

Although the prevalence of oral anticoagulation treatment increased from 52.4% to 60.7% over the time period, there are substantive opportunities to improve oral anticoagulation for stroke prevention in individuals with AF.²⁰⁷

 - In the PINNACLE registry, females were significantly less likely to receive oral anticoagulation at all levels of CHA₂DS₂-VASc scores (56.7% versus 61.3%; *P*<0.001).²⁰⁸
 - An analysis in the PINNACLE registry also reported that receipt of warfarin compared with a DOAC varied significantly by type of

insurance: Patients with military, private, and Medicare insurance were more likely to receive newer anticoagulants than individuals with Medicaid or other insurance.²⁰⁹

- A randomized trial tested the effect of an alert embedded in the electronic health record on anti-coagulation prescribing targeting primary care clinicians.²¹⁰ In the limited-sized trial (N=562), the alert improved anticoagulation therapy (11% [33/314] versus 5%
- A meta-analysis of inappropriate dosing of DOACs (N=15 studies) concluded that underdosing was associated with an increased risk of all-cause mortality (HR, 1.28 [95% CI, 1.10–1.49]) and overdosing with an increased risk of major bleeding (HR, 1.41 [95% CI, 1.07–1.85]).²¹¹ Further analysis (N=12 studies) determined that age, history of bleeding, hypertension, HF, and low creatinine clearance were related to underdosing of DOAC. Underdosing had a null effect on bleeding risk, whereas overdosing was associated with increased risk of major bleeding (HR, 1.41 [95% CI, 1.07–1.85]).
- The GLORIA-AF Registry reported North American anticoagulation patterns in 3320

DOAC use was low (35.8% NH White individuals, 29.3% NH Black individuals, 40.0% Hispanic individuals). NH Black individuals were less likely to initiate DOACs than NH White individuals (OR, 0.75 [95% CI, 0.66–0.85]); in contrast, the odds of DOAC initiation did not differ between Hispanic individuals and NH White individuals (OR, 1.02 [95% CI, 0.88–1.18]).²¹⁴

patients with AF between 2011 and 2014, observing that factors associated with increased likelihood of receiving indicated oral anticoagulant prescription included nonparoxysmal AF (OR, 2.02), prior stroke/TIA (OR, 2.00), specialist care (OR, 1.50), more concomitant medications (OR, 1.47), commercial insurance (OR, 1.41), and HF (OR, 1.44), whereas factors inversely related were antiplatelet drugs (OR, 0.18), prior falls (OR, 0.41), and prior bleeding (OR, 0.50).²¹²

- The prevalence of individuals with frailty (defined with 5 different measures to identify frailty) with AF has prompted attention toward provision of oral anticoagulation in a population at high risk for stroke and falls or bleeding. A systematic review of

determined in multivariable-adjusted analysis that Black individuals (OR, 0.75 [95% CI, 0.56–0.99]) were significantly less likely to receive oral anti-coagulation than White individuals.²¹⁵ This difference was attenuated by adjustment for social and economic factors (OR, 0.78 [95% CI, 0.59–1.04]).

The difference between Hispanic and White individuals was not significant.

– An analysis of the GWTG-AFIB registry (N=69 553) determined that Black individuals were less likely than White individuals to be discharged on oral anticoagulation (OR, 0.75 [95% CI, 0.68–0.84]).²¹⁶ In 16 307 individuals with 1-year follow-up data, the risks of bleeding (HR, 2.08 [95% CI, 1.53–2.83]), stroke (HR, 2.07 [95% CI, 1.34–3.20]), and mortality (HR, 1.22 [95% CI, 1.02–1.47]) were higher in Black individuals compared with White individuals.

– In the Florida Puerto Rico AF Stroke Study, a registry of individuals with ischemic stroke and AF (N=24 040), Black individuals were more likely to receive warfarin at hospital discharge after stroke (OR, 1.22 [95% CI, 1.07–1.40]) compared with references of White race.²¹⁷ In contrast, Black race was not associated with likelihood of receipt of a DOAC compared with White race. Likewise, Hispanic ethnicity was not associated with likelihood of receipt of warfarin or DOAC compared

with White race.
frailty included 12 studies (N=212 111) comprising individuals 77 to 85 years of age, of whom 56% were categorized as frail; 52% of individuals categorized as frail received anticoagulation compared with 67% of those categorized as not frail.²¹³

• Racial differences in access to oral anticoagulation have been identified.

– In a 5% sample of Medicare beneficiaries, NH Black individuals were significantly less likely to receive oral anticoagulation (OR, 0.84 [95% CI, 0.78–0.91]) than NH White individuals. There was no difference between Hispanic individuals (OR, 0.92 [95% CI, 0.83–1.01]) and NH White individuals. Among initiators of oral anticoagulation,

*Disparities in Treatment
(See Chart 18-10)*

- An administrative data analysis of individuals in Ontario, Canada, determined that residence in the fifth quintile of neighborhood-based material deprivation was associated with decreased 1-year likelihood of cardiology visits (HR, 0.84 [95% CI, 0.82–0.86]), anticoagulation (HR, 0.97 [95% CI, 0.95–0.98]), receipt of an echocardiogram (HR, 0.97 [95% CI, 0.96–0.99]), cardioversion (HR, 0.80 [95% CI, 0.76–0.84]), or ablation (HR, 0.45 [95% CI, 0.30–0.67]; Chart 18-10).¹²¹

Role of Coordinated Care

- A systematic review and meta-analysis identified 3 studies of coordinated systems of care that included 1383 patients.²¹⁸ The investigators reported that AF integrated care approaches were associated

with reduced all-cause
0.32–0.80]; $P=0.003$) and
izations (OR, 0.58 [95% CI,
but not with cerebrovascular
tions related to AF.

Shared Decision-Making (Chart 18-11)

- Shared decision-making for
tion is a Class 2b
society guidelines.⁵⁵ A toolkit
of a novel tool for shared
tissue trial (N=1001) and
yielded a 7-point, clinically
in the median 1-month
those randomized to the
0; maximum, 81.3]) compared
[minimum, 0; maximum,
cal significance (Mann-
 $P=0.007$).²¹⁹ At 6 months, the
conflict scores were 6.2
81.3) in those randomized to
pared to 10.9 (minimum, 0;
randomized to the control
- A second clinical trial (N=922)
mentation of a decision aide
Patient involvement in
through video recordings)
higher in the intervention arm
ence, 4.2 points [95% CI, 2.8–
between-arm difference was
duration (intervention arm,
dard care arm, 31±17
between-arm difference, 1.1
to 2.5]).

Mortality

ICD-9 427.3; ICD-10 I48.

(See Chart 18-12)

- In 2022, AF was the underlying cause of death in
28 936 people and was listed on 233 966 US
death certificates (any-mention mortality; unpub-
lished NHLBI tabulation using NVSS²²¹).
- The AAMR attributable to any mention of AF was
6.9 per 100 000 people in 2022 (95% CI, 6.8–
7.0; unpublished NHLBI tabulation using CDC
WONDER²²²). Although there was significant

percentage increases were as
Mississippi (+26.4%),
(+24.8%), and New
females, Oregon (+54.6%),
Utah (+42.5%), and Nebraska

- The association of AF with
remained stable over time. In
the association of AF with all-
1.9 (95% CI, 1.7–2.2)
(95% CI, 1.3–1.6) between
1.7 (95% CI, 1.5–2.0)
($P_{\text{trend}}=0.70$).²²⁵
- From 2006 to 2015, all-cause
decreased in individuals
(N=679 416) in the Korean
Service (Chart 18-12).⁵⁴ The
cause mortality decreased by
diagnosed in 2013 relative to
2006 (HR, 0.70 [95% CI,
AF is also associated with
subgroups of individuals,
 - Individuals with other
and procedures, including
CABG,²²⁹ post-CABG²³⁰
replacement (transcatheter
PAD,^{233,234} and stroke.²³⁵
 - Individuals with AF have
with concomitant HF,
HFREF.²³⁶ In a meta-
timing of AF in relation to
to mortality, the risk of
dent AF was higher (RR,
2.49]) than that associated
1.19 [95% CI, 1.03–1.38];
 $P_{\text{interaction}}<0.001$).²³⁷ A
(N=52 447) determined that
had 3.3-fold increased 3-
between-study heterogeneity
($P<0.001$), a meta-analysis of 30
studies (N=4 371 714) identified that
the adjusted risk of death was
significantly higher in females
with AF than in males (RR, 1.12 [95%
CI, 1.07–1.17]).²²³
- The GBD Study indicates increases
in sex-specific, age-standardized
mortality estimates across US
states between 1990 and 2017.²²⁴
The greatest

- incident HF (95% CI, 3.08–3.43).²³⁸
- AF is also associated with an increased risk of death in individuals with other conditions, including diabetes,^{239,240} and critical illness in the ICU²⁴¹; in individuals after primary PCI²⁴²; and in individuals ≥80 years of age with hypertension.²⁴³
 - In the ARIC study, the rate difference for all-cause mortality for individuals with versus without AF per 1000 PY was 106.0 (95% CI, 86.0–125.9) in Black participants, which was higher than the 55.9 (95% CI, 48.1–63.7) rate difference in mortality observed for White participants.²⁴⁴
 - There was substantial variation in mortality with AF in US counties from 1980 to 2014.²⁴⁵ Investigators estimated that there were ≈22 700 (95% UI, 19 300–26 300) deaths attributable to AF in 2014 and 191 500 (95% UI, 168 000–215 300) YLL. In an examination of county-level data, the age-standardized AF mortality rates were 5.6 per 100 000

for the 10th percentile and 9.7 per 100 000 for the 90th percentile. The counties with age-standardized death rates >90th percentile were clustered in Oregon; California; Utah; Idaho; northeastern Montana; areas east of Kansas City, MO; and south-west West Virginia.²⁴⁵

- In a study using the NIS for the period of 2010 to 2015 (N=3 264 258), adjusted in-hospital mortality in the setting of AF was higher among individuals with private insurance. Medicaid recipients were significantly less likely to be discharged to home (55.3%) than those with private insurance (61.3%) and were noted to have longer median length of stay (5 days [interquartile range, 3–9 days]) compared with those with private insurance (4 days [interquartile range, 2–8 days]).²⁴⁶
- Serial cross-sectional analyses of annual US death certificate data for cardiovascular mortality identified an increase in AAMR per 100 000 population in those diagnosed with AF from 18.0 (95% CI, 17.8–18.2) in 2011 to 22.3 (95% CI, 22.0–22.4) in 2018.²⁴⁷
- Investigators conducted multivariable cross-sectional analyses of the NIS between 2012 and 2014 (N=248 731) and observed that patients admitted to rural hospitals (n=29 785) had a 17% higher risk of death than those admitted to urban hospitals (OR, 1.17 [95% CI, 1.04–1.32]).²⁴⁸
- AF has been associated with increased mortality in patients with COVID-19. A meta-analysis of

covariates.²⁵² This association was stronger in females (HR, 5.26 [95% CI, 3.28–8.44]) than in males (HR, 2.68 [95% CI, 1.66–4.32]).

- In the ARIC study (N=14 941), incident AF was associated with adjusted increased risk of extracranial systemic emboli (HR, 3.58 [95% CI, 3.28–8.44]) compared with those without AF.²⁵²
- Risk of embolism studies published in 2020 including 23 studies and 108 745 patients with COVID-19 showed that AF was associated with increased mortality (pooled effect size, 1.14 [95% CI, 1.03–1.26]).²⁴⁹
- In a Swedish study based on 75 primary care centers, an adjusted analysis of patients diagnosed with AF revealed that males living in low-SES neighborhoods were 49% (HR, 1.49 [95% CI, 1.13–1.96]) more likely to die than their counterparts living in middle-income neighborhoods over a median follow-up of 3.5 years (interquartile range, 1.5–5.5 years). The results were similar in models that additionally adjusted for anticoagulant and statin treatment (HR, 1.39 [95% CI, 1.05–1.83]).²⁵⁰
- In another study from the same group, unmarried and divorced males and males with lower educational attainment with AF had a higher risk of mortality than their married and better-educated male counterparts.²⁵¹

Complications

Extracranial Systemic Embolic Events

- Among 14 941 participants in the ARIC study, incident AF was associated with an increased risk of extracranial systemic embolic events (HR, 3.58 [95% CI, 2.57–5.00]) after adjustment for

Stroke

• A systematic review of prospective studies found wide variability in stroke risk between studies and between patients with AF, ranging from 0.5%/y to 9.3%/y.²⁵³

• Before the widespread use of anticoagulant drugs, after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke. Although the RR of stroke associated with AF ($\approx$ 3- to 5-fold increased risk) has not varied substantively with advancing age, the proportion of strokes attributable to AF has increased significantly. In the FHS, AF accounted for $\approx$ 1.5% of strokes in individuals 50 to 59 years of age and $\approx$ 23.5% in those 80 to 89 years of age.²⁵⁴

• In Medicare analyses that were adjusted for comorbidities, Black people (HR, 1.46 [95% CI, 1.38–1.55]; $P<0.001$) and Hispanic people (HR, 1.11 [95% CI, 1.03–1.18]; $P<0.001$) had a higher risk of stroke than White people with AF.²⁵⁵ The increased risk persisted in analyses adjusted for anticoagulant therapy status. Additional analyses from the Medicare registry demonstrated that the addition of Black race to the CHA₂DS₂-VASc scoring system significantly improved the prediction of stroke events among patients with newly diagnosed AF who were $\geq$ 65 years of age.²⁵⁶

• In an analysis of individuals with AF receiving care in a multihospital health system, Black individuals with AF were more likely to be younger and female and to have more cardiovascular risk factors than White individuals with AF. In addition, in adjusted analyses, compared with White participants with AF, Black participants with new-onset AF were more likely to have an ischemic stroke precede (OR, 1.37 [95% CI, 1.03–1.81]) or follow (HR, 1.67 [95% CI, 1.30–2.14]) the diagnosis of AF. The rate of ischemic stroke per year after AF diagnosis was 1.5% (95% CI, 1.3%–1.8%) in White participants and 2.5% (95% CI, 2.1%–2.9%) in Black participants.²⁵⁷

• In patients with COVID-19 in a global database, risk of ischemic stroke and other thromboembolic complications was higher in those with AF compared with those without AF (9.9% versus 7.0%; RR, 1.41 [95% CI, 1.26–1.59]).²⁵⁸

- A meta-analysis that examined and presence of AF reported multivariable-adjusted 2-fold compared with males (RR, 2.711); however, the studies significant heterogeneity.²²³

Cognition and Dementia

- A meta-analysis of 11 112 876 participants with and without acute stroke (HR, 1.34 [95% CI, 1.24–1.44] of dementia in individuals with those without AF.²⁵⁹ Another >2 million participants in 14 and 2 randomized studies and increased risk of incident CI, 1.23–1.511; $P<0.0001$).²⁶⁰ of 6 studies including ≈1.6 million participants examined that the association of AF with incident dementia was 1.06 [95% CI, 0.55–2.06] in age and RR, 1.50 [95% CI, 1.06–2.11] (<70 years of age).²⁶¹
- In a multicenter study of AF (mean, 73 years of age) among 1390 patients without TIA, clinically silent infarcts patients (18%) with small (mean, 201 (15%) with large (mean, 201 (15%) with large according to brain MRIs.²⁶² analyses of all the vascular noncortical or cortical infarcts association with reduced risk of dementia [95% CI, –0.40 to –0.13]; $P<0.001$), even when restricted to individuals with clinically silent infarcts.
- In the REGARDS study, participants with self-reported or ECG-ascertained AF had significantly lower scores on cognitive testing compared with those without (eg, MoCA, Word List Learning, and Delayed Recall tasks). Over 8.1 mean years of follow-up, declines in Word List Learning scores were steeper in those with AF compared with those without AF.²⁶³ None of the other cognitive measures showed a significant decline in those with and without AF.
- An administrative study in the United Kingdom examined oral anticoagulation and risk of

reduced risk of dementia warfarin over 0.3 to 3.7 years [95% CI, 0.80–0.98]; the association was heterogeneous by the region in which studies were conducted. The association in dementia risk in studies was identified in Europe (n=4) or North America (n=1; HR, 0.68–0.861 and HR, 0.85 respectively) but not those in Asia (n=6; HR, 0.96 [95% CI, 0.81–1.14]).

- A cross-sectional analysis of a large population-based study (N=1490) determined that regular, once-weekly exercise reduced probability of incident dementia [95% CI, 0.63–0.981], (OR, 0.78 [95% CI, 0.62–0.981]).

Physical Disability and Subjective

- In systematic reviews of incident prospective and cross-sectional studies, physical disability has been associated with physical disability and quality of life.²⁶⁷
- Females with AF have been shown to have lower quality of life than males. In the ORBIT-AF study, females had significantly lower AF-specific quality of life (mean, 80; interquartile range, 75–85) compared with males (mean, 83; interquartile range, 78–88). A smaller, single-center study that females with AF reported lower quality of life than males with the same degree of dementia and cognitive impairment in individuals with AF.
- DOAC users were significantly less likely to receive a diagnosis of dementia (HR, 0.84 [95% CI, 0.73–0.98]) or MCI (HR, 0.74 [95% CI, 0.65–0.84]) than those treated with a vitamin K antagonist over 501 days (interquartile range, 199–978 days) of follow-up observation.²⁶⁴
- A systematic review (10 studies; N=342 624) determined that receipt of a DOAC was associated with

Falls

- AF has been associated with increased risk of falls.
A meta-analysis of 7 studies (N=36 444) concluded that individuals with AF have 1.2-fold increased risk of falls (OR, 1.20 [95% CI, 1.07–1.33]) relative to those without AF. Heterogeneity of studies was limited ($I^2=37\%$).²⁷⁰

Heart Failure

(See Charts 18-13 and 18-14)

- AF and HF share many antecedent risk factors, and develop the other condition.^{88,271}
- In the community, estimates of the incidence of HFpEF was 3.3 per 100 PY of follow-up (95% CI, [95% CI, 1.9–2.4]).²⁷²
- A study of Medicare beneficiaries (N=39 710) new-onset HF, HF hospitalization, and mortality in

≈40% of people with either AF or HF will

HF in individuals with AF ranged from 3.3²⁷¹ to Minnesota, in individuals with AF, the incidence of 3.0–3.7), which was more common than HFrEF (2.1

examined the relationship between AF burden and

those with newly implanted cardiac devices and prevalent AF. A 10% increase in burden of AF at 1 year after device implantation was associated with new HF (HR, 1.09 [95% CI, 1.06–1.12]) and mortality (HR, 1.05 [95% CI, 1.01–1.10]). Among those with prevalent HF, a 10% increased AF burden was associated with HF hospitalization (HR, 1.05 [95% CI, 1.04–1.06]) and mortality (HR, 1.06 [95% CI, 1.05–1.08]).^{.273}

compared outcomes with (n=1854) or without (n=11 279) HF in individuals with AF treated with a DOAC (edoxaban).^{.274} Individuals with HF had higher annual event rates of major bleeding (1.73%/y versus 0.86%/y, respectively) and mortality (8.30%/y versus 3.17%/y) than those without (Chart 18-13).

- An analysis in the REGARDS study (N=25 787) determined that cohort participants with AF (n=1896) had multivariable-adjusted increased risk of HFrEF (HR, 1.87 [95% CI, 1.38–2.54]) and HFpEF (HR, 1.65 [95% CI, 1.20–2.28]) over a 14-year follow-up (Chart 18-14).^{.275}
- A meta-analysis of 9 studies reported that individuals with AF have a 5-fold increased risk of HF (RR, 4.62 [95% CI, 3.13–6.83]).^{.276}

Myocardial Infarction

- A meta-analysis of 16 cohort studies reported

sudden death (pooled RR, 2.04 [95% CI, 1.77–2.35]; $P<0.01$). When the meta-analysis was restricted to 7 studies that conducted multivariable analyses, AF remained associated with an increased risk of sudden death (pooled RR, 2.22 [95% CI, 1.59–3.09]; $P<0.01$).^{.280}

- An analysis of a French national database (N= 3 381 472) that AF was associated with a 1.54 (95% CI, 1.26–1.85) increased risk of MI in follow-up.^{.276}
- For individuals with AF in ARIC,^{.244} a higher risk of MI was observed in Black people than White people.
- In ARIC, AF as a time-varying independent variable was associated with a 63% increased risk of MI (HR, 1.63 [95% CI, 1.32–2.02]). In further analysis, AF was associated with an adjusted increased risk of NSTEMI (HR, 1.80 [95% CI, 1.39–2.31]) but not STEMI (HR, 0.49 [95% CI, 0.18–1.34]; P for comparison of HR=0.004).^{.277}

Chronic Kidney Disease

- In a health plan registry of people with CKD (N=206 229), new-onset AF (n=16 463) was associated with an adjusted 1.67-fold (95% CI, 1.46–1.91) increased risk of developing ESKD compared with no AF (74 versus 64 per 1000 PY of follow-up).^{.278}

risk (HR, 1.17 [95% CI, 1.11–1.23]) for ventricular arrhythmias than those without AF.²⁸¹ A mediation analysis identified the odds of cardiac arrest mediated by AF-associated ventricular arrhythmias as an OR of 1.04 (95% CI, 1.04–1.04).

AF Type and Complications

- A meta-analysis of 12 studies (N=99 996) reported that compared with paroxysmal AF, nonparoxysmal AF was associated with a multivariable-adjusted increased risk of thromboembolism (HR, 1.38 [95% CI, 1.19–1.61]; $P<0.001$) and death (HR, 1.22 [95% CI, 1.09–1.37]; $P<0.001$).²⁸²
- In the Canadian Registry of Atrial Fibrillation, 755 patients with paroxysmal AF were followed up for a median of 6.35 years. At 1, 5, and 10 years, 8.6%, 24.3%, and 36.3%, respectively, had progressed to persistent AF. Within 10 years, >50% of the patients had progressed to persistent AF or had died.²⁸³

Atrial Flutter Versus AF

- Using a 5% sample of Medicare beneficiaries from 2008 to 2014, investigators identified 18 900 ischemic strokes among 318 138 individuals with AF and 14 953 with atrial flutter. The study reported the annual stroke rate to be 2.02% (95% CI, 1.99%–2.05%) in individuals with AF and 1.38% (95% CI, 1.22%–1.57%) in those with atrial flutter. After adjustment for demographics and vascular risk factors, the risk of stroke was significantly lower in individuals with atrial flutter than in those with AF (HR, 0.69 [95% CI, 0.61–0.79]).²⁸⁴
- A national Taiwanese study compared the prognoses of 175 420 individuals with AF and 6239 individuals with atrial flutter. Using propensity scoring, the study showed that compared with individuals with atrial flutter, those with AF had significantly
 - A multinational consortium of 81 cohorts higher

(N=24 353 175) determined that in those with SCD and VF CKD (n=605 596), AF was associated with increased risk of requiring renal replacement therapy (n=93 600; HR, 1.37 [95% CI, 1.05–1.77]).²⁷⁹

- In a meta-analysis of 27 studies including 8401 individuals with AF and 67 608 controls without

[95% CI, 1.42–1.87]), HF hospitalization (1.70-fold [95% CI, 1.46–1.97]), and all-cause mortality (1.08-fold [95% CI, 1.03–1.13]).²⁸⁵

Hospitalizations and Ambulatory Care Visits

• According to HCUP data,²⁸⁶ in 2021, there were 442 909 hospital discharges with AF and atrial flutter as the principal diagnosis (unpublished NHLBI tabulation). AF, AF was associated with a

442 909 hospital discharges with AF and atrial

- There were 8 365 000 physician (NAMCS, unpublished NHLBI and 677 971 ED visits in 2021 ter (HCUP).²⁸⁶ unpublished
- Using cross-sectional data HCUP's Nationwide ED NVSS, investigators as a primary diagnosis visits and 453 060 length of stay of 3.5 days (SE.

listed as a comorbid condition was included, there were ≈4 million (3.6% of total) ED visits and 3.5 million (12.0% of total) hospitalizations.²⁸⁸

- A meta-analysis of 35 prospective studies including 311 314 patients with AF reported an all-cause hospital admission rate of 43.7 (95% CI, 38.5–48.9) per 100 PY. In studies (n=24) that reported admission causes (n=234 028 patients with AF), cardiovascular hospitalizations were more frequent than noncardiovascular hospitalizations (26.3 [95% CI, 22.7–29.9] versus 15.7 [95% CI, 12.5–18.9], respectively).²⁸⁹
- A retrospective analysis of administrative data using MarketScan Research Databases (N=3

– Type of care: ambulatory, prescribed facility, 15.3%; and ED.

- A systematic review that emic stroke in individuals with ies from 9 countries. In to 2015 values, the analysis related health care costs were and \$41 420 for lower-income economies.

398 490) identified that individuals with AF (n=156 732) had 9 (95% CI, 8.96–9.12) ambulatory visits, 0.3 (95% CI, 0.33–0.34) inpatient admissions, and 2.7 (95% CI, 2.71–2.77) prescribed medications more than those without AF.²⁹⁰ Among those with AF, patients living in rural areas had 1.99 fewer (95% CI, –2.26 to –1.71) and 0.05 more (95% CI, 0.02–0.8) emergency department visits than patients with AF living in metropolitan areas.

- Costs of AF have been estimated for higher-income countries. In Denmark, for example, investigators estimated that the 3-year societal costs of AF were approximately €20 403 to €26 544 per person and €219 to €295 million total.²⁹³

Global Burden of AF

(See Table 18-1 and Charts 18-15 and 18-16)

- Based on 204 countries and territories in 2021²⁹⁴:
 - AF/atrial flutter was 0.34 (95% UI, 0.29–0.37) million, with 0.13 (95% UI, 0.12–0.15) million among males and 0.20 (95% UI, 0.17–0.23) million among females (Table 18-1). Among regions, age-standardized mortality estimated for AF was highest for Australasia followed by Western Europe. Mortality was lowest for Central Asia and high-income Asia Pacific (Chart 18-15).
 - Globally, 52.55 (95% UI, 43.14–64.96) million individuals had prevalent AF/atrial flutter in 2021, with 27.90 (95% UI, 23.03–34.65) million among males and 24.65 (95% UI, 20.03–30.93) million among females (Table 18-1).

Cost

– Age-standardized prevalence of AF

- A study examining public and private health insurer records from 1996 to 2016 reported that AF was 33rd in spending for health conditions with an estimated \$28.4 (95% CI, \$24.6–\$33.8) billion in 2016 dollars.²⁹¹ The annualized rate of change standardized to the population for 2016 was 3.4%.

The estimates varied by the following features:

- Age group: <20 years, 0%; 20 to 64 years, 25.0%; and ≥65 years, 75.0%.
- Type of payer: public insurance, 56.4%; private insurance, 36.9%; and out of pocket, 6.7%.

America, Australasia, and Western Europe. North Africa and the Middle East had the lowest age-standardized prevalence rates (Chart 18-16).

- Investigators conducted a prospective registry of 15 400 patients with AF presenting to EDs in 47 countries. They observed substantial regional variability in annual AF mortality: South America (17%) and Africa (20%) had double the mortality rate of North America, Western Europe, and Australia (10%; $P<0.001$). In this cohort, HF deaths (30%) exceeded deaths attributable to stroke (8%).²⁹⁵

Table 18-1. Global Mortality and Prevalence of AF, by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	0.34 (0.29 to 0.37)	52.55 (43.14 to 64.96)	0.13 (0.12 to 0.15)	27.90 (23.03 to 34.65)	0.20 (0.17 to 0.23)	24.65 (20.03 to 30.93)
Percent change (%) in total	195.92 (166.25 to 226.52)	136.57 (128.15 to 148.08)	215.63 (184.37 to 263.52)	142.76 (132.38 to 154.48)	184.22 (152.85 to 216.52)	129.93 (121.22 to 141.15)
Percent change (%) in total	46.62 (39.16 to 53.56)	40.62 (38.03 to 43.13)	49.68 (40.07 to 60.28)	39.70 (36.94 to 42.32)	44.67 (36.12 to 53.36)	41.68 (39.08 to 44.12)
Rate per 100,000, age	4.36 (3.69 to 4.75)	620.51 (511.36 to 768.88)	4.44 (3.94 to 4.81)	728.88 (601.91 to 895.81)	4.29 (3.53 to 4.80)	529.12 (430.79 to 663.14)
Percent change (%) in rate, age standardized,	2.92 (−6.01 to 12.35)	0.64 (−3.28 to 5.75)	5.65 (−3.74 to 19.94)	0.15 (−4.10 to 5.80)	1.07 (−8.97 to 11.90)	−0.08 (−3.89 to 5.01)
Percent change (%) in rate, age standardized,	−0.83 (−5.50 to 3.71)	1.96 (0.33 to 3.35)	0.10 (−5.90 to 6.74)	0.66 (−1.02 to 1.97)	−1.42 (−7.24 to 4.53)	3.16 (1.51 to 4.71)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AF indicates atrial fibrillation; GBD, Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.²⁹⁴

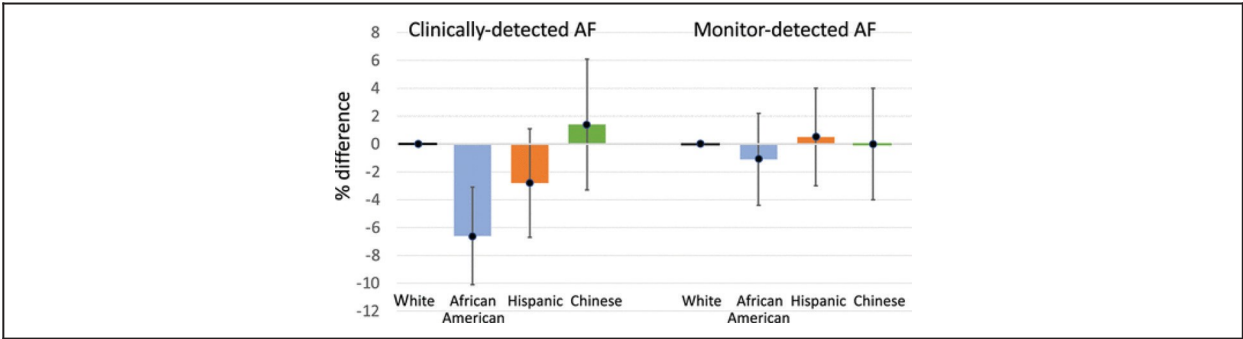


Chart 18-1. Adjusted percent difference in AF prevalence compared with White individuals for clinically detected AF (2000–2018) and monitor-detected AF (2016–2018) in the MESA Study.

Adjusted for age, sex, height, weight, treated hypertension, current smoking, diabetes, SBP, history of HF, and history of MI; estimates for monitor-detected AF are also adjusted for monitoring duration.

Vertical lines indicate 95% CI.

AF indicates atrial fibrillation; HF, heart failure; MESA, Multi-Ethnic

Study of Atherosclerosis; MI, myocardial infarction; and SBP, systolic blood pressure.

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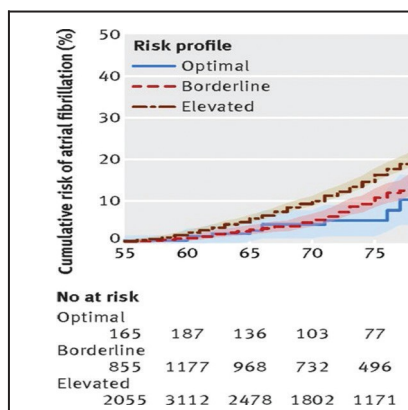


Chart 18-2. Lifetime risk (cumulative of age) for AF at different ages (through sex in the FHS, 1968 to 2014).

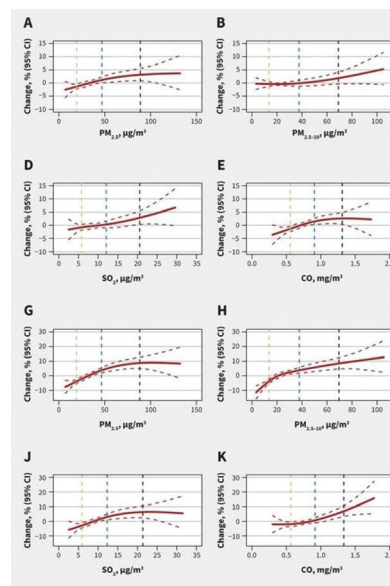
AF indicates atrial fibrillation; and FHS.

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Chart 18-4. Nationwide, time-stratified case-crossover analysis of air pollution data spanning 2015 to 2021 from 322 cities in China in relation to presentation with symptomatic AF or SVT.

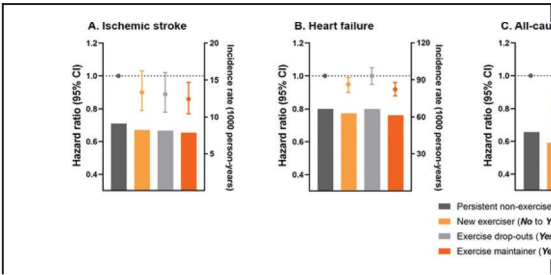


Chart 18-3. Retrospective analysis conducted in the Korean National Health Insurance Service of individuals (N=66 692) with newly diagnosed AF who underwent self-reported exercise assessment 2 years before and after AF diagnosis, 2010 to 2016.

ischemic stroke, HF, and all-cause death according to the change in exercise status. Bars denote weighted incidence rates; dots, HRs; and whiskers, 95% CIs computed by weighted Cox proportional hazards models with inverse probability of treatment weighting. AF indicates atrial fibrillation; HF, heart failure; and HR, hazard ratio. Source: Adapted from Ahn et al.⁸⁴ Copyright © 2021, The Authors. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC), which permits noncommercial reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Exposure-response curves for the concentrations of 6 air pollutants percentage change in the odds of the outcome compared with the odds at the median concentration over a lag period of 0 to 24 hours. Solid red lines represent the point estimates; intervals between

dashed red lines represent 95% CIs. The other dashed lines represent the concentration of air pollutants (green, 25th percentile; blue, 75th percentile; black, 95th percentile). AF indicates atrial fibrillation; CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{2.5-10}, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; SO₂, sulfur dioxide; and SVT, supraventricular tachycardia. Source: Reprinted from Xue et al.¹⁰² Copyright © 2023 The Authors. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License, which permits use, distribution and reproduction in any

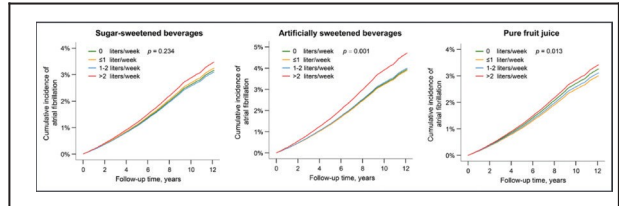


Chart 18-5. Multivariable-adjusted cumulative incidence of AF according to consumption of SSBs, ASBs, and pure fruit juice.

The unit of beverages consumption is liter per week. Models were adjusted for age; sex; ethnicity (White/others); education level (university or college degree/others); the Townsend deprivation index; alcohol consumption; current smoking; ideal PA level; sleep duration; BMI; SBP; TC; eGFR; OSA; CHD; HF; diabetes; the PRS for AF; and the consumption of vegetables, fruits, red meat, processed meat, coffee, total fat, total sugar, and total energy and mutually adjusted for 2 additional beverages. *P* value was for the log-rank test.

AF indicates atrial fibrillation; ASB, artificially sweetened apnea; PA, physical activity; PRS, polygenic risk score; SBP, systolic blood pressure; SSB, sugar-sweetened beverage; and TC, total cholesterol.

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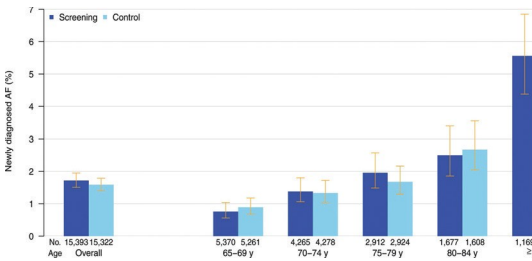


Chart 18-7. Proportion of adults by age category with newly diagnosed AF by screening (n=15 393) at a primary care visit compared with control subjects (n=15 322) who were not screened in a single US health care system: VITAL-AF RCT.

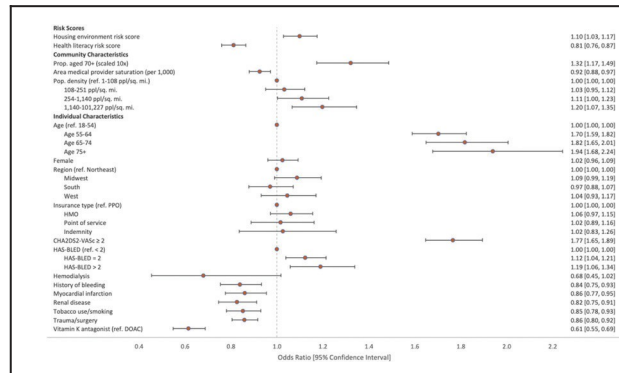


Chart 18-6. Multivariable-adjusted regressions of associations between community-level (determined by US 3-digit zip code) and patient-level (determined from IQVIA PharMetrics Plus claims data from January 2016–June 2020) characteristics and proportion of days covered at 360 days.

(ZIP-3) level. Proportional community-level measures are scaled by a factor of 10. For example, a 1-unit increase in “Prop. aged 70 and older” is equivalent to a 10% increase in the prevalence of residents aged ≥70 years in the ZIP-3 area. Other measures represent median or mean values. DOAC indicates direct-acting oral anticoagulant; HAS-BLED, atrial fibrillation bleeding risk score (hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, elderly, drug and alcohol use); HMO, health maintenance organization; pop, population; ppl, people; PPO, preferred provider organization; prop, proportion; and ref, referent group.

		CHA ₂ DS ₂ -VASc Score			
		0	1	2	3-4
		n=2922 (13.4%)	n=2151 (9.9%)	n=4554 (20.9%)	n=7164 (32.9%)
Maximum Daily AF Duration	No AF	0.33% 40 events	0.62% 46 events	0.70% 95 events	0.83% 139 events
	AF 6 min–23.5 h	0.52% 11 events	0.32% 4 events	0.62% 17 events	1.28% 42 events
	AF ≥23.5h	0.86% 4 events	0.50% 3 events	1.52% 19 events	1.77% 28 events

Chart 18-8. Risk of stroke and systemic embolism in nonanticoagulated patients (N=21 768) by AF duration and CHA₂DS₂-VASc score from the Optum electronic health record deidentified database, 2007 to 2017.

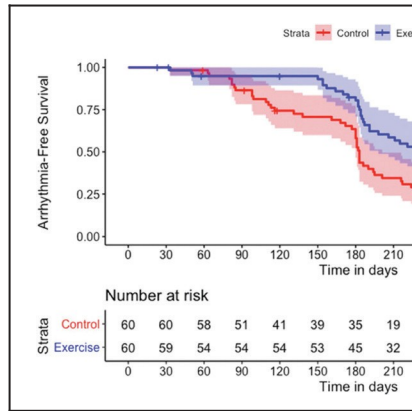
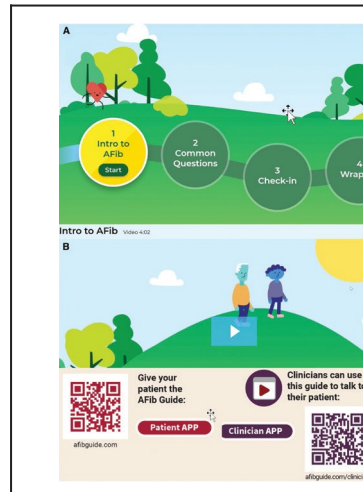


Chart 18-9. An exercise and PA program the ACTIVE-AF RCT.

Proportion of study participants free from

follow-up.

ACTIVE-AF indicates A Lifestyle-based Physical Activity Intervention for Patients with Symptomatic AF; AF, atrial fibrillation; PA, physical activity; and RCT, randomized controlled trial.



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Chart 18-11. Randomized comparative-effectiveness trial of individuals ≥18 years of age with nonvalvular AF conducted at 5 US sites (December 18, 2019–August 17, 2022) to evaluate a shared decision-making pathway for stroke prevention.

A, Screenshot of patient web app navigation screen leading to 4 parts of the video: (1) patient video, (2) frequently asked questions, (3) brief quiz, and (4) worksheet. **B,** Screenshot of opening scene of patient

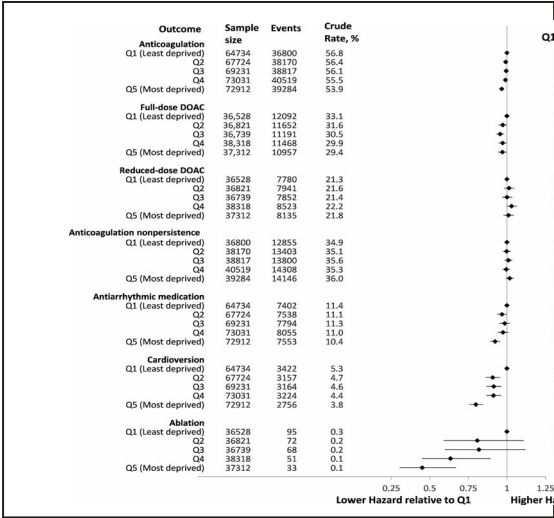


Chart 18-10. Treatment and interventions related to AF within 1 year of incident diagnosis by quintile of material deprivation in the Canadian province of Ontario.

HRs with 95% CIs for therapies and treatment relevant for AF. Material deprivation derived from Ontario, Canada, census tract-level indices (mean population, 400–700 people) with analysis conducted at the individual level. AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; HR, hazard ratio; and Q, quintile. Source: Reprinted from Abdel-Qadir et al.¹²¹ Copyright © 2022 The

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video with animated characters who take the journey to decide about anticoagulation for AF stroke prevention. **C,** Screenshot of an example of stroke reduction estimate based on AF stroke risk that the clinician may use through the clinician web app. **D,** First page of the worksheet given to the patient to indicate key messages. The second page (not shown) has space for questions that the patient has for the clinician visit. **E,** QR codes to the patient tool and clinician tool. AF/Afib indicates atrial fibrillation; app/APP, application; and RCT, randomized controlled trial. Source: Reprinted from Wang et al.²¹⁹ Copyright © 2022 The Authors. Published on behalf of the American Heart Association, Inc, by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is noncommercial and no modifications or adaptations are made.

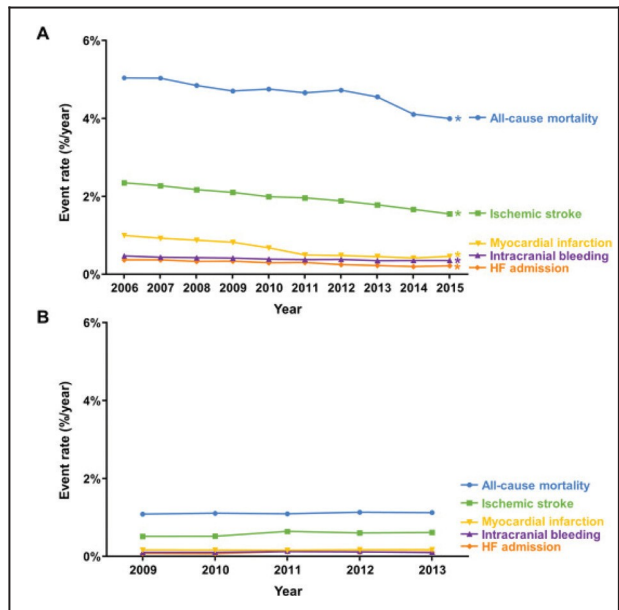


Chart 18-12. Temporal trends of the 1-year adverse event rates from 2006 to 2015 in (A) 679 416 adults with newly diagnosed AF and (B) those without AF in the Korean National Health Insurance Service database.

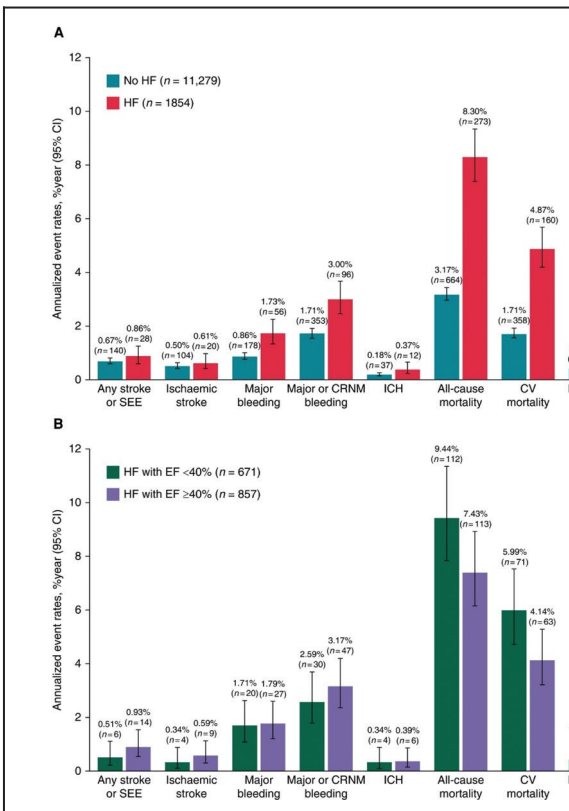


Chart 18-13. Two-year clinical outcomes for participants in the ETNA-AF-Europe multinational registry in Europe, Japan, Korea, and Taiwan, stratified by HF and EF status from 2015 to 2020.

A, Patients with or without HF. **B,** Patients with HF and EF <40% or ≥40%. For 326 patients with HF, the EF was not documented. CRNM indicates clinically relevant nonmajor; CV, cardiovascular; EF, ejection fraction; ETNA-AF-EU, Edoxaban Treatment in Routine Clinical Practice For Patients With Non-Valvular AF; HF, heart failure; ICH, intracranial hemorrhage; MI, myocardial infarction; and SEE, systemic embolic events.

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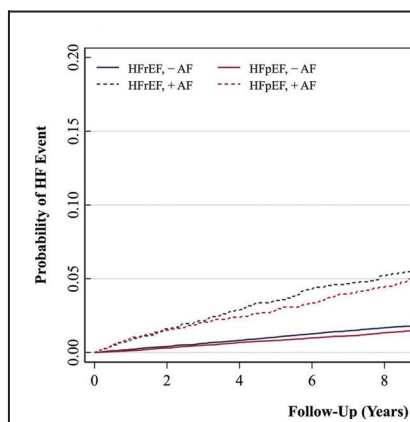


Chart 18-14. Kaplan-Meier estimates for incident HFpEF or HFrEF by concomitant AF status in the REGARDS Study (N=25 787).

Prevalent AF ascertained by baseline ECG or participant self-report of diagnosis. Analysis of HF subtype difference adjusted for age, sex, race, income, education, geographic region, smoking history, SBP, diabetes, BMI, LDL, LVH by ECG, eGFR, baseline CHD status and

CHD as a time-varying covariate, and medications. AF indicates atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; and SBP, systolic blood pressure.

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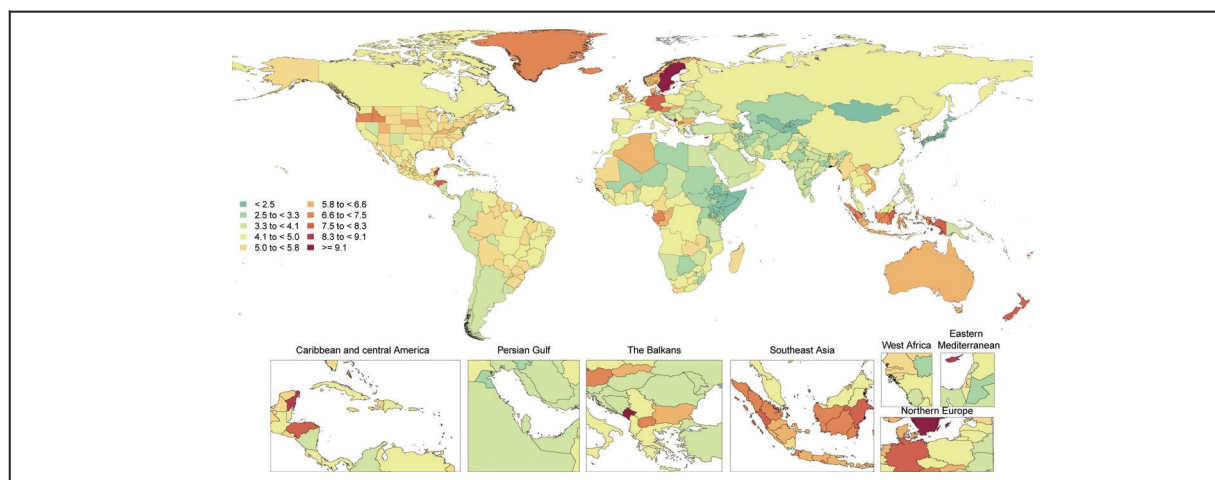


Chart 18-15. Age-standardized global mortality rates of AF and atrial flutter per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AF indicates atrial fibrillation; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

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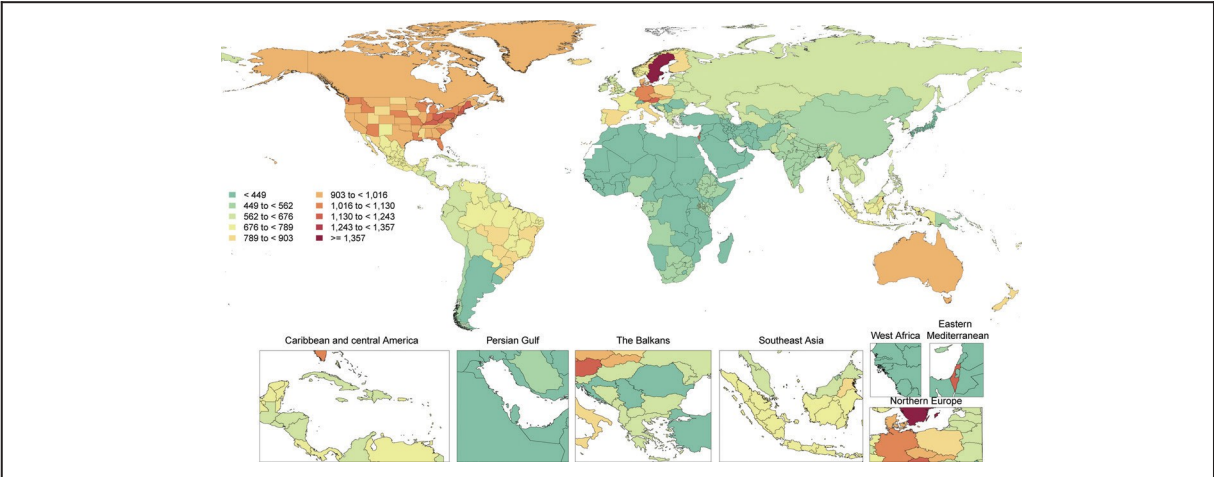


Chart 18-16. Age-standardized global prevalence rates of AF and atrial flutter per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

AF indicates atrial fibrillation; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

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REFERENCES

1. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA, Reunanen A, Huikuri HV. Prognostic significance of prolonged PR interval in the general population. *Eur Heart J*. 2014;35:123–129. doi: 10.1093/eurheartj/eh176

2. Awamleh Garcia P, Alonso Martin JJ, Graupner Abad C, Jimenez Hernandez RM, Curcio Ruigomez A, Talavera Calle P, Cristobal Varela C, Serrano Antolin J, Muniz J, Gomez Doblas JJ, et al; Investigators of the OFRECE Study. Prevalence of electrocardiographic patterns associated with sudden cardiac death in the Spanish population aged 40 years or older: results of the OFRECE Study. *Rev Esp Cardiol (Engl Ed)*. 2017;70:801–807. doi: 10.1016/j.rec.2016.11.039

3. Piwonska A, Piwonski J, Szczesniewska D, Drygas W. Population prevalence of electrocardiographic abnormalities: results of the Polish WAWKARD study. *Kardiol Pol*. 2019;77:859–867. doi: 10.33963/KP.14911

4. Paixão GMM, Lima EM, Quadros AB, Cabral DPR, Coelho RR, Oliveira DM, Nascimento JS, Gomes PR, Ribeiro AL. Association between atrioventricular block and mortality in primary care patients: the

CODE study. *Arq Bras Cardiol*. 2022;119:564–571. doi: 10.36660/abc.20210763

5. Wolbrette DL and Naccarelli GV. Bradycardias: sinus nodal dysfunction and atrioventricular conduction disturbances. In: Topol EJ, Califf RM, Prystowsky EN, Thomas JD, Thompson PD, eds. *Textbook of Cardiovascular Medicine*. 3rd ed. Lippincott Williams & Wilkins; 2007:1038–1049.

6. Shan R, Ning Y, Ma Y, Liu S, Wu J, Fan X, Lv J, Wang B, Li S, Li L. Prevalence and risk factors of atrioventricular block among 15 million Chinese health examination participants in 2018: a nation-wide cross-sectional study. *BMC Cardiovasc Disord*. 2021;21:289. doi: 10.1186/s12872-021-02105-3

7. Fedorowski A, Rosengren P, Pirouzifard M, Sundquist J, Sundquist K, Sutton B. Familial associations of complete atrioventricular block: a national family study in Sweden. *Circ Genom Precis Med*. 2023;16:e003654. doi: 10.1161/CIRCGEN.121.003654

8. Santos J, Ribeiro ALP, Andrade-Junior D, Marcolino MS. Prevalence of electrocardiographic abnormalities in primary care patients according to sex and age group: a retrospective observational study. *Sao Paulo Med J*. 2018;136:20–28. doi: 10.1590/1516-3180.2017.0222290817

9. Diederichsen SZ, Xing LY, Frodi DM, Kongebro EK, Haugan KJ, Graff C, S, Krieger D, Brandes A, Kober L, et al. Prevalence and prognostic significance of bradyarrhythmias in patients screened for atrial fibrillation

- vs usual care: post hoc analysis of the LOOP randomized clinical trial. *JAMA Cardiol.* 2023;8:326-334. doi: 10.1001/jamacardio.2022.5526 10. Coromilas EJ, Kochav S, Goldenthal I, Biviano A, Garan H, Goldbarg S, Kim JH, Yeo I, Tracy C, Ayanian S, et al. Worldwide survey of COVID-19-associated arrhythmias. *Circ Arrhythm Electrophysiol.* 2021;14:e009458. doi: 10.1161/CIRCEP.120.009458
11. Soliman EZ, Alonso A, Misialek JR, Jain A, Watson KE, Lloyd-Jones DM, Lima J, Shea S, Burke GL, Heckbert SR. Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Electrocardiol.* 2013;46:702–706. doi: 10.1016/j.jelectrocard.2013.05.006
12. Teo YH, Han R, Leong S, Teo YN, Syn NL, Wee CF, Tan BKJ, Wong RC, Chai P, Kojodjojo P, et al. Prevalence, types and treatment of bradycardia in obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med.* 2022;89:104–113. doi: 10.1016/j.sleep.2021.12.003
13. Kerola T, Eranti A, Aro AL, Haukilahti MA, Holkeri A, Junttila MJ, Kentta TV, Rissanen H, Vittinghoff E, Knekt P, et al. Risk factors associated with atrioventricular block. *JAMA Netw Open.* 2019;2:e194176. doi: 10.1001/jamanetworkopen.2019.4176
14. Xing LY, Diederichsen SZ, Hojberg S, Krieger DW, Graff C, Olesen MS, Nielsen JB, Brandes A, Kober L, Haugan KJ, et al. Electrocardiographic markers of subclinical atrial fibrillation detected by implantable loop recorder: insights from the LOOP study. *Europace.* 2023;25:euad014. doi: 10.1093/europace/euad014
15. Holkeri A, Eranti A, Haukilahti MAE, Kerola T, Kentta TV, Tikkanen JT, Anttonen O, Noponen K, Seppanen T, Rissanen H, et al. Predicting sudden cardiac death in a general population using an electrocardiographic risk score. *Heart.* 2020;106:427–433. doi: 10.1136/heartjnl-2019-315437 16. Auffret V, Loirat A, Leurent G, Martins RP, Filippi E, Coudert I, Hacot JP, Gilard M, Castellani P, Rialan A, et al. High-degree atrioventricular block complicating ST segment elevation myocardial infarction in the contemporary era. *Heart.* 2016;102:40–49. doi: 10.1136/heartjnl-2015-308260 17. Akhtar Z, Leung LWM, Kontogiannis C, Zuberi Z, Bajpai A, Sharma S, Chen Z, Beeton I, Sohal M, Gallagher MM. Prevalence of bradyarrhythmias needing pacing in COVID-19. *Pacing Clin Electrophysiol.* 2021;44:1340–1346. doi: 10.1111/pace.14313
18. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the

- American College of Cardiology/American on Clinical Practice Guidelines and the correction appears in *Circulation*. 2019;140:e382–e482. doi:
19. Jensen PN, Gronroos NN, Chen LY, Folsom SR, Alonso A. Incidence of and risk factors the general population. *J Am Coll Cardiol*. 10.1016/j.jacc.2014.03.056
 20. Dvsssekilde JR, Christiansen MK, Johansen Jensen HK. Familial risk of atrioventricular *Heart*. 2022;108:1194–1199. doi:
 21. Milanesi R, Baruscotti M, Gneccchi-Ruscione bradycardia associated with a mutation in *N Engl J Med*. 2006;354:151–157. doi: 10.1056/NEJMoa052475
 22. Makiyama T, Akao M, Tsuji K, Doi T, Ohno S, Takenaka K, Kobori A, Ninomiya T, Yoshida H, Takano M, et al. High risk for bradyarrhythmic complications in patients with Brugada syndrome caused by *SCN5A* gene mutations. *J Am Coll Cardiol*. 2005;46:2100–2106. doi: 10.1016/j.jacc.2005.08.043
 23. Postma AV, Denjoy I, Kamblock J,
 35. Andreassen L, Ahlberg G, HM AE, Hartmann JP, Paludan-Muller C, et al: DBDS Genomic Consortium. 5. and *MYH6* associate with AVNRT. 10.1161/CIRCRESAHA.122.321556
 36. James CA, Jonabloed JDH, Svrris P, Pilichou K, Domingo AM. International evidence based rhythmogenic right ventricular resource framework. *Circ Genom* 10.1161/CIRCGEN.120.003273
 37. Chang SH, Kuo CF, Chou IJ, See LC, Doherty M, Wen MS, et al. Outcomes Alders M, Lupoglazoff JM, Vaksman G, Dubosq-Bidot L, Sebillon P, Mannens MM, Guicheney P, et al. Catecholaminergic polymorphic ventricular tachycardia: *RYR2* mutations, bradycardia, and follow up of the patients. *J Med Genet*. 2005;42:863–870. doi: 10.1136/jmg.2004.028993

- ventricular tachycardia during pregnancy. *Circulation*. 2017;135:616–618. doi: 10.1161/CIRCULATIONAHA.116.025064
38. Carnlof C, Iwarzon M, Jensen-Urstad M, Gadler F, Insulander P. Women with PSVT are often misdiagnosed, referred later than men, and have more symptoms after ablation. *Scand Cardiovasc J*. 2017;51:299–307. doi: 10.1080/14017431.2017.1385837
39. Tan ESJ, Chan SP, Seow SC, Teo WS, Ching CK, Chong DTT, Tan VH, Chia PL, Foo DCG, Kojodjojo P; HRAS Investigators. Outcomes of supra-ventricular tachycardia ablation: results from the Singapore ablation and cardiac devices registry. *Pacing Clin Electrophysiol*. 2022;45:50–58. doi: 10.1111/pace.14410
24. Yamada N, Asano Y, Fujita M, Yamazaki S, Inanobe A, Matsuura N, Kobayashi H, Ohno S, Ebana Y, Tsukamoto O, et al. Mutant *KCNJ3* and *KCNJ5* potassium channels as novel molecular targets in bradyarrhythmias and atrial fibrillation. *Circulation*. 2019;139:2157–2169. doi: 10.1161/CIRCULATIONAHA.118.036761
25. Kuss J, Stallmeyer B, Goldstein M, Rinne S, Pees C, Zumhagen S, Seebohm G, Decher N, Pott L, Kienitz MC, et al. Familial sinus node disease caused by a gain of GIRK (G-protein activated inwardly rectifying K(+) channel) channel function. *Circ Genom Precis Med*. 2019;12:e002238. doi: 10.1161/CIRCGEN.118.002238
26. Le Scouarnec S, Bhasin N, Vieyres C, Hund TJ, Cunha SR, Koval O, Marionneau C, Chen B, Wu Y, Demolombe S, et al. Dysfunction in ankyrin-B-dependent ion channel and transporter targeting causes human sinus node disease. *Proc Natl Acad Sci U S A*. 2008;105:15617–15622. doi: 10.1073/pnas.0805500105
27. Liu H, El Zein L, Kruse M, Guinamard R, Beckmann A, Bozio A, Kurtbay G, Megarbane A, Ohmert I, Blaysat G, et al. Gain-of-function mutations in *TRPM4* cause autosomal dominant isolated cardiac con-

40. Anand RG, Rosenthal GL, Van Hare GF, Snyder CS. Is the mechanism of supraventricular tachycardia in pediatrics influenced by age, gender or ethnicity? *Congenit Heart Dis.* 2009;4:464–468. doi: 10.1111/j.1747-0803.2009.00336.x

41. Quattrocelli A, Lang J, Davis A, Pflaumer A. Age makes a difference: symptoms in pediatric supraventricular tachycardia. *J Arrhythm.* 2018;34:565–571. doi: 10.1002/joa3.12103

42. Yu L, Ye X, Yang Z, Yang W, Zhang B; China National Diabetes and Metabolic Disorders Study Group. Prevalences and associated factors of electrocardiographic abnormalities in Chinese adults: a cross-sectional study. *BMC Cardiovasc Disord.* 2020;20:414. doi: 10.1186/s12872-020-01698-5

43. Sano S, Komori S, Amano T, Kohno I, Ishihara T, Sawanobori T, Ijiri H, Tamura K. Prevalence of ventricular preexcitation in Japanese schoolchildren. *Heart.* 1998;79:374–378. doi: 10.1136/hrt.79.4.374

44. Arnar DO, Mairesse GH, Boriani G, Calkins H, Chin A, Coats A, Deharo JC, Svendsen JH, Heidebuchel H, Isa R, et al; ESC Scientific Document Group; EHRA Scientific Documents Committee. Management of asymptomatic pre-excitation disease. *Circ Cardiovasc Genet.* 2010;3:374–385. doi: 10.1161/CIRCGENETICS.109.930867

45. Resdal Dyssekilde J, Frederiksen TC, Christiansen MK, Hasle Sorensen R, Pedersen LN, Loof Moller P, Christensen LS, Larsen JM, Thomsen KK, Lindhardt TB, et al. Diagnostic yield of genetic testing in young patients with atrioventricular block of unknown cause. *J Am Heart Assoc.* 2022;11:e025643. doi: 10.1161/JAHA.121.025643

46. Bodin A, Bisson A, Gaborit C, Herbert J, Clementy N, Babuty D, Lip GYH, Fauchier L. Ischemic stroke in patients with sinus node disease, atrial fibrillation, and other cardiac conditions. *Stroke.* 2020;51:1674–1681. doi: 10.1161/STROKEAHA.120.029048

47. Rehorn M, Sacks NC, Emden MR, Healey B, Preib MT, Cyr PL, Pokorney SD. Prevalence and incidence of patients with paroxysmal supraventricular tachycardia in the United States. *J Cardiovasc Electrophysiol.* 2021;32:2199–2206. doi: 10.1111/jce.15109

48. Go AS, Hlatky MA, Liu TI, Fan D, Garcia EA, Sung SH, Solomon MD. Contemporary burden and correlates of symptomatic paroxysmal supraventricular tachycardia. *J Am Heart Assoc.* 2018;7:e008759. doi: 10.1161/JAHA.118.008759

49. Raisi-Estabragh Z, Kobo O, Elbadawi A, Velagapudi P, Sharma G, Bullock-Palmer RP, Petersen SE, Mehta LS, Ullah W, Roguin A, et al. Differential patterns and outcomes of 20.6 million cardiovascular emergency department encounters for men and women in the United States. *J Am Heart Assoc.* 2022;11:e026432. doi: 10.1161/JAHA.122.026432

50. Michowitz Y, Anis-Heusler A, Reinstein E, Tovia-Brodie O, Glick A, Belhassen B. Familial occurrence of atrioventricular nodal reentrant tachycardia. *Circ Arrhythm Electrophysiol.* 2017;10:e004680. doi: 10.1161/CIRCEP.116.004680

51. Andreasen L, Ahlberg G, Tang C, Andreasen C, Hartmann JP, Tfelt-Hansen J, Behr ER, Pehrson S, Haunso S, LuCamp, et al. Next-generation sequencing of AV nodal reentrant tachycardia patients identifies broad spectrum of variants in ion channel genes. *Eur J Hum Genet.* 2018;26:660–668. doi: 10.1038/s41431-017-0092-0

- (EHRA) consensus document. *Europace*. 2019;21:844–845. doi: 10.1093/europace/euz046
45. Bunch TJ, May HT, Bair TL, Anderson JL, Crandall BG, Cutler MJ, Jacobs V, Mallender C, Muhlestein JB, Osborn JS, et al. Long-term natural history of Adult Wolff-Parkinson-White syndrome patients treated with and without catheter ablation. *Circ Arrhythm Electrophysiol*. 2015;8:1465–1471. doi: 10.1161/CIRCEP.115.003013
46. Janson CM, Millenson ME, Okunowo O, Dai D, Christmyer Z, Tan RB, Ramesh Iyer V, Shah MJ, O'Byrne ML. Incidence of life-threatening events in children with Wolff-Parkinson-White syndrome: analysis of a large claims database. *Heart Rhythm*. 2022;19:642–647. doi: 10.1016/j.hrthm.2021.12.009
47. Escudero CA, Ceresnak SR, Collins KK, Pass RH, Aziz PF, Blafox AD, Ortega MC, Cannon BC, Cohen MI, Dechert BE, et al. Loss of ventricular preexcitation during noninvasive testing does not exclude high-risk accessory pathways: a multicenter study of WPW in children. *Heart Rhythm*. 2020;17:1729–1737. doi: 10.1016/j.hrthm.2020.05.035
48. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112:1142–1147. doi: 10.1016/j.amjcard.2013.05.063
49. Turakhia MP, Guo JD, Keshishian A, Delinger R, Sun X, Ferri M, Russ C, Cato M, Yuce H, Hlavacek P. Contemporary prevalence estimates of undiagnosed and diagnosed atrial fibrillation in the United States. *Clin Cardiol*. 2023;46:484–493. doi: 10.1002/clc.23983
50. Albertsen N, Riahi S, Pedersen ML, Skovgaard N, Andersen S. The prevalence of atrial fibrillation in Greenland: a register-based cross-sectional study based on disease classifications and prescriptions of oral anticoagulants. *Int J Circumpolar Health*. 2022;81:2030522. doi: 10.1080/22423982.2022.2030522
51. Williams BA, Chamberlain AM, Blankenship JC, Hylek EM, Voyce S. Trends in atrial fibrillation incidence rates within an integrated health care

delivery system, 2006 to 2018. *JAMA Netw Open*. 2020;3:e2014874. doi: 10.1001/jamanetworkopen.2020.14874

52. Heckbert SR, Austin TR, Jensen PN, Chen LY, Post WS, Floyd JS, Soliman EZ, Kronmal RA, Psaty BM. Differences by race/ethnicity in the prevalence of clinically detected and monitor-detected atrial fibrillation: MESA. *Circ Arrhythm Electrophysiol*. 2020;13:e007698. doi: 10.1161/CIRCEP.119.007698

53. Eberly LA, Shultz K, Merino M, Brueckner MY, Benally E, Tennison A, Biggs S, Hardie L, Tian Y, Nathan AS, et al. Cardiovascular disease burden and outcomes among American Indian and Alaska Native Medicare \$eneficiaries. *JAMA Netw Open*. 2023;6:e2334923. doi: 10.1001/jamanetworkopen.2023.34923

54. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, MH, Joung B, et al. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. *Am Heart J*. 2018;202:20–26. doi: 10.1016/j.ahj.2018.04.017

55. Joglar JA, Chung MK, Armbuster AL, Benjamin EJ, Chyou JY, Cronin EM, Deswal A, Eckhardt LL, Goldberger ZD, Gopinathannair R, et al; on behalf of the Peer Review Committee Members. 2023 ACC/AHA/ACCP/ HRS guideline for the diagnosis and management of atrial fibrillation: a report of the risk factors and the risk of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2022;15:e010409. doi: 10.1161/CIRCEP.121.010409

67. Brant LCC, Ribeiro AH, Pinto-Filho MM, Kornej J, Preis SR, Fetterman JL, Eromosele OB, Magnani JW, Murabito JM, Larson MG, et al. Association Between electrocardiographic age and cardiovascular events in community settings: the Framingham Heart Study. *Circ Cardiovasc Qual Outcomes*. 2023;16:e009821. doi: 10.1161/CIRCOUTCOMES.122.009821

American College of Cardiology/American Heart Association Committee on Clinical Practice Guidelines [published corrections *Circulation*. 2024;149:e167, *Circulation*. 2024;149:e936, *Circulation*. 2024;149:e1413]. *Circulation*. 2024;149:e1–e156. doi: 10.1161/CIR.0000000000001193

56. Khurshid S, Ashburner JM, Ellinor PT, McManus DD, Atlas SJ, Singer DE, Lubitz SA. Prevalence and incidence of atrial fibrillation among older primary care patients. *JAMA Network Open*. 2023;6:e2255838. doi: 10.1001/jamanetworkopen.2022.55838

57. Wu J, Nadarajah R, Nakao YM, Nakao K, Wilkinson C, Mamas MA, Camm

Joint
appear in
and

- Shim J, Kim JS, Kim YH. Impact of the duration and degree of hypertension and body weight on new-onset atrial fibrillation: a nationwide population-based study. *Hypertension*. 2019;74:e45–e51. doi: 10.1161/HYPERTENSIONAHA.119.13672
70. Aune D, Mahamat-Saleh Y, Kobeissi E, Feng T, Heath AK, Janszky I. Blood pressure, hypertension and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol*. 2023;38:145–178. doi: 10.1007/s10654-022-00914-0
71. Asad Z, Abbas M, Javed I, Korantzopoulos P, Stavrakis S. Obesity is associated with incident atrial fibrillation independent of gender: a meta-analysis. *J Cardiovasc Electrophysiol*. 2018;29:725–732. doi: 10.1111/jce.13458
72. Donnellan E, Wazni OM, Elshazly M, Kanj M, Hussein AA, Baranowski B, Kochar A, Trulock K, Aminian A, Schauer P, et al. Impact of bariatric surgery on atrial fibrillation type. *Circ Arrhythm Electrophysiol*. 2020;13:e007626. doi: 10.1161/CIRCEP.119.007626
73. Garnvik LE, Malmö V, Janszky I, Wisløff U, Loennechen JP, Nes BM. Physical activity modifies the risk of atrial fibrillation in obese individuals: the HUNT3 study. *Eur J Prev Cardiol*. 2020;25:1646–1652. doi: 10.1177/2047487318784365
- AJ, Gale CP. Temporal trends and patterns in atrial fibrillation incidence: a population-based study of 3.4 million individuals. *Lancet Reg Health Eur*. 2022;17:100386. doi: 10.1016/j.lanepe.2022.100386
58. Sanchez JM, Jolly SE, Dewland TA, Tseng ZH, Nah G, Vittinghoff

74. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis. *Eur J Clin Nutr*. 2019;73:100–110. doi: 10.1038/s41430-018-0100-1.

10.1161/CIRCULATIONAHA.119.042882

59. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loefer LR, Soliman EZ, Alonso A. Lifetime risk of atrial fibrillation by race and socioeconomic status: ARIC Study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol*. 2018;11:e006350. doi: 10.1161/CIRCEP.118.006350.

60. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, Chen SA. Lifetime risks, projected numbers, and

adverse outcomes in asian patients with atrial fibrillation: a report from the Taiwan nationwide AF cohort study. *Chest*. 2018;153:453–466. doi: 10.1016/j.chest.2017.10.001.

61. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njolstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, et al; BiomarcARE Consortium. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarcARE Consortium (Biomarker for Cardiovascular

75. Jones NR, Taylor KS, Taylor CJ, Aveyard P. Weight change and the risk of incident atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2019;105:1799–1805. doi: 10.1136/heartjnl-2019-314931
76. Chatterjee NA, Giulianini F, Geelhoed B, Lunetta KL, Misialek JR, Genetic obesity and the risk of atrial fibrillation: causal estimates 10.1161/CIRCULATIONAHA.116.024921
77. Zhou Y, Zha L, Pan S. The risk of atrial fibrillation increases with ear- 2022;19:1388–1398. doi: 10.7150/ijms.72334
78. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the prospective studies. *Eur J Prev Cardiol*. 2018;25:1437–1451. doi: Risk Assessment in Europe). *Circulation*. 2017;136:1588–1597. doi: 10.1161/CIRCULATIONAHA.117.028981
62. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, Trinquart L, McManus DD, Staerk L, Lin H, et al. Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. *Circulation*. 2018;137:1027–1038. doi: 10.1161/CIRCULATIONAHA.117.031431
63. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ*. 2018;361:k1453. doi: 10.1136/bmj.k1453
64. Holt A, Gislason GH, Schou M, Zareini B, Biering-Sørensen T, Phelps M, Kragholm K, Andersson C, Fosbøl EL, Hansen ML, et al. New-onset atrial fibrillation: incidence, characteristics, and related events following a national COVID-19 lockdown of 5.6 million people. *Eur Heart J*. 2020;41:3072–3079. doi: 10.1093/eurheartj/ehaa494
65. Hernandez I, Gabriel N, He M, Guo J, Tadrous M, Suda KJ, Magnani JW. Effect of the COVID-19 pandemic on adversity in individuals receiving anticoagulation for atrial fibrillation: a nationally representative administrative health claims analysis. *Am Heart J Plus*. 2022;13:100096. doi: 10.1016/j.ahjo.2022.100096
66. Matsuoka S, Kaneko H, Okada A, Morita K, Itoh H, Michihata N, Jo T, Takeda N, Morita H, Fujiu K, et al. Age modified relationship between modifiable risk of atrial fibrillation: a systematic review and meta-analysis of 10.1177/2047487318780435
- Niemeijer MN, Rienstra M, Rose LM, Smith AV, Arking DE, et al. from mendelian randomization. *Circulation*. 2017;135:741–754. doi: 10.1177/2047487318780435
- lier onset of obesity: a mendelian randomization study. *Int J Med Sci*. 2017;18:1000–1008. doi: 10.1177/2047487318780435
- risk of atrial fibrillation: a systematic review and meta-analysis of 10.1177/2047487318780435

79. Qi W, Zhang N, Korantzopoulos P, Letsas KP, Cheng M, Di F, Tse G, Liu T, Li G. Serum glycated hemoglobin level as a predictor of atrial fibrillation: a systematic review with meta-analysis and meta-regression. *PLoS One*. 2017;12:e0170955. doi: 10.1371/journal.pone.0170955
80. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabetes Complications*. 2018;32:501–511. doi: 10.1016/j.jdiacomp.2018.02.004
81. Guo S, Huang Y, Liu X, Ma J, Zhu W. Association of type 1 diabetes mellitus and risk of atrial fibrillation: systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2023;199:110629. doi: 10.1016/j.diabres.2023.110629
82. Xiong Z, Liu T, Tse G, Gong M, Gladding PA, Smail BH, Stiles MK, Gillis AM, Zhao J. A machine learning aided systematic review and meta-analysis of the relative risk of atrial fibrillation in patients with diabetes mellitus. *Front Physiol*. 2018;9:835. doi: 10.3389/fphys.2018.00835
83. Anagnostopoulos I, Kousta M, Kossyvakis C, Lakka E, Vrachatis D, Deftereos S, Vassilikos VP, Giannopoulos G. Weekly physical activity and incident atrial fibrillation in females: a dose-response meta-analysis. *Int J Cardiol*. 2023;370:191–196. doi: 10.1016/j.ijcard.2022.11.007
84. Ahn HJ, Lee SR, Choi EK, Han KD, Jung JH, Lim JH, Yun JP, Kwon S, Oh S, Lip GYH. Association between exercise habits and stroke, heart failure, and mortality in Korean patients with incident atrial fibrillation: a nationwide

105. Sun Y, Yu B, Yu Y, Wang B, Tan X, Lu Y, Wang Y, Zhang K, Wang N. Sweetened beverages, genetic susceptibility, and incident atrial fibrillation: a prospective cohort study. *Circ Arrhythm Electrophysiol*. 2024;17:e012145. doi: 10.1161/CIRCEP.123.012145
106. Rosman L, Lampert R, Ramsey CM, Dziura J, Chui PW, Brandt C, Haskell S, Burg MM. Posttraumatic stress disorder and risk for early incident atrial fibrillation: a prospective cohort study of 1.1 million young adults. *J Am Heart Assoc*. 2019;8:e013741. doi: 10.1161/JAHA.119.013741
107. Garg PK, O'Neal WT, Diez-Roux AV, Alonso A, Soliman EZ, Heckbert S. Negative affect and risk of atrial fibrillation: MESA. *J Am Heart Assoc*. 2019;8:e010603. doi: 10.1161/JAHA.118.010603
108. Garg PK, Claxton JS, Soliman EZ, Chen LY, Lewis TT, Mosley T Jr, Alonso A. Associations of anger, vital exhaustion, anti-depressant use, and poor social ties with incident atrial fibrillation: the Atherosclerosis Risk in Communities Study. *Eur J Prev Cardiol*. 2020;28:633–640. doi: 10.1177/2047487319897163
109. Fransson EI, Nordin M, Magnusson Hanson LL, Westerlund H. Job strain and atrial fibrillation: results from the Swedish Longitudinal Occupational Survey of Health and meta-analysis of three studies. *Eur J Prev Cardiol*. 2018;25:1142–1149. doi: 10.1177/2047487318777387
110. Filardo G, Damiano RJ Jr, Ailawadi G, Thourani VH, Pollock BD, Sass DM, Phan TK, Nguyen H, da Graca B. Epidemiology of new-onset atrial fibrillation following coronary artery bypass graft surgery. *Heart*. 2018;104:985–992. doi: 10.1136/heartjnl-2017-312150
111. Cikes M, Planinc I, Claggett B, Cunningham J, Milicic D, Sweitzer N, Senni M, Gori M, Linssen G, Shah SJ, et al. Atrial fibrillation in heart failure with preserved ejection fraction: the PARAGON-HF trial. *JACC Heart Fail*. 2022;7:167–174. doi: 10.1001/jamacardio.2021.5010
94. Marcus GM, Modrow MF, Schmid CH, Sigona K, Nah G, Yang J, Chu TC, Joyce S, Gettabecha S, Ogomori K, et al. Individualized studies of triggers of paroxysmal atrial fibrillation: the I-STOP-AFib randomized clinical trial. *JAMA Cardiol*. 2022;7:167–174. doi: 10.1001/jamacardio.2021.5010

- 2022;10:336–346. doi: 10.1016/j.jchf.2022.01.018
112. Chebbout R, Heywood EG, Drake TM, Wild JRL, Lee J, Wilson M, Lee MJ. A systematic review of the incidence of and risk factors for postoperative atrial fibrillation following general surgery. *Anaesthesia*. 2018;73:490–498.
95. Grindal AW, Sparrow RT, McIntyre WF, Conen D, Healey JS, Wong JA. doi: 10.1111/anae.14118
- Alcohol Consumption and atrial arrhythmia recurrence after atrial fibrillation ablation: a systematic review and meta-analysis. *Can J Cardiol*. 2023;39:266–273. doi: 10.1016/j.cjca.2022.12.010
96. Zhao E, Chen S, Du Y, Zhang Y. Association between sleep apnea hypopnea syndrome and the risk of atrial fibrillation: a meta-analysis of cohort study. *Biomed Res Int*. 2018;2018:5215868. doi: 10.1155/2018/5215868
97. Carrasco OG, Gómez Carrasco BM, Gómez G, Espinoza-Rojas R, Orihuela-Manrique EJ, García-Lara RA, Loayza-Castro JA, Zefías-Trujillo GZ, Vera-Ponce VJ, Cruz-Vargas JADL. Obstructive sleep apnea syndrome associated with atrial fibrillation in adult patients: a systematic review and meta-analysis. *Int J Stat Med Res*. 2023;12:43–50. doi: 10.6000/1929-6029.2023.12.06
98. Chokesuwattanaskul R, Thongprayoon C, Sharma K, Congrete S, Tanawuttiwat T, Cheungpasitporn W. Associations of sleep quality with incident atrial fibrillation: a meta-analysis. *Intern Med J*. 2018;48:964–972.

113. Xiao FP, Chen MY, Wang L, He H, Jia ZQ, Kuai L, Zhou HB, Liu M, Hong M. Outcomes of new-onset atrial fibrillation in patients with sepsis: a systematic review and meta-analysis of 225,841 patients. *Am J Emerg Med.* 2021;42:23–30. doi: 10.1016/j.ajem.2020.12.062
114. Liao SC, Shao SC, Cheng CW, Chen YC, Hung MJ. Incidence rate and clinical impacts of arrhythmia following COVID-19: a systematic review and meta-analysis of 17,435 patients. *Crit Care.* 2020;24:690. doi: 10.1186/s13054-020-03368-6
115. Szarpak L, Filipiak KJ, Skwarek A, Pruc M, Rahnama M, Denegri A, Jachowicz M, Dawidowska M, Gasecka A, Jaguszewski MJ, et al. Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19: a systematic review and meta-analysis. *Cardiol J.* 2022;29:33–43. doi: 10.5603/CJ.a2021.0167
116. Alexandre J, Boismoreau L, Morice PM, Sassier M, Da-Silva A, Plane AF, Font J, Milliez P, Legallois D, Dolladille C. Atrial fibrillation incidence associated with exposure to anticancer drugs used as monotherapy in clinical trials. 99. Chen J, Li F, Wang Y, Cai D, Chen Y, Mei Z, Chen L. Short sleep duration and atrial fibrillation risk: a comprehensive analysis of observational cohort studies and genetic study. *Eur J Intern Med.* 2023;114:84–92. doi: 10.1016/j.ejim.2023.05.001
100. Arafa A, Kokubo Y, Shimamoto K, Kashima R, Watanabe E, Sakai Y, Li J, Teramoto M, Sheerah HA, Kusano K. Sleep duration and atrial fibrillation risk in the context of predictive, preventive, and personalized medicine: the Suita Study and meta-analysis of prospective cohort studies. *EPMA J.* 2022;13:77–86. doi: 10.1007/s13167-022-00275-4
101. Yue C, Yang F, Li F, Chen Y. Association between air pollutants and atrial fibrillation in general population: a systematic review and meta-analysis. *Ecotoxicol Environ Saf.* 2021;208:111508. doi: 10.1016/j.ecoenv.2020.111508

JACC CardioOncol. 2023;5:216–226. doi: 10.1016/j.jacc.2022.11.019

117. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of hypertension and atrial fibrillation: systematic review and meta-analysis. *PLoS One*. 2019;14:e0211228. doi: 10.1371/journal.pone.0211228

118. Zhang M, Li LL, Zhao QQ, Peng XD, Wu K, Li X, Ruan YF, Bai R, Liu N, Ma CS. The Association of new-onset atrial fibrillation and risk of cancer: a systematic review and meta-analysis. *Cardiol Res Pract*. 2020;2020:2372067. doi: 10.1155/2020/2372067

119. Essien UR, Kornej J, Johnson AE, Schulson LB, Benjamin EJ, Magnani JW. Social determinants of atrial fibrillation. *Nat Rev Cardiol*. 2021;18:763–773. doi: 10.1038/s41569-021-00561-0

120. Essien UR, McCabe ME, Kershaw KN, Youmans QR, Fine MJ, Yancy CW, Khan SS. Association between neighborhood-level poverty and

- incident atrial fibrillation: a retrospective cohort study. *J Gen Intern Med*. 2021;37:1436–1443. doi: 10.1007/s11606-021-06976-2
121. Abdel-Qadir H, Akiyamen LE, Fang J, Pang A, Ha ACT, Jackevicius CA, Alter DA, Austin PC, Atzema CL, Bhatia RS, et al. Association of neighborhood-level material deprivation with atrial fibrillation care in a single-payer health care system: a population-based cohort study. *Circulation*. 2022;146:159–171. doi: 10.1161/CIRCULATIONAHA.122.058949
122. Holland EM, Dilsaver DB, Walters RW, Kim MH. Relationship of health-related social needs, social determinants of health, and catheter ablation utilization in atrial fibrillation: social needs and application of atrial fibrillation ablation. *J Interv Card Chamberlain AM, Alonso A, Magnani JW. Association of household income and adverse outcomes in patients with atrial fibrillation. Heart*. 2020;106:1679–1685. doi: 10.1136/heartjnl-2019-316065
124. Boyd LM, Colavecchia AC, Townsend KA, Kmitch L, Broder L, Hegeman-Dingle RR, Ateya M, Lattimer A, Bosch R, Alvir J. Associations of community and individual social determinants of health with medication adherence in patients with atrial fibrillation: a retrospective cohort study. *J Am Heart Assoc*. 2023;12:e026745. doi: 10.1161/JAHA.122.026745
125. Tertulien T, Chen Y, Althouse AD, Essien UR, Johnson A, Magnani JW. Association of
137. Bundy JD, Heckbert SR, Chen LY, Lloyd-Jones DM, Greenland P. Evaluation of risk prediction models of atrial fibrillation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol*. 2020;125:55–62. doi: 10.1016/j.amjcard.2019.09.032
138. Pfister R, Bragelmann J, Michels G, Wareham NJ, Luben R, Khaw KT. Performance of the CHARGE-AF risk model for incident atrial fibrillation in the EPIC Norfolk cohort. *Eur J Prev Cardiol*. 2015;22:932–939. doi: 10.1177/2047487314544045
139. Pollock BD, Filardo G, da Graca B, Phan TK, Ailawadi G, Thourani V, Damiano RJ Jr, Edgerton JR. Predicting new-onset income and educational attainment in hospitalization events in atrial fibrillation. *Am J Prev Cardiol*. 2021;7:100201. doi: 10.1016/j.ajpc.2021.100201
126. Vinter N, Calvert P, Kronborg MB, Cosedis-Nielsen J, Gupta D, Ding WY, Trinquart L, Johnsen SP, Frost L, Lip GYH. Social determinants of health and recurrence of atrial fibrillation after catheter ablation: a Danish nationwide cohort study. *Eur Heart J Qual Care Clin Outcomes*. 2023;9:632–638. doi: 10.1093/ehjqcco/qcac071
127. Khatib R, Glowacki N, Byrne J, Brady P. Impact of social determinants of health on anticoagulant use among patients with atrial fibrillation: systematic review and meta-analysis. *Medicine (Baltimore)*. 2022;101:e29997. doi:

- H, Nielen MMJ. CHARGE-AF in a national routine primary care electronic health records database in the Netherlands: validation for 5-year risk of atrial fibrillation and implications for patient selection in atrial fibrillation screening. *Open Heart*. 2021;8:e001459. doi: 10.1136/openhrt-2020-001459
141. Tiwari P, Colborn KL, Smith DE, Xing F, Ghosh D, Rosenberg MA. Assessment of a machine learning model applied to harmonized electronic health record data for the prediction of incident atrial fibrillation. *JAMA Netw Open*. 2020;3:e1919396. doi: 10.1001/jamanetworkopen.2019.19396
142. Vitolo M, Imberti JF, Maisano A, Albini A, Bonini N, Valenti AC, Malavasi VL, Proietti M, Healey JS, Lip GY, et al. Device-detected atrial high rate episodes and the risk of stroke/thrombo-embolism and atrial fibrillation incidence: a systematic review and meta-analysis. *Eur J Intern Med*. 2021;92:100–106. doi: 10.1016/j.ejim.2021.05.038
143. Meng Y, Zhang Y, Zhu C, Nie C, Liu P, Chang S, Wang S. Atrial high-rate episode burden and stroke risks for patients with device-detected subclinical atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol*. 2023;371:211–220. doi: 10.1016/j.ijcard.2022.09.046
144. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, et al; AF-Screen Collaborators. Screening for atrial fibrillation: a report of the AF-SCREEN international collaboration. *Circulation*. 2017;135:1851–1867. doi: 10.1097/
128. Garg PK, O'Neal WT, Ogunsua A, Thacker EL, Howard G, Soliman EZ, Cushman M. Usefulness of the American Heart Association's Life Simple 7 to predict the risk of atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol*. 2018;121:199–204. doi: 10.1016/j.amjcard.2017.09.033
129. Garg PK, O'Neal WT, Chen LY, Loehr LR, Sotoodehnia N, Soliman EZ, Alonso A. American Heart Association's Life Simple 7 and risk of atrial fibrillation in a population without known cardiovascular disease: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Heart Assoc*.

145. Benjamin EJ, Go AS, Desvigne-Nickens P, Anderson CD, Casadei B, Chen LY, Crijns H, Freedman B, Hills MT, Healey JS, et al. Research priorities in atrial fibrillation screening: a report from a National Heart, Lung, and Blood Institute virtual workshop. *Circulation*. 2021;143:372–388. doi: 10.1161/CIRCULATIONAHA.120.047633
146. Turakhia MP, Shafrin J, Bognar K, Trocio J, Abdulsattar Y, Wiederkehr D, Goldman DP. Estimated prevalence of undiagnosed atrial fibrillation in the United States. *PLoS One*. 2018;13:e0195088. doi: 10.1371/journal.pone.0195088
130. Wang W, Norby FL, Rooney MR, Zhang M, Gutierrez A, Garg P, Soliman EZ, Alonso A, Dudley SC Jr, Lutsey PL, et al. Association of Life's Simple 7 with atrial fibrillation burden (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2020;137:31–38. doi: 10.1016/j.amjcard.2020.09.033
131. Ogunmoroti O, Michos ED, Aronis KN, Salami JA, Blankstein R, Virani SS, Spatz ES, Allen NB, Rana JS, Blumenthal RS, et al. Life's Simple 7 and the risk of atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2018;275:174–181. doi: 10.1016/j.atherosclerosis.2018.05.050
132. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, Ambrose M, Alonso A. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol*. 2011;107:85–91. doi: 10.1016/j.amjcard.2010.09.033

147. Halimi F, Sabouret P, Huberman JP, Ouazana L, Guedj D, Djouadi K, Dhanjal TS, Goette A, Lafont C, Lellouche N. Atrial fibrillation detection with long-term continuous Holter ECG recording in patients with high cardiovascular risk and clinical palpitations: the prospective after study. *Clin Res Cardiol.* 2023;112:807–814. doi: 10.1007/s00392-022-02109-9
148. Himmelreich JCL, Lucassen WAM, Coutinho JM, Harskamp RE, de Groot JR, van Weert HCPM. 14-Day Holter monitoring for atrial fibrillation after ischemic stroke: The yield of guideline-recommended monitoring duration. *Eur Stroke J.* 2023;8:157–167. doi: 10.1177/23969873221146027
149. Gladstone DJ, Wachter R, Schmalstieg-Bahr K, Quinn FR, Hummers E, Ivers N, Marsden T, Thornton A, Djuric A, Suerbaum J, et al; SCREEN-AF Investigators and Coordinators. Screening for atrial fibrillation in the older population: a randomized clinical trial. *JAMA Cardiol.* 2021;6:558-567. doi: 10.1016/j.amjcard.2010.08.049
- 10.1001/jamacardio.2021.0038
133. Schnabel RB, Aspelund T, Li G, Sullivan LM, Suchy-Dicey A, Harris TB, Pencina MJ, D'Agostino RB Sr., Levy D, Kannel WB, et al. Validation of an atrial fibrillation risk algorithm in Whites and African Americans. *Arch Intern Med.* 2010;170:1909–1917. doi: 10.1001/archinternmed.2010.434
134. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J.* 2013;34:2243–2251. doi: 10.1093/eurheartj/ehs033
135. Segan L, Canovas R, Nanayakkara S, Chieng D, Prabhu S, Voskoboinik A,

150. Svendsen JH, Diederichsen SZ, Hojberg S, Krieger DW, Graff C, Kronborg C, Olesen MS, Nielsen JB, Holst AG, Brandes A, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP study): a randomised controlled trial. *Lancet*. 2021;398:1507–1516. doi: 10.1016/S0140-6736(21)01698-6
151. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet*. 2021;398:1498– doi: 10.1016/j.eurheartj.2021.05.015
- prediction: the HARMS2-AF risk score. *Eur Heart J*. 2023;44:3443–3452. doi: 10.1093/eurheartj/ehad375
136. Shulman E, Kargoli F, Aagaard P, Hoch E, Di Biase L, Fisher J, Gross J, Kim S, Krumerman A, Ferrick KJ. Validation of the Framingham Heart Study and CHARGE-AF risk scores for atrial fibrillation in Hispanics, African-Americans, and Non-Hispanic Whites. *Am J Cardiol*. 2016;117:76–83. doi: 10.1016/j.amjcard.2015.10.009

10.1016/S0140-6736(21)01637-8

152. Lyth J, Svennberg E, Bernfort L, Aronsson M, Frykman V, Al-Khalili F, Friberg L, Rosenqvist M, Engdahl J, Levin L. Cost-effectiveness of population screening for atrial fibrillation: the STROKESTOP study. *Eur Heart J*. 2023;44:196–204. doi: 10.1093/eurheartj/ehac547
153. Gruwez H, Barthels M, Haemers P, Verbrugge FH, Dhont S, Meekers E, Wouters F, Nuyens D, Pison L, Vandervoort P, et al. Detecting paroxysmal

atrial fibrillation from an electrocardiogram in sinus rhythm: external validation of the AI approach. *JACC Clin Electrophysiol*. 2023;9:1771–1782. doi: 10.1016/j.jacep.2023.04.008

154. Lubitz SA, Atlas SJ, Ashburner JM, Lianopoulos ATT, Borowsky LH.

Guan W, Khurshid S, Ellinor PT, Chang Y, McManus DD, et al. Screening

for atrial fibrillation in older adults at primary care visits: VITAL-AF

randomized controlled trial. *Circulation*. 2022;145:946– doi: 10.1161/CIRCULATIONAHA.121.057014

155. Halahakone U, Senanayake S, McCreanor V, Parsonage W, Kularatna S.

Brain D. Cost-effectiveness of screening to identify patients with atrial

fibrillation: a systematic review. *Heart Lung Circ*. 2023;32:678–695. doi: 10.1016/j.hlc.2023.03.014

156. Andrade JG, Shah A, Godin R, Janitz T, Kongnakorn T, Brown I, Dhandra

D, Dhamane A, Nault I. Cost-effectiveness of atrial fibrillation

screening in Canadian community practice. *Heart Rhythm* 2023;4:103–110. doi: 10.1016/j.hrro.2022.11.003

157. Jonas DE, Kahwati LC, Yun JDY, Middleton JC, Coker-Schwimmer M,

Asher GN. Screening for atrial fibrillation with electrocardiography: evi-

dence report and systematic review for the US Preventive Services

Task Force. *JAMA*. 2018;320:485–498. doi: 10.1001/jama.2018.4190

158. Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis

EM, Donahue KE, Doubeni CA, Epling JW Jr., Kubik M, et al; US

Preventive Services Task Force. Screening for atrial fibrillation: US

Preventive Services Task Force recommendation statement. *JAMA*. 2022;327:360–367. doi: 10.1001/jama.2021.23732

159. Lowres N, Olivier J, Chao TF, Chen SA, Chen Y, Diederichsen A,

Fitzmaurice DA, Gomez-Doblas JJ, Harbison J, Healey JS, et al.

Estimated stroke risk, yield, and number needed to screen for atrial

fibrillation detected through single time screening: a multicountry

patient-level meta-analysis of 141,220 screened individuals. *PLoS Med*.

2019;16:e1002903. doi: 10.1371/journal.pmed.1002903

160. Petryszyn P, Niewinski P, Staniak A, Piotrowski P, Well A, Well M,

popula

10.100

170. Roselli

Almore

wide

1233.

171. Nielsen

SE.

driven

Nat

172.

A.

Large-

Jeskowiak I, Lip G, Ponikowski P. Effectiveness of

screening for atrial fibrillation and its determinants: a

meta-analysis. *PLoS One*. 2019;14:e0213198. doi: 10.1371/journal.pone.0213198

161. Elbadawi A, Sedhom R, Gad M, Hamed M, Elwagdy A,

Barakat AF, Khalid U, Mamas MA, Birnbaum Y,

Elgendy IY, et al. Screening for atrial fibrillation in the

elderly: a network meta-analysis of randomized trials. *Eur J*

Intern Med.

2022;105:38–45. doi: 10.1016/j.ijim.2022.07.015

162. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS,

Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane

A, Cheung L, et al; Apple Heart Study Investigators. Large-

scale assessment of a smartwatch to identify atrial

fibrillation. *N Engl J Med*. 2019;381:1909–1917. doi: 10.1056/NEJMoa1901183

163. Kaplan RM, Koehler J, Ziegler PD, Sarkar S, Zweibel

S, Passman RS. Stroke risk as a function of atrial fibrillation

duration and

- Genet.* 2015;47:435–444. doi: 10.1038/ng.3247
173. Xiong H, Yang Q, Zhang X, Wang P, Chen F, Liu Y, Wang P, Zhao Y, Li S, Huang Y, et al. Significant association of rare variant p.Gly8Ser in cardiac sodium channel beta4-subunit *SCN4B* with atrial fibrillation. *Ann Hum Genet.* 2019;83:239–248. doi: 10.1111/ahg.12305
 174. Olson TM, Alekseev AE, Liu XK, Park S, Zingman LV, Bienengraeber M, Sattiraju S, Ballew JD, Jahangir A, Terzic A. Kv1.5 channelopathy due to loss-of-function mutation causes human atrial fibrillation. *Hum Mol Genet.* 2006;15:2185–2191. doi: 10.1093/hmg/ddl143
 175. Ahlberg G, Refsgaard L, Lundegaard PR, Andreassen L, Ranthe MF, Linscheid N, Nielsen JB, Melbye M, Haunso S, Sajadieh A, et al. Rare truncating variants in the sarcomeric protein titin associate with familial and early-onset atrial fibrillation. *Nat Commun.* 2018;9:4316. doi: 10.1038/s41467-018-06618-y
 176. Choi SH, Weng LC, Roselli C, Lin H, Haggerty CM, Shoemaker MB, Barnard J, Arking DE, Chasman DI, Albert CM, et al; DiscovEHR study and the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Association between titin loss-of-function variants and early-onset atrial fibrillation. *JAMA.* 2018;320:2354–2364. doi: 10.1001/jama.2018.18179
 177. Norby FL, Tang W, Pankow JS, Lutsey PL, Alonso A, Steffan B, Chen LY, Zhang M, Shippee ND, Ballantyne CM, et al. Proteomics and risk of atrial fibrillation in older adults (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol.* 2021;161:42–50. doi: 10.1016/j.amjcard.2021.08.064
 178. Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, Ahola-Olli A, Kurki M, Karjalainen J, Palta P, et al; FinnGen. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiovascular diseases and common cancers. *Nat Med.* 2020;26:549–557. doi: 10.1038/s41591-020-0800-0
 179. Lubitz SA, Yin X, Lin HJ, Kolek M, Smith JG, Trompet S, Rienstra M, Rost NS, Teixeira PL, Almgren P, et al; AFGen Consortium. Genetic risk prediction of atrial fibrillation. *Circulation.* 2017;135:1311–1320. doi: 10.1161/CIRCULATIONAHA.116.024143
 180. Miyazawa K, Ito S, Ieki H, CHA₂DS₂-VASc score. *Circulation.* 2019;140:1639–1646. doi: 10.1161/CIRCULATIONAHA.119.041303
 181. Lopez-Sainz A, Dominguez F, Lopes LR, Ochoa JP, Barriales-Villa R, Climent V, Linschoten M, Tiron C, Chiriat C, Marques N, et al; European Genetic Cardiomyopathies Initiative Investigators. Clinical features and natural history of *PRKAG2* variant cardiac glycogenosis. *J Am Coll Cardiol.* 2020;76:186–197. doi: 10.1016/j.jacc.2020.05.029
 182. Akhtar MM, Lorenzini M, Cicerchia M, Ochoa JP, Hey TM, Sabater Molina M, Restrepo-Cordoba MA, Dal Ferro M, Stolfo D, Johnson R, et al. Clinical phenotypes and prognosis of dilated cardiomyopathy caused by truncating variants in the *TTN* gene. *Circ Heart Fail.* 2020;13:e006832. doi: 10.1161/CIRCHEARTFAILURE.119.006832
 183. Yoneda ZT, Anderson KC, Quintana JA, O'Neill MJ, Sims RA, Glazer AM, Shaffer CM, Crawford DM, Stricker T, Ye F, et al. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol.* 2021;6:1371–1379. doi: 10.1001/jamacardio.2021.3370
 184. Chalazan B, Mol D, Darbar FA, Ornelas-Loredo A, Al-Azzam B, Chen Y, Tofovic D, Sridhar A, Alzahrani Z, Ellinor P, et al. Association of rare genetic variants and early-onset atrial fibrillation in ethnic minority individuals. *JAMA Cardiol.* 2021;6:811–819. doi: 10.1001/jamacardio.2021.0994
 185. Alzahrani Z, Ornelas-Loredo A, Darbar SD, Farooqui A, Mol D, Chalazan B, Villagrana NE, McCauley M, Lazar S, Wissner E, et al. Association between family history and early-onset atrial fibrillation across racial and ethnic groups. *JAMA Netw Open.* 2018;1:e182497. doi: 10.1001/jamanetworkopen.2018.2497
 186. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Huang LH, Zhang W, Doherty M, Wen MS, et al. Association of a family history of atrial fibrillation with incidence and outcomes of atrial fibrillation: a

fibrillation unveils disease biology and enables cardioembolic risk predic-tion. *Nat Genet.* 2023;55:187–197. doi: 10.1038/s41588-022-01284-9 181. Norland K, Sveinbjornsson G, Thorolfsdottir RB, Davidsson OB, Tragante V, Rajamani S, Helgadóttir A, Gretarsdóttir S, van Setten J, Asselbergs FW, et al. Sequence variants with large effects on cardiac electrophysiology and disease. *Nat Commun.* 2019;10:4803. doi: 10.1038/s41467-019-12682-9

182. Ntalla I, Weng LC, Cartwright JH, Hall AW, Sveinbjornsson G, Tucker NR, Choi SH, Chaffin MD, Roselli C, Barnes MR, et al. Multi-ancestry GWAS of the electrocardiographic PR interval identifies 202 loci underlying cardiac conduction. *Nat Commun.* 2020;11:2542. doi: 10.1038/s41467-020-15706-x

183. Zhao D, Bartz TM, Sotoodehnia N, Post WS, Heckbert SR, Alonso A, Longchamps RJ, Castellani CA, Hong YS, Rotter JI, et al. Mitochondrial DNA copy number and incident atrial fibrillation. *BMC Med.* 2020;18:246. doi: 10.1186/s12916-020-01715-6

184. Choi SH, Jurgens SJ, Weng LC, Pirruccello JP, Roselli C, Chaffin M, Lee CJ, Hall AW, Khera AV, Lunetta KL, et al. Monogenic and polygenic contributions to atrial fibrillation risk: results from a national biobank. *Circ Res.* 2020;126:200–209. doi: 10.1161/CIRCRESAHA.119.315686

185. Shetty NS, Pampana A, Patel N, Li P, Arora G, Arora P. High-proportion spliced-in titin truncating variants in African and European ancestry in the All of Us research program. *Nat Cardiovasc Res.* 2024;3:140–144. doi: 10.1038/s44161-023-00417-5

186. Wang B, Lunetta KL, Dupuis J, Lubitz SA, Trinquart L, Yao L, Ellinor PT, Benjamin EJ, Lin H. Integrative omics approach to identifying genes

- associated with atrial fibrillation. *Circ Res*. 2020;126:350–360. doi: 10.1161/CIRCRESAHA.119.315179
187. Jameson HS, Hanley A, Hill MC, Xiao L, Ye J, Bapat A, Ronzier E, Hall AW, Hucker WJ, Clauss S. et al. Loss of ^{Cardiovascular Research} mellitus and obesity and on mortality in patients with preexisting heart failure: a nationwide, matched, observational cohort study. *J Am Heart Assoc*. 2021;10:e019323. doi: 10.1161/JAHA.120.019323
190. Pathak R, Evans M, Middeldorp M, Mahajan R, Mehta A, Megan M, Twomey D, Wong C, Hendriks J, Abhayaratna W. Cost-effectiveness and clinical effectiveness of the risk factor management clinic in atrial fibrillation. *JACC Clin Physiol*. 2017;3:436–447. doi: 10.1016/j.jacep.2016.12.015
191. Mehra R, Chung MK, Olshansky B, Dobrev D, Jackson CL, Kundel V, Linz D, Redeker NS, Redline S, Sanders P, et al; on behalf of the 201. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brügemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkier R, et al; RACE 3 Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J*. 2018;39:2987–2996. doi: 10.1093/eurheartj/ehx739
202. Elliott AD, Verdicchio CV, Mahajan R, Middeldorp ME, Gallagher C, Mishima RS, Hendriks JML, Pathak RK, Thomas G, Lau DH, et al. An exercise and physical activity program in patients with atrial fibrillation: the ACTIVE-AF randomized controlled trial. *JACC Clin Electrophysiol*. 2023;9:455–465. doi: 10.1016/j.jacep.2022.12.002
203. Reading SR, Go AS, Fang MC, Singer DE, Liu IA, Black MH, Udaltsova N, Reynolds K; Anticoagulation and Risk Factors in Atrial Fibrillation–Network (ATRIA-CVRN) Investigators. American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology; and Stroke Council. Sleep-disordered breathing and cardiac arrhythmias in adults: mechanistic insights and clinical implications: a scientific statement from the American Heart Association. *Circulation*. 2022;146:e119–e136. doi: 10.1161/CIR.0000000000001082
192. Traaen GM, Aakerøy L, Hunt TE, Øverland B, Bendz C, Sande L, Aakhus S, Fagerland MW, Steinshamn S, Anfinson OG, et al. Effect of continuous positive airway pressure on arrhythmia in atrial fibrillation and sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med*. 2021;204:573–582. doi: 10.1164/rccm.202011-4133OC

- Health literacy and awareness of atrial fibrillation. *J Am Heart Assoc.* 2017;6:e005128. doi: 10.1161/JAHA.116.005128
204. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, Bhatt DL, Smith EE, Olson DM, Maisch L, et al. Association of preceding anti-thrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. *JAMA.* 2017;317:1057–1067. doi: 10.1001/jama.2017.1371
 205. Healey JS, Lopes RD, Granger CB, Alings M, Rivard L, McIntyre WF, Atar D, Birnie DH, Boriani G, Camm AJ, et al; ARTESIA Investigators. Apixaban for stroke prevention in subclinical atrial fibrillation. *N Engl J Med.* 2024;390:107–117. doi: 10.1056/NEJMoa2310234
 206. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Oral Anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE Registry. *JAMA Cardiol.* 2016;1:55–62. doi: 10.1001/jamacardio.2015.0374
 207. Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol.* 2017;69:2475–2484. doi: 10.1016/j.jacc.2017.03.540
193. Silberberg A, Tan MK, Yan AT, Angaran P, Dorian P, Bucci C, Gregoire JC, Bell AD, Gladstone DJ, Green MS, et al; FREEDOM AF and CONNECT AF Investigators. Use of evidence-based therapy for cardio-vascular risk factors in canadian outpatients with atrial fibrillation: from the Facilitating Review and Education to Optimize Stroke Prevention in Atrial Fibrillation (FREEDOM AF) and Co-ordinated National Network to Engage Physicians in the Care and Treatment of Patients With Atrial Fibrillation (CONNECT AF). *Am J Cardiol.* 2017;120:582–587. doi: 10.1016/j.amjcard.2017.05.027
 194. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, Ghazi L, Blackshear JL, Chonchol M, Fine LJ, et al. Effect of intensive

208. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, Masoudi FA, Turchin A, Song Y, Doros G, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR) PINNACLE Registry. *J Am Heart Assoc.* 2017;6:e005801. doi: 10.1161/JAHA.117.005801
209. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, et al; ACC PINNACLE Investigators. Association of insurance type with receipt of oral anticoagulation in insured patients with atrial fibrillation: a report from the American College of Cardiology NCDR PINNACLE registry. *Am Heart J.* 2018;195:50–59. doi: 10.1016/j.ahj.2017.08.010
- blood pressure lowering on the risk of atrial fibrillation. *Hypertension.* 2020;75:1491–1496. doi: 10.1161/HYPERTENSIONAHA.120.14766
195. Sfairopoulos D, Liu T, Zhang N, Tse G, Bazoukis G, Letsas K, Goudis C, Milionis H, Vrettos A, Korantzopoulos P. Association between sodium-glucose cotransporter-2 inhibitors and incident atrial fibrillation/atrial flutter.

210. Eckman MH, Wise R, KnocheImann C, Mardis R, Leonard AC, Wright S, Gummadi A, Dixon E, Becker RC, Schauer DP, et al. Can a best practice advisory improve anticoagulation prescribing to reduce stroke risk in patients with atrial fibrillation? *J Cardiol*. 2024;83:285–290. doi: 10.1016/j.jjcc.2023.08.005

ter in heart of 211. V, de Groot JR, Sanmartin Fernandez M, Segura T,

10.1007/s10741-022-10281-3

196. Oliveri F, Bongiorno A, Compagnoni S, Fasolino A, Gentile FR, Pepe

A, Tua L. Statin and postcardiac surgery atrial fibrillation prevention: a systematic review and meta-analysis. *J Cardiovasc Pharmacol*. 2022;80:180–186. doi:

- Blomstrom-Lundqvist C, Hargroves D, Antoniou S, Williams H, Worsley A, Harris J, et al. Outcomes and drivers of inappropriate dosing of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2023;109:178–185. doi: 10.1097/FJC.0000000000001294
197. Agarwal S, Beard CW, Khosla J, Clifton S, Anwaar MF, Ghani A, Farhat K, Pырpyris N, Momani J, Munir MB, et al. Safety and efficacy of colchicine for the prevention of post-operative atrial fibrillation in patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Europace*. 2023;25:euad169. doi: 10.1093/europace/euad169
198. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, et al. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med*. 2020;382:20–28. doi: 10.1056/NEJMoa1817591
199. Ahmed AS, Miller J, Foreman J, Golden K, Shah A, Field J, Gilge J, Clark B, Joshi S, Nair G, et al. Prophylactic colchicine after radiofrequency ab-lation of atrial fibrillation: the PAPERS study. *JACC Clin Electrophysiol*. 2023;9:1060–1066. doi: 10.1016/j.jacep.2023.02.003
200. Conen D, Ke Wang M, Popova E, Chan MTV, Landoni G, Cata JP, Reimer C, McLean SR, Srinathan SK, Reyes JCT, et al; COP-AF Investigators. Effect of colchicine on perioperative atrial fibrillation and myocardial injury after non-cardiac surgery in patients undergoing major thoracic surgery (COP-AF): an international randomised trial. *Lancet*. 2023;402:1627–1635. doi: 10.1016/S0140-6736(23)01689-6

212. McIntyre WF, Conen D, Olshansky B, Halperin JL, Hayek E, Huisman MV, American patients with atrial fibrillation: the GLORIA-AF registry program. *Clin Cardiol*. 2018;41:744–751. doi: 10.1002/clc.22936
213. Bul M, Shaikh F, McDonagh J, Ferguson C. Frailty and oral anticoagulant prescription in adults with atrial fibrillation: a systematic review. *Aging Med (Milton)*. 2023;6:195–206. doi: 10.1002/agm2.12214
214. Essien UR, Magnani JW, Chen N, Gellad WF, Fine MJ, Hernandez I. Race/ethnicity and sex-related differences in direct oral anticoagulant initiation in newly diagnosed atrial fibrillation: a retrospective study of Medicare data. *J Natl Med Assoc*. 2020;112:103–108. doi: 10.1016/j.jnma.2019.10.003
215. Essien UR, Holmes DN, Jackson LR 2nd, Fonarow GC, Mahaffey KW, Reiffel JA, Steinberg BA, Allen LA, Chan PS, Freeman JV, et al. Association of race/ethnicity with oral anticoagulant use in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II. *JAMA Cardiol*. 2018;3:1174–1182. doi: 10.1001/jamacardio.2018.3945
216. Essien UR, Chiswell K, Kaltenbach LA, Wang TY, Fonarow GC, Thomas KL, Turakhia MP, Benjamin EJ, Rodriguez F, Fang MC, et al. Association

- of race and ethnicity with oral comes in patients with atrial fibrillation: Guidelines-Atrial Fibrillation Registry. *JAMA*. doi: 10.1001/jamacardio.2022.3704
217. Sur NB, Wang K, Di Tullio MR, Gutierrez H, García-Rivera EJ, Zevallos JC. Burden temporal trends in the use of emic stroke and atrial fibrillation. *Stroke*. 10.1161/STROKEAHA.118.023959
218. Gallagher C, Elliott AD, Wong CX, R, Lau DH, Sanders P, Hendriks JML. a systematic review and meta-analysis. 10.1136/heartint-2016-310952
219. Wang PJ, Lu Y, Mahaffey KW, Lin A, Morin DP, Sears SF, Chung MK, Russo AM, Lin B, Piccini J, et al. Randomized clinical trial to evaluate an atrial fibrillation stroke prevention shared decision-making pathway. *J Am Heart Assoc*. 2023;12:e028562. doi: 10.1161/JAHA.122.028562
220. Kunneman M, Branda ME, Hargraves IG, Sivilly AL, Lee AT, Gorr H, Burnett B, Suzuki T, Jackson EA, Hess E, et al; Shared Decision Making for Atrial Fibrillation (SDM4AFib) Trial Investigators. Assessment of shared decision-making for stroke prevention in patients with atrial fibrillation: a randomized clinical trial. *JAMA Intern Med*. 2020;180:1215–1224. doi:
234. Vrsalovic M, Presecki AV. Atrial and mortality in patients with meta-analysis of prospective studies. doi: 10.1002/cic.22813
235. Lin HJ, Wolf PA, Kelly-Haves M, D'Agostino RB. Stroke severity in *Stroke*. 1996;27:1760–1764. doi:
236. Chen M, Lu X, Huang J, Zhang J. nificance of atrial fibrillation in heart left ventricular function: insights from a 2014;16:1317–1322. doi:
237. Odutayo A, Wong CX, Williams R. tance of atrial fibrillation timing and 10.1001/jamainternmed.2020.2908
221. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
222. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database.

- failure: a systematic review and meta-analysis. *J Card Fail.* 2017;23:56–62. doi: 10.1016/j.cardfail.2016.08.005
238. Weber C, Hung J, Hickling S, Nedkoff L, Murray K, Li I, Briffa TG. Incidence, predictors and mortality risk of new heart failure in patients hospitalised with atrial fibrillation. *Heart.* 2021;107:1320–1326. doi: 10.1136/heartjnl-2020-318648
239. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, Bigger T, Cushman W, Goff D, Soliman EZ, et al. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol.* 2014;114:1217–1222. doi: 10.1016/j.amjcard.2014.07.045
240. Echouffo-Tcheugui JB, Shrader P, Thomas L, Gersh BJ, Kowey PR, Mahaffey KW, Singer DE, Hylek EM, Go AS, Peterson ED, et al. Care patterns and outcomes in atrial fibrillation patients with and without diabetes: ORBIT-AF Registry. *J Am Coll Cardiol.* 2017;70:1325–1335. doi: 10.1016/j.jacc.2017.07.755
223. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ.* 2016;532:h7013. doi: 10.1136/bmj.h7013
224. DeLago AJ, Essa M, Ghajar A, Hammond-Haley M, Parvez A, Nawaz I, Shalhoub J, Marshall DC, Nazarian S, Calkins H, et al. Incidence and mortality trends of atrial fibrillation/atrial flutter in the United States 1990 to 2017. *Am J Cardiol.* 2021;148:78–83. doi: 10.1016/j.amjcard.2021.02.014
225. Vinter N, Huang Q, Fenger-Grøn M, Frost L, Benjamin EJ, Trinquart L. Trends in excess mortality associated with atrial fibrillation over 45 years (Framingham Heart Study): community based cohort study. *BMJ.* 2020;370:m2724. doi: 10.1136/bmj.m2724
226. Masri A, Kanj M, Thamilarasan M, Wazni O, Smedira NG, Lever HM, Desai MY. Outcomes in hypertrophic cardiomyopathy patients with and without atrial fibrillation: a survival meta-analysis. *Cardiovasc Diagn Ther.* 2017;7:36–44. doi: 10.21037/cdt.2016.11.23
227. Alphonse P, Virk S, Collins J, Campbell T, Thomas SP, Semsarian C, Kumar S. Prognostic impact of atrial fibrillation in hypertrophic cardiomyopathy: a systematic review. *Clin Res Cardiol.* 2021;110:544–554. doi: 10.1007/s00392-020-01730-w
228. Camen S, Csengeri D, Geelhoed B, Niiranen T, Gianfagna F, Vishram-Nielsen JK, Costanzo S, Söderberg S, Vartiainen E, Börschel CS, et al. Risk factors, subsequent disease onset, and prognostic impact of myocardial infarction and atrial fibrillation. *J Am Heart Assoc.* 2022;11:e024299. doi: 10.1161/JAHA.121.024299
229. Saxena A, Virk SA, Bowman S, Chan L, Jeremy R, Bannon PG. Preoperative atrial fibrillation portends poor outcomes after coronary bypass graft surgery: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg.* 2018;155:1524–1533.e2. doi: 10.1016/j.jtcvs.2017.11.048
230. Phan K, Ha HS, Phan S, Medi C, Thomas SP, Yan TD. New-onset atrial fibrillation following coronary bypass surgery predicts long-term mortality: a systematic review and meta-analysis. *Eur J Cardiothorac Surg.* 2015;48:817–824. doi: 10.1093/ejcts/ezu551
231. Brener MI, George I, Kosmidou I, Nazif T, Zhang Z, Dizon JM, Garan H, Malaisrie SC, Makkar R, Mack M, et al. Atrial fibrillation is associated with mortality in intermediate surgical risk patients with severe aortic stenosis: analyses from the PARTNER 2A and PARTNER S3i trials. *J Am Heart Assoc.* 2021;10:e019584. doi: 10.1161/JAHA.120.019584
232. Mojoli M, Gersh BJ, Barioli A, Masiero G, Tellaroli P, D'Amico G, Tarantini G. Impact of atrial fibrillation on outcomes of patients treated by transcatheter aortic valve implantation: a systematic review and meta-analysis. *Am Heart J.* 2017;192:64–75. doi: 10.1016/j.ahj.2017.07.005
233. Vitalis A, Shantsila A, Proietti M, Vohra RK, Kay M, Olshansky B, Lip GYH. Peripheral arterial disease in patients with atrial fibrillation: the AFFIRM study. *Am J Med.* 2021;134:514–518. doi: 10.1016/j.amjmed.2020.08.026

241. Kanjanahattakij N, Rattanawong P, Krishnamoorthy P, Horn B, Chongsathidkiet P, Garvia V, Putthapiban P, Sirinvaravong N, Figueredo VM. New-onset atrial fibrillation is associated with increased mortality in critically ill patients: a systematic review and meta-analysis. *Acta Cardiol*. 2019;74:162–169. doi: 10.1080/00015385.2018.1477035
242. Garg L, Agrawal S, Agarwal M, Shah M, Garg A, Patel B, Agarwal N, Nanda S, Sharma A, Cox D. Influence of atrial fibrillation on outcomes in patients who underwent primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Am J Cardiol*. 2018;121:684–689. doi: 10.1016/j.amjcard.2017.12.003
243. Antikainen RL, Peters R, Beckett NS, Rajkumar C, Bulpitt CJ. Atrial fibrillation and the risk of cardiovascular disease and mortality in the Hypertension in the Very Elderly Trial. *J Hypertens*. 2020;38:839–844. doi: 10.1097/HJH.0000000000002346
244. Magnani JW, Norby FL, Agarwal SK, Soliman EZ, Chen LY, Loehr LR, Alonso A. Racial differences in atrial fibrillation-related cardiovascular disease and mortality: the Atherosclerosis Risk in Communities (ARIC) study. *JAMA Cardiol*. 2016;1:433–441. doi: 10.1001/jamacardio.2016.1025
245. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. *JAMA*. 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
246. Doshi R, Al-Khafaji JF, Dave M, Taha M, Patel K, Goyal H, Gullapalli N. Comparison of baseline characteristics and in-hospital outcomes in Medicaid versus private insurance hospitalizations for atrial fibrillation. *Am J Cardiol*. 2019;123:776–781. doi: 10.1016/j.amjcard.2018.11.045
247. Tanaka Y, Shah NS, Passman R, Greenland P, Lloyd-Jones DM, Khan SS. Trends in Cardiovascular mortality related to atrial fibrillation in the United States, 2011 to 2018. *J Am Heart Assoc*. 2021;10:e020163. doi: 10.1161/JAHA.120.020163
248. O'Neal WT, Sandesara PB, Kelli HM, Venkatesh S, Soliman EZ. Urban-rural differences in mortality for atrial fibrillation hospitalizations in the United States. *Heart Rhythm*. 2018;15:175–179. doi: 10.1016/j.hrthm.2017.10.019
249. Yang H, Liang X, Xu J, Hou H, Wang Y. Meta-analysis of atrial fibrillation in patients with COVID-19. *Am J Cardiol*. 2021;144:152–156. doi: 10.1016/j.amjcard.2021.01.010
250. Wandell P, Carlsson AC, Gasevic D, Sundquist J, Sundquist K. Neighbourhood socio-economic status and all-cause mortality in adults with atrial fibrillation: a cohort study of patients treated in primary care in Sweden. *Int J Cardiol*. 2016;202:776–781. doi: 10.1016/j.ijcard.2015.09.027
251. Wändell P, Carlsson AC, Gasevic D, Holzmann MJ, Årnlöv J, Sundquist J, Sundquist K. Socioeconomic factors and mortality in patients with atrial fibrillation: a cohort study in Swedish primary care. *Eur J Public Health*. 2018;28:1103–1109. doi: 10.1093/eurpub/cky075

252. Shi M, Chen LY, Bekwelem W, Norby FL, Soliman EZ, Alam AB, Alonso A. Association of atrial fibrillation with incidence of extracranial systemic embolic events: the ARIC study. *J Am Heart Assoc.* 2020;9:e016724. doi: 10.1161/JAHA.120.016724
253. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation.* 2017;135:208–219. doi: 10.1161/CIRCULATIONAHA.116.024057
254. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke.* 1991;22:983–988. doi: 10.1161/01.str.22.8.983
255. Kabra R, Cram P, Girotra S, Vaughan Sarrazin M. Effect of race on outcomes (stroke and death) in patients >65 years with atrial fibrillation. 256. Kabra R, Girotra S, Vaughan Sarrazin M. Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA₂DS₂-VASc score. *J Am Coll Cardiol.* 2016;68:461–470. doi: 10.1016/j.jacc.2016.05.044
- with syncope and falls in older adults: a systematic review and meta-analysis. *Mayo Clin Proc.* 2020;95:676–687. doi: 10.1016/j.mayocp.2019.09.029
271. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation.* 2003;107:2920–2925. doi: 10.1161/01.CIR.0000072767.89944.6E
272. Chamberlain AM, Gersh BJ, Alonso A, Kopecky SL, Killian JM, Weston SA, Roger VL. No decline in the risk of heart failure after incident atrial fibrillation: a community study assessing trends overall and by ejection fraction. *Heart Rhythm.* 2017;14:791–798.
257. Patel PJ, Katz R, Borovskiy Y, Killian A, Levine JM, McNaughton NW, Callans D, Supple G, Dixit S, Epstein AE, et al. Race and stroke in an atrial fibrillation inception cohort: findings from the Penn Atrial Fibrillation Free study. *Heart Rhythm.* 2018;15:487–493. doi:

- Mark DB, Nabutovsky Y, Greiner MA, Piccini JP. Atrial fibrillation burden and heart failure: data from 39,710 individuals with cardiac implanted electronic devices. *Heart Rhythm*. 2021;18:709–716. doi: 10.1016/j.hrthm.2021.01.021
274. Schnabel RB, Ameri P, Siller-Matula JM, Diemberger I, Gwechenberger M, Pecun L, Manu MC, Souza J, De Caterina R, Kirchhof P. Outcomes of patients with atrial fibrillation on oral anticoagulation with and without heart failure: the ETNA-AF-Europe registry. *Europace*. 2023;25:euaad280. doi: 10.1016/j.hrthm.2017.11.025
258. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Atrial fibrillation and the risk of 30-day incident thromboembolic events, and mortality in adults $\geq$ 50 years with COVID-19. *J Arrhythm*. 2021;37:231–237. doi: 10.1002/joa3.12458
259. Liu DS, Chen J, Jian WM, Zhang GR, Liu ZR. The association of atrial fibrillation and dementia incidence: a meta-analysis of prospective cohort studies. *J Geriatr Cardiol*. 2019;16:298–306. doi: 10.11909/j.issn.1671-5411.2019.03.006
260. Islam MM, Poly TN, Walther BA, Yang HC, Wu CC, Lin MC, Chien SC, Li YC. Association between atrial fibrillation and dementia: a meta-analysis. *Front Aging Neurosci*. 2019;11:305. doi: 10.3389/fnagi.2019.00305
261. Giannone ME, Filippini T, Whelton PK, Chiari A, Vitolo M, Boriani G, Vinceti M. Atrial fibrillation and the risk of early-onset dementia: a systematic review and meta-analysis. *J Am Heart Assoc*. 2022;11:e025653. doi: 10.1161/JAHA.122.025653
262. Conen D, Rodondi N, Muller A, Beer JH, Ammann P, Moschovitis G, Auricchio A, Hayoz D, Kobza R, Shah D, et al; Swiss-AF Study Investigators. Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *J Am Coll Cardiol*. 2019;73:989–999. doi: 10.1016/j.jacc.2018.12.039
263. Bailey MJ, Soliman EZ, McClure LA, Howard G, Howard VJ, Judd SE,

275. Nicoli CD, O'Neal WT, Levitan EB, Singleton MJ, Judd SE, Howard G, Safford MM, Soliman EZ. Atrial fibrillation and risk of incident heart failure with reduced versus preserved ejection fraction. *Heart*. 2022;108:353–359. doi: 10.1136/heartjnl-2021-319122
276. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24:1555–1566. doi: 10.1177/2047487317715769
277. Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, Cushman M, Alonso A. Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2015;131:1843–1850. doi: 10.1161/CIRCULATIONAHA.114.014145
278. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation*. 2013;127:569–574. doi: 10.1161/CIRCULATIONAHA.112.123992
279. Mark PB, Carrero JJ, Matsushita K, Sang Y, Ballew SH, Grams ME, Coresh J, Surapaneni A, Brunskill NJ, Chalmers J, et al. Major cardiovascular events and subsequent risk of kidney failure with replacement therapy: a CKD Prognosis Consortium study. *Eur Heart J*. 2023;44:1157–1166. doi: 10.1093/eurheartj/ehac825
- Unverzagt FW, Wadley V, Sachs BC, Hughes TM. Relation of atrial fibrillation to cognitive decline (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] study). *Am J Cardiol*. 2021;148:60–68. doi: 10.1016/j.amjcard.2021.02.036
- Anticoagulant prescribing for atrial fibrillation and risk of incident dementia. *Heart*. 2021;107:1898–1904. doi: 10.1136/heartjnl-2021-319672
265. Fong KY, Chan YH, Wang Y, Yeo C, Rosario BH, Lip GYH, Tan VH.
264. Cadogan SL, Powell E, Wing K, Wong AY, Smeeth L, Warren-Gash C.

280. Rattanawong P, Upala S, Rianguiwat T, Jaruvongvanich V, Sanguankee A, Vutthikraivit W, Chung EH. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. *J Interv Card Electrophysiol.* 2018;51:91–104. doi: 10.1007/s10840-017-0308-9
281. Fawzy AM, Bisson A, Bodin A, Herbert J, Lip GYH, Fauchier L. Atrial fibrillation and the risk of ventricular arrhythmias and cardiac arrest: a nationwide population-based study. *J Clin Med.* 2023;12:1075. doi: 10.3390/jcm12031075
- Dementia risk of direct oral anticoagulants versus warfarin for atrial fibrillation: systematic review and meta-analysis. *JACC Asia.* 2023;3:776–786. doi: 10.1016/j.jacasi.2023.07.012
266. Herber E, Aeschbacher S, Coslovsky M, Schwendinger F, Hennings E, Gasser A, Di Valentino M, Rigamonti E, Reichlin T, Rodondi N, et al; SWISS-

282. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J*. 2016;37:1591–1602. doi: 10.1093/eurheartj/ehw007
- AF Investigators. Physical activity and brain health in patients with atrial fibrillation. *Eur J Neurol*. 2023;30:567–577. doi: 10.1111/ene.15660
267. Zhang L, Gallagher R, Neubeck L. Health-related quality of life in atrial fibrillation patients over 65 years: a review. *Eur J Prev Cardiol*. 2015;22:987–1002. doi: 10.1177/2047487314538855

283. Padfield GJ, Steinberg C, Swampillai J, Qian H, Connolly SJ, Dorian P, Green MS, Humphries KH, Klein GJ, Sheldon R, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. *Heart Rhythm*. 2017;14:801–807. doi: 10.1016/j.hrthm.2017.01.038
268. Piccini JP, Simon DN, Steinberg BA, Thomas L, Allen LA, Fonarow GC, Gersh B, Hylek E, Kowey PR, Reiffel JA, et al; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients. Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the ORBIT-AF Registry. *JAMA Cardiol*. 2016;1:282–291. doi: 10.1001/jamacardio.2016.0529
269. Silva RL, Guhl EN, Althouse AD, Herbert B, Sharbaugh M, Essien UR, Hausmann LRM, Magnani JW. Sex differences in atrial fibrillation: patient-

284. Al-Kawaz M, Omran SS, Parikh NS, Elkind MSV, Soliman EZ, Kamel H. Comparative risks of ischemic stroke in atrial flutter versus atrial fibrillation. *J Stroke Cerebrovasc Dis*. 2018;27:839–844. doi: 10.1016/j.jstrokecerebrovasdis.2017.10.025
285. Lin YS, Chen TH, Chi CC, Lin MS, Tung TH, Liu CH, Chen YL, Chen MC. Different Implications of heart failure, ischemic stroke, and mortality between nonvalvular atrial fibrillation and atrial flutter: a view from a national cohort study. *J Am Heart Assoc*. 2017;6:e006406. doi: 10.1161/JAHA.117.006406
270. Malik V, Gallagher C, Linz D, Elliott AD, Emami M, Kadhimi K, Mishima R, Hendriks JML, Mahajan R, Arnolda L, et al. Atrial fibrillation is associated reported outcomes and the persistent toll on women. *Am J Prev Cardiol*. 2021;8:100252. doi: 10.1016/j.ajpc.2021.100252
286. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024.

287. Centers for Disease Control and Prevention Health Statistics. National Ambulatory public use data files. Accessed May 1.
288. Jackson SL, Tong X, Yin X, George MG. ment, hospital inpatient, and mortality United States, 2006 to 2014. *Am J Cardiol*. 10.1016/j.amcard.2017.08.017
289. Mevre P, Blum S, Berger S, Aeschbacher S, S. Conen D. Risk of hospital admissions in svstematic review and meta-analysis. *Can* doi: 10.1016/j.cica.2019.05.024
290. Jiang S, Seslar SP, Sloan LA, Hansen RN. Health care resource utilization and costs associated with atrial fibrillation and rural-urban disparities. *J Manag Care Spec Pharm*. 2022;28:1321–1330. doi: 10.18553/jmcp.2022.28.11.1321
291. Dieleman JL, Cao J, Chapin A, Chen A, Matvasz T, Scott KW, et al. US and health condition, 1996-2016. 10.1001/jama.2020.0734
292. Li X, Tse VC, Au-Doung LW. Wona stroke on atrial fibrillation-related *Euronace*. 2017;19:937–947. doi:
293. Johnsen SP, Dalby LW, Tackstrom T. of atrial fibrillation: a nationwide study *Res*. 2017;17:714. doi:
294. *Global Burden of Disease Study and Evaluation*. University of Washington.

295. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet*. 2016;388:1161–1169. doi: 10.1016/s0140-6736(16)30968-0

19. SUDDEN CARDIAC ARREST,
VENTRICULAR ARRHYTHMIAS,
AND INHERITED
CHANNELOPATHIES

See Tables 19-1 through 19-7 and Charts 19-1 through 19-5

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Cardiac Arrest (Including VF and Ventricular
Flutter)

ICD-9 427.4, 427.5; ICD-10 I46.0, I46.1,
I46.9, I49.0.

2022, United States: Underlying cause mortality—19
171. Any-mention mortality—417 957.

Tachycardia

ICD-9 427.0, 427.1, 427.2; ICD-10 I47.1,
I47.2, I47.9.

2022, United States: Underlying cause mortality—
1291. Any-mention mortality—11 380.

Sudden Cardiac Arrest

Cardiac arrest is the cessation of cardiac mechanical
activity as confirmed by the absence of signs of circu-
lation.¹ An operational definition of SCA is unexpected
cardiac arrest that results in attempts to restore circu-

epidemiology and statistics pertaining
to adult OHCA, adult IHCA, pediatric
OHCA, pediatric IHCA, SCA/SCD not
associated with location, and special
circumstances in separate
subheadings for ease of use.

Incidence and Cause

(See Tables 19-1 through 19-3)

1. The ongoing CADES registry.

lation. If resuscitation attempts are unsuccessful, this situation
is referred to as SCD. SCA results from many disease
processes; an ILCOR consensus statement rec-ommends
categorizing cardiac arrest into events with external causes
(drowning, trauma, asphyxia, electrocu-tion, and drug
overdose) or events with medical causes.² Because of
fundamental differences in the underlying pathogenesis and
system of care, epidemiological data for OHCA and IHCA are
collected and reported sepa-rately. For similar reasons, data
for infants (<1 year of age), children (1–18 years of age), and
adults are re-ported separately. To that end, this chapter
addresses

The 2025 AHA Statistical Update uses language that conveys respect and specificity
when referencing race and ethnicity. Instead of referring to groups very broadly with
collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as
adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients,
White females).

As the AHA continues its focus on health equity to address structural racism, we
are working to reconcile language used in previously published data sources and
studies when this information is compiled in the annual Statistical Update. We strive to
use terms from the original data sources or published studies (mostly from the past 5
years) that may not be as inclusive as the terms used in 2025. As style guidelines for
scientific writing evolve, they will serve as guidance for data sources and publications
and how they are cited in future Statistical Updates.

dence of EMS-treated OHCA among individuals of any age in >2300 EMS agencies in the United States. Differences in bystander intervention and survival by race and ethnicity, sex, and neighborhood characteristics are listed in Table 19-1.

- Incidence of EMS-treated OHCA in US people of any age is 83.4 individuals per 100 000 population according to the 2023 CARES registry, with great variation between states (range, 47.3–138.6; Table 19-2).
- In 2023, location of OHCA in adults was most often a home or residence (71.0%) followed by public settings (18.2%) and nursing homes (10.7%; Table 19-3).³
- The initial recorded cardiac rhythm was VF, VT, or shockable by an automated external defibrillator in 17.8% of EMS-treated adult OHCA in 2023 (Table 19-3).
- Of 2937 OHCA cases of SCA in people 2 to 45 years of age from 2009 to 2012 in Toronto, 1892 (64.4%) had presumed cardiac cause by Utstein definitions, but after detailed investigation, only 608 (20.7%) had an adjudicated pathology of cardiac cause.⁴ Noncardiac causes included 130 (4.4%) blunt, penetrating, or burn injury traumas; 687 (23.4%) suicides; 521 (17.7%) drug overdoses; 288 (9.8%) acute noncardiac illnesses (eg, terminal illness); 218 (7.4%) motor vehicle collisions; 106 (3.6%) noncardiac vascular causes; 32 (1.1%) drownings; and 24 (0.82%) homicides.
- In a Swedish study that integrated data from 3 national registries between 2007 and 2021, 5.2% of the 66 261 cardiac arrests were attributable to poisoning. The most common cause of poisoning was polysubstance use.⁵
- Among 608 OHCA with a cardiac cause in people 2 to 45 years of age from 2009 to 2012 in Toronto, 243 (40%) were attributed to CHD, 174 (28.6%) were attributed to structural diseases of the myocardium, 98 (16.1%) were attributed to sudden unexplained death, 15 (2.5%) were attributed to other cardiac causes (anomalous coronary arteries, congenital HD, and tamponade), and 78 (12.8%) remained unspecified.⁴
- OHCA has been attributed to various causes, including cardiac (53%), respiratory (18%), neurological (3%), toxicological (6%), other (9%), and

unknown (11%), in a observational study.⁶

COVID-19 Effects on OHCA

The COVID-19 pandemic has had incidence of OHCA.

- In New York City, the incidence by EMS (March 1–April 25, over the same period 1 year with the pre–COVID-19 experiencing OHCA during and more likely to be Asian, >1 race than White. There of asystole and pulseless shockable rhythms) during the compared with the control
- Early in the COVID-19 pandemic, OHCA in the United States 2019, primarily in 19 mortality (adjusted mean CI, 37.1–40.1) per 1 million COVID-19 mortality (adjusted 28.7 [95% CI, 26.7–30.6] per 1
- A study of nontraumatic OHCA calls in 3 counties in southeast Michigan between January 1 and May 31 of both 2019 and 2020 showed a 60% increase in OHCA calls during the pandemic months compared with the control period.⁹ The increase in OHCA calls slightly lagged but otherwise mirrored the rise and fall of confirmed COVID-19 cases in the counties. OHCA increased disproportionately among individuals ≥85 years of age, Black individuals, and residents of nursing facilities. In 2020, patients with OHCA were 53% less likely to receive an advanced airway device compared with 2019 (397 patients [21.4%] in 2020 versus 529 [45.5%] in 2019; $P<0.001$). Of the calls received, the proportion that were for individuals who died in the field increased by 42% (1400 patients [75.5%] in 2020 versus 619 [53.3%] in 2019; $P<0.001$). A similar significant increase in OHCA and dead-on-arrival EMS responses was observed in Los Angeles, CA, in 2020 starting around the time of California's stay-at-home order compared with 2018 and 2019 ($P<0.001$).¹⁰
 - A meta-analysis that included 10 studies from multiple countries found a 119% increase in OHCA during the pandemic compared with earlier control periods. For the patients with known outcomes ($n=10\,992$), mortality was 85% compared with 62% for the control periods.¹¹
 - In a Swiss study, a significant contribution to the increase in OHCA was attributable to delay in seeking care for AMI. A delay in symptom onset to contact with the medical system was measured during the COVID-19 pandemic compared with control (112 minutes versus 60 minutes; $P=0.049$).¹²
- In a 2024 meta-analysis, a in 10 studies were analyzed dence of OHCA, rates of vival outcomes during the first compared with prepandemic where weekly COVID-19 est ($>136/100\,000$ per week), increased significantly, and of bystander CPR (OR, 0.49 $P=0.005$) compared with
- In a large US registry, rates of after OHCA were, on the first wave of the pandemic 2020) compared with the 2019 (23.0% versus 29.8%; 0.82 [95% CI, 0.78–0.87]; in sustained ROSC paralleled of COVID-19 mortality in the from 11% to 15% in low rates of COVID-19 communities with high or very 19 mortality.⁸

Secular Trends

- Crude incidence of OHCA increased significantly from 64.75 to 76.10 per 100 000 from 2002 to 2014 in a registry of 30 560 patients from Queensland, Australia.¹⁴ Rates of ROSC also increased from 6.31 to 9.99 per 100 000.
- A national database of 120 365 adult medical OHCA in the Republic of Korea from 2006 to 2015 reported increases over time in layperson CPR (1.2% to 17.0%), age- and sex-adjusted survival (3.0% to 8.0%), and good functional recovery (0.9% to 5.8%).¹⁵ Layperson CPR rates increased more in the highest socioeconomic quintile (1.6% to 32.5%) than in the lowest socioeconomic quintile (1.6% to 15.3%).
- A nationwide study in Japan analyzed patients with OHCA who arrested and were defibrillated by lay-people between 2005 and 2019.¹⁶ In this cohort, the RR reduction and NNT of compression-only CPR were 7.6% and 22.1, respectively, for favorable neurological outcomes with the exception of the years 2005 and 2013.

Risk Factors

- The first 3 to 6 months after AMI are considered a high-risk period for OHCA. However, the actual risk data have been based on older studies that antedated current standards of care for patients with AMI. A survey of >120 000 AMI survivors from 2009 to 2017 in the Swedish Cardiopulmonary Resuscitation Registry followed up for up to 90 days after hospital discharge found the incidence of OHCA to be 0.29%, which translates to 116 per

100 000 PY (if everyone were followed up for 90 days; 0.19% at 30 days or 228 per 100 000 PY).¹⁷• MI with OHCA or cardiac arrest in the ED occurred in 9682 of 252 882 patients (3.8%) from 224 hospitals in the NCDR ACTION Registry (2594 or 1.6% of patients with NSTEMI and 7088 or 7.5% of patients with STEMI).¹⁸

- Of 4729 patients with STEMI in Los Angeles County, California, from 2011 to 2014, 422
- In a clinical trial of a wearable defibrillator in 2302 patients with reduced EF (<35%) after AMI, 44

discharge, but the difference was attenuated after adjustment for differences in clinical characteristics (30.1% versus 42.7%; aOR, 0.85 [95% CI, 0.67–1.08]).²⁷ Females were less likely to have a good neurological outcome at discharge from the index hospitalization (21.4% versus 34.0%; aOR, 0.74 [95% CI, 0.57–0.96]) and at 6 months after arrest (16.7% versus

were more likely to undergo withdrawal of lifesaving therapy (55.6% versus 42.8%; aOR, 1.35 [95% CI, 1.09–1.66]).

patients (1.9%) had arrhythmic sudden death, 21 (0.9%) had appropriate defibrillator shock, and 86 (3.7%) had death attributable to any cause during the first 90 days.²⁰

- Incidence of OHCA increased with daily atmospheric levels of particulate matter in 249 372

OHCAs in Japan from 2014 to 2015 (OR, 1.016 [95% CI, 1.009–1.023] per 10- $\mu\text{g}/\text{m}^3$ increase in PM2.5).²¹

Similar findings were reported recently from Israel and Italy.^{22,23}

- Data from the German Resuscitation Registry found that 20 344 women (34.6%) and 38 454 men (65.4%) were resuscitated after OHCA between 2006 and 2022.²⁸ Women received less mechanical CPR (OR, 1.22 [95% CI, 1.13–1.32]; $P<0.001$) and less targeted temperature control (OR, 1.08 [95% CI, 1.00–1.17]; $P<0.05$), which may have contributed to better neurological outcomes for men at discharge (Cerebral Performance Category 1 or 2;

OR, 1.1 [95% CI, 1.015–1.191]; $P=0.021$).

Sex

Variability in survival and neurological recovery after OHCA by sex has been reported by the following studies: • Females compared with males with OHCA are older, less likely to present with shockable rhythms, and less likely to collapse in

public. Despite these survival, 1 study found higher rates of survival 30 days relative to

factors that would reduce that females have equivalent or survival to hospital discharge or to

Social Determinants of Health/Health Equity

- A study of the NIS from 2006 through 2018 identified patients with OHCA who survived to hospital admission and IHCA.²⁹ Over the study period, the proportion of patients with SCA who were Black increased from 11.9% to 18.8%. Compared with patients of other races and ethnicities, Black people hospitalized for SCA were younger (61.1 years of age versus 65.9 years of age; $P<0.001$), had a nonshockable rhythm, and more often received layperson CPR. There was no difference between sexes in survival of the event or survival to hospital discharge after adjustment for measured confounding factors.
- In a registry that included 40 159 OHCA from 2009 to 2012 in Singapore, Japan, the Republic of Korea, Malaysia, Thailand, Taiwan, and the United Arab Emirates, females represented 40% of individuals experiencing an OHCA.²⁵ Females were older, more often presented in a
- In an EMS-based registry of 3862 OHCA from

slightly higher Charlson Comorbidity Index (1.50 versus 1.47; $P<0.001$), and had a greater proportion of females (49% versus 42%; $P<0.001$). Black people with SCA were less likely to undergo cardiac catheterization (9.5% versus 15.0%; OR, 0.61 [95% CI, 0.59–0.63]; $P<0.001$) compared with patients of other races and ethnicities and were more likely to die during the hospitalization (OR, 1.09 [95% CI, 1.08–1.11]; $P<0.001$). This study was not designed to adequately examine the patient, health system, and structural factors responsible for these

2013 to 2015 that includes 90% of the population of New Zealand, OHCA was more common in males (69%) than females (31%).²⁶ This study found the same differences between sexes in

differences.

age, rhythm, location of arrest, and witnessed collapse, as well as the absence of any difference in survival of the event or 30-day survival after adjustment for these

- In a large artificial intelligence–guided statistical and geographic information system analysis of a prospectively collected multicenter dataset of adult patients who sequentially presented to Houston metro area hospitals from January 1, 2007, to January 1, 2016, Black people were disproportionately more likely to have OHCA and, compared
- In contrast to the previous studies, in a prospective multicenter international registry of 2407 patients admitted to ICUs after OHCA from 2012 to 2017, females were less likely to survive to hospital

with White people, were significantly more likely to have poor neurological disposition (OR, 2.21 [95% CI, 1.25–3.92]; $P=0.006$) and to be discharged to a facility instead of home (OR, 1.39 [95% CI,

1.05–1.85]; $P=0.023$).³⁰ At a additional \$10 000 above the income was associated with a total number of cardiac –4.26 to –1.46; $P<0.001$); zip income above \$54 600 \$20 650 in 2007 to \$24 300 in of 4) had 14.62 fewer arrests institutional level, compared nital svstem. the university

commercially and Medicare-insured patients had the lowest odds of death (OR, 0.45; $P<0.001$) fol-

lowed by the main private hospital serving primarily commercially insured patients (OR, 0.62; $P=0.017$).

Geographic information system maps showed con-vergence of the greater density of poor neurological outcome cases and greater density of poorer Black residences, suggesting the intersectionality of risk based on race and ethnicity and low income.

- In a meta-analysis examining race including 53 507 Black patients (22.4%) who experienced OHCA, Black race was associated with worse outcomes.³² The study revealed significantly worse outcomes on all measures in Black

were unchanged from 2013 per 100 000 population. In mortality for rural-dwelling 8.9 to 7.7 per 100 000

- In a national database of 120 OHCA in the Republic of there were differences from socioeconomic quintiles for 11.4%). survival to hospital and good functional recovery patients, including survival to hospital discharge (OR, 0.81 [95% CI, 0.68–0.96]; $P=0.01$), ROSC (OR, 0.79 [95% CI, 0.69–0.89]; $P=0.0002$), and good neurological outcomes (OR, 0.80 [95% CI, 0.68–0.93]; $P=0.003$).
- OHCA incidence in 123 municipalities surrounding Paris has strong geographic variations (RR varies from 0.23–2) based on 3414 cases from 2013 to 2015. Municipalities with a high SCA incidence are characterized by a lower SES and more social depri-vation as measured with the Human Development

- The incidence of OHCA per 100 000 PY was 30.9 in women and 87.1 in men in an OHCA registry from a Dutch province.³⁶ Compared with the high-est household income quintile, the aHR to experi-ence OHCA from the second highest to the lowest household income quintiles ranged from 1.24 (95% CI, 1.01–1.51) to 1.75 (95% CI, 1.46–2.10) in women and from 0.95 (95% CI, 0.68–1.34) to 2.30 (95% CI, 1.74–3.05) in men.

Awareness and Treatment

- Prevalence of reported current training in CPR was 18% and prevalence of having CPR training at some point was 65% in a survey of 9022 people in the United States in 2015.³⁷ The prevalence of CPR training was lower in Hispanic/Latino people, older people, people with less formal education, and lower-income groups.
- Those with prior CPR training include 90% of citizens in Norway³⁸; 68% of citizens in Victoria, Australia³⁹; and 61.1% of laypeople in the United Kingdom⁴⁰ according to surveys.
- Prevalence of prior CPR training among 1076 adults in all states and territories in Australia was 540 Index 2.³³ (55.7%). The majority of respondents replied “unsure”
 - In King County, Washington, the presence of more pharmacies or medical facilities was not associ-ated with lower rates of OHCA or shorter response times; in fact, OHCA was more common in census tracts with more pharmacies or other medical facili- ties (OR, 1.28 [95% CI, 1.03–1.59]).³⁴
 - In an analysis of 347 705 SCDs in the United States between 1999 and 2019 from CDC WONDER, AAMRs were higher in rural than in urban coun- ties.³⁵ In urban counties, rates of SCD declined

- (n=404, 37.6%) or “no” (n=316, 29.4%) when asked if they knew the difference between a cardiac arrest and a heart attack. Of respondents with CPR training, 227 (42%) received training >5 years ago.⁴¹
- Laypeople with knowledge of automated external defibrillators include 69.3% of people in the United Kingdom and 66% in Philadelphia, PA.^{40,42} A total of 58% of Philadelphia respondents⁴² but only 2.1% of UK respondents⁴⁰ reported that they would actually use an automated external defibrillator during a cardiac arrest.
- from 1999 through 2013 (−0.05 [95% CI, −0.09 to −0.01]) but then increased through the end of the study period (0.08 [95% CI, 0.03–0.12]). In rural counties, AAMRs attributable to SCD declined throughout the study period, but the rate of decline slowed after 2013 (−0.29 versus −0.14). AAMRs for urban-dwelling males increased from 2013 onward from 4.8 to 5.7 per 100 000 population. AAMRs for rural-dwelling males were unchanged from 2013 onward: 9.3 versus 9.3 per 100 000 population. AAMRs for urban-dwelling females

- A survey of 5456 households in Beijing, China; Shanghai, China; and Bangalore, India found that 26%, 15%, and 3% of respondents, respectively, were trained in CPR.⁴³
- A survey of 501 inhabitants of Vienna, Austria, found that 52% would recognize cardiac arrest, 50% were willing to use an automated external defibrillator, and 33% were willing to do CPR.⁴⁴
- Laypeople in the United States initiated CPR in 40% of OHCA in CARES 2022 data.³

- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.⁴⁵
- Layperson CPR among 4525 witnessed pediatric OHCA was 831 of 1669 (36.9%) for female patients versus 1336 of 2856 (46.8%) for male patients.⁴⁶ Laypeople in the United States were less likely to initiate CPR for people with OHCA in low-income Black neighborhoods (OR, 0.49 [95% CI, 0.41–0.58])⁴⁷ or in predominantly Hispanic high-income White neighborhoods.⁴⁸
- Examining 2013 to 2019 CARES data shows that 32.2% of arrests occurred in Black individuals or Hispanic individuals. Black individuals and Hispanic individuals were less likely to receive layperson CPR at home (aOR, 0.74 [95% CI, 0.72–0.76]) and in public (aOR, 0.63 [95% CI, 0.60–0.66]) compared with White individuals with OHCA.⁴⁹ This disparity without OHCA (6%) in a Los Angeles, CA, registry of 4729 patients with STEMI from 2011 to 2014.¹⁹ Survival to 30 days was lower for 2516 patients in nursing homes (1.7% [95% CI, 1.2%–2.2%]) than for 24 483 patients in private homes (4.9% [95% CI, 4.6%–5.2%]) in a national database in Denmark from 2001 to 2014.⁵³
- An observational study of 104 patients persisted despite the racial makeup of the community in which they arrested and the economic strata.
- Layperson CPR rates varied from 1.3% to 72% in an international study including 35 communities across 25 countries.⁵⁰ Rates of layperson CPR correlated with gross domestic product per capita (0.772; $P<0.01$; $r_2=0.596$). Socioeconomically advantaged communities most likely have more resources to provide CPR education.

cardiac and thoracic CT, and abdominopelvic CT within 1.9±1.0 hours of hospital arrival.⁵⁴ Presumed causes of OHCA were identified in 39%. Potentially life-threatening complications of resuscitation were identified in 13% of cases.

- A meta-analysis was conducted to explore long-term survival from OHCA attributable to a suspected cardiac cause.⁵⁵ In 11 800 patients with OHCA, the median survival for patients surviving to hospital discharge was 5 years (interquartile range, 2.3–7.9 years). Survival to 10 years after hospital discharge was 63.9% (95% CI, 62.3%–65.4%).

Treatment

- Immediate coronary angiography compared with no STEMI was not associated with improved LV function regardless of whether

standard of care in patients with OHCA and tion in short-term measures,

Mortality

(See Tables 19-2 through 19-4)

- Based on a total of 139 822 OHCA in 2023, there was variation in survival to hospital discharge between states reporting data (range, 7.5%–15.0%; Table 19-2). Survival to hospital discharge after EMS-treated adult OHCA was 10.2% in the 2023

CARES registry on the basis of 135 723 adult cases (Table 19-3). Survival to hospital discharge with good functional status was 8.1% in 2023.³

- Survival to hospital admission after EMS-treated nontraumatic OHCA in 2023 was 26.1% for all

PCI was performed.⁵⁶ However, in a Korean prospective presentations, with higher survival rates in public places (38.0%) and lower survival rates in homes/residences (24.6%) and nursing homes (15.8%) in the 2023 CARES registry (Table 19-4).

- Survival to hospital discharge varied between regions of the United States, being higher in the Midwest (aOR, 1.16 [95% CI, 1.02–1.32]) and the South (aOR, 1.24 [95% CI, 1.09–1.40]) relative to the Northeast, in 154 177 patients hospitalized

tive registry of 678 patients, high-risk patients who had early coronary angiography exhibited improved neurological function at 6 months (OR, 2.36 [95% CI, 1.61–3.46]), whereas low-risk patients showed no benefit (OR, 1.64 [95% CI, 0.57–4.72]).⁵⁷

- A multicenter RCT of 530 patients resuscitated from OHCA with no evidence of STEMI compared outcomes with immediate and delayed coronary angiography.⁵⁸ At 30 days, mortality was 54% in the immediate angiography group versus 46% in the delayed angiography group (HR, 1.28 [95% CI, 1.00–1.63]; $P=0.06$). Death or severe neurological deficit occurred in 64.3% of the immediate angiography group versus 55.6% of the delayed angiography group (RR, 1.16 [95% CI, 1.00–1.34]).
- Multiple methods have been examined to predict neurological recovery and overall survival early after resuscitation from OHCA. Elevated serum levels of several biomarkers, including taurine⁵⁹ and neuron-specific enolase,^{60–62} correlate with poorer outcomes after OHCA in the NIS (2002–2013).⁵¹
- Survival at 1, 5, 10, and 15 years was 92.2%, 81.4%, 70.1%, and 62.3%, respectively, among 3449 patients surviving to hospital discharge after OHCA from 2000 to 2014 in Victoria, Australia.⁵² Patients with STEMI who had OHCA had higher in-hospital mortality (38%) than patients with STEMI

- Guidelines recommend targeted temperature management to prevent hypoxic-ischemic brain damage in patients with coma after cardiac arrest.⁶³ However, the benefit of this treatment has been questioned. An open-label RCT of 1861 comatose adults resuscitated after OHCA with a cardiac cause compared

survival with targeted and normothermia. improve survival ($P=0.37$). quality of life at 6 months.⁶⁴ A multiple trials also found a thermia in individuals with mends temperature control for of OHCA to a temperature of the ideal target temperature remains unclear.⁶⁶

- Markers of systemic inflammation elevated in comatose patients OHCA, and higher levels are outcomes. In an RCT of kin-6 receptor antibody, OHCA had reduced 72 hours by 96% ($P<0.0001$). were reduced by 23% at 48 addition, troponin T levels at 12 hours ($P=0.008$). at 6 months were not tocilizumab ($P=0.9$). In neurological function were not ($P=0.82$).⁶⁷
- An RCT conducted with a 2×2 explored optimal BP targets sure, 63 mm Hg versus 77 oxygen targets (arterial oxygen [PaO_2], 9–10 kPa in resuscitated patients with cardiac cause of arrest. The a composite outcome of death with a Cerebral Performance assess optimal BP, 789 the 2 arms. There was no outcome event (HR, 1.08 $P=0.56$) between the 2 target of the optimal oxygen target restrictive strategies, no primary outcome event aets (HR, 0.95 [95% CI, 0.75–
- A multicenter RCT randomized 1700 patients from 63 ICUs in 17 countries to 24 hours of mild hyper-capnia (target partial pressure of arterial carbon dioxide, 50 to 55 mm Hg) or normocapnia (target partial pressure of arterial carbon dioxide, 35 to 45 mm Hg).⁷⁰ There was no difference in the primary outcome of attaining a favorable neurological out-come at 6 months (RR, 0.98 [95% CI, 0.87–1.11]; $P=0.76$).

standard resuscitation (OR, 2.85]; difference, 9.5% [95% $P=0.09$).⁷¹ However, the trial powered to detect a clinically

Other Outcomes

- Functional recovery continues months after OHCA in
- Of 287 people who survived OHCA, 47% had reduced bid activities, and 27% of before the OHCA were on
- Of 153 survivors of OHCA 18 Paris, France, between 2000 returned to work after a days.⁷⁵ Younger patients with for whom cardiac arrest were more likely to return to
- Of 206 patients who survived in Finland, 188 (91.3%) were Among 95 patients who were arrest, 69 (72.6%) had 23 (24.2) had stopped work their medical condition.
- Among 195 family caregivers vivors, anxiety was present in and depression was found in at 12 months.⁷⁷
- Among OHCA survivors, the sion (19%), anxiety (26%), disorder (20%) is significant, for further screening, options.⁷⁸
- Among 7321 patients with survived to ICU admission, onset HF.⁷⁹ Strong predictors were age (60–75 years of 9–14.4]), history of MI (HR, 2.98]), history of CI, 1.45–5.94]), or new-onset (HR, 4.5 [95% CI, 3.46–
- In a single-center RCT of 256 adults with a wit-nessed OHCA of presumed cardiac origin without ROSC, early intra-arrest transport, extracorporeal CPR, and invasive assessment and treatment did not significantly improve survival with neurologi-cally favorable outcome at 180 days compared with

Global Burden

- International comparisons of cardiac arrest epidemiology must take into account differences in case ascertainment. OHCA usually is identified through EMS systems, and regional and cultural differences in the use of EMS affect results.⁸⁰
- A prospective data collection concerning 10 682 OHCA cases from 27 European countries in October 2014 found an incidence of 84 per 100 000 people, with CPR attempted in 19 to 104 cases per 100 000 people.⁸¹ Return of pulse occurred in 28.6% (range for countries, 9%–50%), with 10.3% attempted surviving to hospital discharge or 30 days.

- In a systematic review accounting for 133 981 patients with EMS-witnessed OHCA treated in 33 countries, the incidence of EMS-treated cases was 4.1 in 100 000 PY (95% CI, 3.5–4.7 per 100 000 PY).⁸² Survival to hospital discharge or at 30 days from arrest was 20% in shockable rhythms and 6% in nonshockable rhythms. Significant global

- A smaller single-center study found that IHCA within the first 48 hours after PCI for STEMI occurred in 11% (44) of 403 patients reviewed.⁹¹

- IHCA incidence was 320 of 21 337 patients (1.50%) with ACS admitted to 3 hospitals in China from 2012 to 2016.⁹²

ED in 17.8%, and noncritical care areas in 38.7% of 40 837 events at 404 hospitals (Table 19-3).

IHCA in Adults

Incidence

(See Tables 19-3 and 19-5)

- Incidence of IHCA is 292 000 people each year on the basis of extrapolation of GWTG data to the total population of hospitalized patients in the United States.^{83,84}

- Incidence of IHCA among 15 953 rapid response team calls in Australia was 159 cases in 152 individuals or 0.62 IHCAs per 1000 multiday admissions (interquartile range, 0.50–1.19).⁸⁵

- In the HCUP NIS for 2021 (unpublished NHLBI tabulation)⁸⁶:
 - There were 28 655 hospital discharges with a primary diagnosis of cardiac arrest.
 - There were 321 670 hospital discharges with all-listed diagnoses of cardiac arrest.
 - There were 191 632 ED discharges with a principal diagnosis of cardiac arrest.

- Initial recorded cardiac

- Incidence of IHCA was 1.7 per 1000 hospital admissions on the basis of 18 069 patients with IHCA in the Swedish Register of CPR between 2006 and 2018.⁸⁷

- After data from GWTG-R were combined with Medicare data from 2014 to 2017, 38 630 patients with IHCA were analyzed to determine the incidence of IHCA of Medicare beneficiaries and hospital variation in IHCA.⁸⁸ The median risk-adjusted IHCA incidence was 8.5 per 1000 admissions (95% CI, 8.2–9.0 per 1000 admissions). IHCA incidence varied across hospitals after adjustment for differences in case-mix index, from 2.4 per 1000 admissions to 25.5 per 1000 admissions (interquartile range, 6.6–11.4; median OR, 1.51 [95% CI, 1.44–1.58]).

Higher case-mix index, higher nurse staffing, and teaching status were associated with less incidence of IHCA.

(GWTG-R, unpublished data, 2023; Table 19-3).

- Additional adult IHCA quality of care data from GWTG-R 2023 are listed in Table 19-5 and Chapter 26 (Quality of Care).
- Intraoperative cardiac arrest in adults occurred with an incidence of 5.7 per 10 000 hospital admissions in which there was an operating room procedure in a 2016 survey of the NIS.⁹³ In-hospital mortality was 36% in patients experiencing intraoperative cardiac arrest.
- Multiple studies have shown that risk for IHCA is predictable and that focused rapid response teams may reduce the risk of IHCA.^{94–97}
- A New York academic medical center review of IHCA from 2012 to 2018 showed lower incidence in females but twice the in-hospital mortality compared with males.⁹⁸

COVID-19 Effects on IHCA Incidence

- A multicenter prospective report from 68 US hospitals described outcomes of IHCA among 701 adults with COVID-19 in ICUs. Of these, 57% received CPR, and 12% survived to hospital discharge.⁹⁹ Among the 48 individuals who survived to hospital discharge, 58.3% had normal or mildly impaired neurological status, whereas 41.7% had moderate to severe neurological dysfunction.
- Compared with 2016 to 2019, patients in the United Kingdom who experienced IHCA during the first wave of the pandemic were younger, male, and of underrepresented race (Asian, Black, multiracial, other).¹⁰⁰ Higher hospital COVID-19 burden was associated with decreased survival to hospital discharge (OR, 0.95 [95% CI, 0.93–0.98]; $P < 0.001$).

- In the Swedish Intensive Care Registry and the Swedish Cardiopulmonary Registry, the incidence of IHCA within the ICU was 16.1 per 1000 admissions.⁸⁹

Risk Prediction

Prodromal Symptoms

- Abnormal vital signs during the 4 hours preceding IHCA occurred in

- IHCA within the first 24 hours after admission for STEMI occurred in 7.8% (136) of 1754 patients

in the ARGEN-IAM-ST. Features associated with IHCA were older age and cardiogenic shock.⁹⁰

- abnormal vital sign occurred in 13.4% of 7851 patients in the 2007 to 2010 GWTG data.¹⁰¹
- Early warning score systems using both clinical criteria and vital signs identified hospitalized patients

with a higher risk of IHCA¹⁰² incidence).

- A comparison using receiver-early warning score accuracy IHCA and other serious in the hospital had AUCs of
- Among 1352 surgical patients IHCA within 30 days. 746 a postoperative complication acute respiratory failure, shock, stroke, transfusion)

Mortality

(See Table 19-3 and Chart 19-1)

- Survival to hospital discharge was 23.6% of adult patients with pulseless IHCAs in GWTG 2023 data (Table 19-3 and Chart 19-1). Among survivors, 79.2% had good functional status (Cerebral Performance Category 1 or 2) at hospital discharge.
- According to data from the GWTG-R registry, there was an increase in survival to hospital discharge in patients who arrested in the ICU between 2006 and 2018.¹⁰⁵ Increases in both ROSC (unadjusted rate, 55.0%–65.4%; aOR per year, 1.04 [95% CI, 1.03–1.05]) and survival to hospital discharge (unadjusted rate, 16.7%–20.5%; aOR per year, 1.03 [95% CI, 1.03–1.04]) were measured.
- Unadjusted survival rate after IHCA was 18.4% in the UK National Cardiac Arrest Audit database between 2011 and 2013. Survival was 49% when the initial rhythm was shockable and 10.5% when the initial rhythm was not shockable.¹⁰⁶
- Unadjusted survival to 30 days after IHCA was 28.3% and survival to 1 year was 25.0% in 18 069 patients from 66 hospitals between 2006 and 2015 in the Swedish register of CPR.⁸⁷
- Survival to hospital discharge after IHCA was lower for males than for females (aOR, 0.90

discharge (25.2% versus were less likely to have come (18.6% versus 21.4%:
 • A multicenter RCT conducted tals compared vasopressin with placebo in 501 active treatment group higher rate of ROSC (42% there was no significant days (9.7% versus 12%. ment of a favorable days (7.6% versus 7.6%, respectively)

Other Outcomes

- [95% CI, 0.83–0.99]) in a Swedish registry of 14 933 cases of IHCA from 2007 to 2014.¹⁰⁷
- Mortality was lower among 348 368 patients with IHCA managed in teaching hospitals (55.3%) than among 376 035 managed in nonteaching hospitals (58.8%), even after adjustment for baseline patient and hospital characteristics (OR, 0.92 [95% CI, 0.90–0.94]).¹⁰⁸
- A propensity-matched analysis of 2000 to 2018 data from 497 US hospitals participating in the AHA GWTG-R registry examined the use of epi-
 nephrine before defibrillation for treatment of IHCA with a shockable rhythm.¹⁰⁹ In this evaluation of 34 820 patients, 28% received epinephrine before defibrillation, contrary to current guidelines. Use of epinephrine delayed defibrillation by 3 minutes (median). Patients treated with epinephrine had a significantly lower chance of survival to hospital

- Among 366 patients discharged after IHCA in a Veterans Administration hospital between 2014 and 2015, 55 (15%) endorsed suicidal ideation during the first 12 months.¹¹¹
- In a single-center study, 102 patients experienced IHCA; 50 survived the arrest event and 47 survived to hospital discharge with a good neurological outcome (mRS score, 0–3).¹¹²

Global Burden of Disease

- Hospitals in Beijing, China, reported an IHCA incidence of 17.5 events per 1000 admissions.¹¹³
- Among 353 adults after IHCA in 6 Kenyan hospitals in 2014 to 2016, 16 (4.2%) survived to hospital discharge.¹¹⁴

OHCA in Pediatric Patients

Incidence

(See Table 19-3)

- In 2023, the location of EMS-treated OHCA was home for 83.0% of children in the CARES data. The location was a public place for 16.7% of the children (Table 19-3).³
- The annual incidence of pediatric OHCA was 8.7 per 100 000 population in Western Australia from 2011 to 2014.¹¹⁵

Secular Trends

- Incidence of pediatric OHCA declined from 1997 to 2014 in Perth, Western Australia, from 14.1 (1997–2000) to 8.7 (2011–2014) per 100 000 population.¹¹⁵ The incidence was even lower among children <1 year of age.
- Incidence of pediatric (<16 years of age) OHCA that was EMS attended (6.7 per 100 000) or EMS treated (4.9 per 100 000) did not change from 2000 to 2016 in Victoria, Australia.¹¹⁶ Survival to hospital discharge increased from 9.4% to 17.7%.

Awareness and Treatment

- In an English study of 2363 pediatric OHCA events, layperson CPR was performed in 69.6% of cases

(1646) overall.¹¹⁷ There was variability in provision of CPR across the different regions studied.

- According to data from a multicenter prospective observational registry in Japan between 2014 and 2019, there were significant increases in the rates of bystander-initiated CPR (50.6% to 62.3%; $P=0.003$) and epinephrine (adrenaline) administration (from 2.4% to 6.9%; $P=0.014$).¹¹⁸ However, the rate survival did not change.
- Despite the majority of pediatric cardiac arrests being secondary to respiratory pathogenesis, few studies have examined the neurological recovery when conventional CPR (ventilation and compression) is applied versus compression-only CPR.¹¹⁹ In this observational study from a nationwide Japanese registry, neurologically favorable 1-month survival rate with no bystander CPR was 2.4%, with compression-only CPR was 3.2%, and with conventional CPR was 6.6% ($P<0.01$). With multivariable logistic regression, conventional CPR was associated with higher neurologically favorable 1-month survival than compression-only CPR (OR, 1.98 [95% CI, 1.03–3.81]).

Mortality

(See Table 19-6)

- Survival to hospital discharge was 7.4% for 1587 children <1 year of age, 14.1% for 1225 children 1 to 12 years of age, and 18.5% for 854 children 13 to 18 years of age in CARES 2023 data (Table 19-6).

occurred in the ICU, 4.5% in the operating room, 4.7% in the ED, and 33.4% in noncritical care areas per the 2023 GWTG data (Table 19-3).

- Additional ICHA in pediatric patients quality of care data from 2023 GWTG-R are listed in Table 19-5 and Chapter 26 (Quality of Care).
- Incidence of IHCA was 1.8 CPR events per 100 pediatric (<18 years)
 - In a registry including 974 children with OHCA from 2009 to 2012 in Singapore, Japan, the Republic of Korea, Malaysia, Thailand, Taiwan, and the United Arab Emirates, 8.6% (range, 0%–9.7%) of children survived to hospital discharge.¹²⁰
 - In Rotterdam, shockable rhythm after 369 pediatric (median age, 3.4 years) OHCA was associated with significantly higher long-term survival and favorable neurological outcome. Fourteen percent had a shockable rhythm. Of these, 39% survived to hospital discharge. After a median follow-up of 25 months, 81% of hospital survivors had a favorable neurological status.¹²¹

IHCA in Pediatric Patients

Incidence

(See Tables 19-3 and 19-5)

- Of 722 events of IHCA in children (1–<18 years of age) at 108 hospitals, 47.5% occurred in the ICU, 5.8% in the operating room, 19.8% in the ED, and 26.7% in noncritical care areas per 2023 GWTG data (Table 19-3). Of the 1274 IHCA events in infants (<1 year of age) at 104 hospitals, 57.4%

- Network dataset of 10 078 pediatric ICU admissions from 2011 to 2013.¹²²
- In a registry of 23 cardiac ICUs in the Pediatric Critical Care Consortium that included 15 908 children between 2014 and 2016, 3.1% of children in ICUs had a cardiac arrest, with substantial variation between centers (range, 1%–5.5%), for a mean incidence of 4.8 cardiac arrests per 1000 cardiac ICU days (range, 1.1–10.4 per 1000 cardiac ICU days).¹²³ • In a meta-analysis that included 131 724 children with cardiac disease admitted to an ICU, 5% (95% CI, 4%–6%) experienced IHCA with in-hospital mortality reaching 51% (95% CI, 42%–59%).¹²⁴ • Initial recorded cardiac arrest rhythm was VF or VT in 8.8% of 722 child (>1–<18 years of age) events at 108 hospitals in GWTG-R in 2023 and 1.9% of 1274 infant (<1 year of age) events at 104 hospitals (Table 19-3).
 - In a secondary analysis of the ICU-RESUS trial, investigators found that in 1276 patients, 184 (16.3%) had a prearrest diagnosis of PH and 101 of 184 patients (54.9%) were receiving inhaled nitric oxide at the time of their IHCA.¹²⁵
 - A retrospective analysis of 3 US pediatric ICUs from 2015 to 2017 found a 7% incidence of cardiac arrest in patients undergoing endotracheal intubation.¹²⁶

Secular Trends (See Chart 19-1)

- Survival to discharge after pulseless IHCA in pediatric patients (children and infants 0–18 years of age) increased from 18.9% to 45.2% between 2000 and 2023 in GWTG data (Chart 19-1).
- A multicenter observational study of 7433 hospitalized pediatric patients who received CPR from 2000 to 2018 found significant increases in survival, from 19% in 2000 to 38% in 2018.¹²⁷ The improvement in survival plateaued after 2010.

Mortality (See Table 19-3)

- Survival to hospital discharge after pulseless IHCA was 42.2% in children 1 to <18 years of age and 45.9% in infants <1 year of age per 2023 GWTG data (GWTG-R, unpublished data; Table 19-3).

- Survival to hospital discharge for in the ICU was 45% in the Critical Care Research 2013.¹²²
- In 429 pediatric IHCA events, during the COVID-19 versus 60%; $P=0.12$).¹²⁸

Global Burden of Disease

- Perioperative cardiac arrest and between middle- and low-global incidence of cardiac perioperatively was 2.54 (95% 1000 anesthetic events, and (95% CI, 35.68–46.68) per events.¹²⁹

findings at autopsy, mechanism for the sudden cardiac rupture, acute HF, embolus (Chart 19-4). In cal events and occult drug in the San Francisco study. When the initial rhythm was VT or VF, the autopsy consistent with sudden when the initial finding was itv, the autopsy was likely to of nonsudden arrhythmic

Risk Factors

(See Chart 19-5)

- SCA and SCD result from

SCA or SCD When Location Is Not Specified

Lifetime Risk and Cumulative Incidence

(See Table 19-7 and Chart 19-2)

- SCD appeared among the multiple causes of death on 12.7% of death certificates in 2022 (417 957 of 3 279 857; Table 19-7). Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.
- In 2022, infants had a higher incidence of SCD (12.1 per 100 000) than older children (1.3–2.3 per 100 000). Among adults, risk of SCD increased exponentially with age, surpassing the risk for infants by 35 to 39 years of age (16.8 per 100 000; Chart 19-2).

Secular Trends

(See Charts 19-3 and 19-4)

- Rate of SCD (6.8% versus 11.4% over 4 years) and hazard of SCD in propensity-matched cohorts (sub-HR, 0.46 [95% CI, 0.30–0.70]) decreased over time in outpatients with HFrEF (<40%) on the basis of 2 multicenter prospective registries (MUSIC [n=641; 2003–2004] and REDINSCOR I [n=1710; 2007–

2011]).¹³⁰ This reduction in SCD was associated with more frequent use of β -blockers (85% versus 71%), mineralocorticoid antagonists (64% versus 44%), ICDs (19% versus 2%), and resynchronization therapy (7.2% versus 4.8%).

- Age-adjusted death rates for any mention of SCD declined from 137.7 per 100 000 population in 1999 to 91.2 per 100 000 population by 2019, increased to 111.2 in 2021, and decreased to 99.6 in 2022 (Chart 19-3).
- In a community-based survey of out-of-hospital SCD, only one-half of the sudden deaths had no specific findings at autopsy. In these cases, the mechanism of death was classified as arrhythmic. However, approximately one-half of the sudden unexpected deaths in each study had specific

processes, each of which can have different risk factors. Among patients with OHCA resuscitated and hospitalized from 2012 to 2016, ACS and other cardiac causes accounted for the largest proportion of causes. Among patients with IHCA, respiratory failure was the most common cause (Chart 19-5).¹³¹ Among patients with DCM considered to be at low arrhythmic risk (LVEF >35% and New York Heart Association class I–III on optimal medical therapy), 14 of 360 (3.9%) had SCD and 16 (4.4%) had major ventricular arrhythmias (SCA or ICD intervention) during a median follow-up of 152 months.¹³² Events were associated with larger LA end-systolic area and arrhythmogenic profile (history of syncope, nonsustained VT, at least 1000 premature ventricular contractions per 24 hours, or at least 50 ventricular couplets per 24 hours at Holter electrocardiographic monitoring).

- A substudy of the DANISH trial of patients with nonischemic systolic HF (EF ≤35%) demonstrated an association of nonsustained VT (HR, 1.47 [95% CI, 1.07–2.03]; $P=0.02$ and HR, 1.89 [95% CI, 1.25–2.87]; $P=0.003$) and frequent ventricular premature depolarizations (HR, 1.38 [95% CI, 1.00–1.90]; $P=0.046$ and HR, 1.78 [95% CI, 1.19–2.66]; $P=0.005$) with total and cardiovascular mortality, respectively, but no relation to SCD.¹³³
- Among 5869 autopsied individuals with SCD, after exclusion of cases with noncardiac causes of death in Finland between 1998 and 2017, ischemic cardiac disease represented 4392 (74.8%) and nonischemic cardiac diseases represented 1477 (25.2%).¹³⁴ Over time, the proportion of ischemic SCD declined from 78.8% (1998–2002) to 72.4% (2013–2017).
- An analysis of 8900 patients enrolled in 3 contemporary therapeutic trials of patients with HFpEF found that those with prior MI had ≈50% increased risk of SCD compared with patients without prior MI.¹³⁵

- Alcohol consumption was not associated with increased risk of ventricular arrhythmia but was associated with SCD in a longitudinal study of 408 712 individuals over a follow-up time of 11.5 years.¹³⁶

Age

(See Chart 19-2)

- In 2022, mortality rates for any mention of SCD decreased with increasing age category (<1, 1–4, and 5–9 years of age) in those 0 to 9 years of age and increased for those ≥10 years of age with each 5-year age category through 84

Sex

- In a prospective postmortem study in San Francisco County, all incident presumed SCDs in people 18 to 90 years of age were autopsied through active surveillance of consecutive out-of-hospital deaths between February 1, 2011, and March 1, 2014.¹³⁷ Among 525 autopsied presumed SCDs in San Francisco County, after adjustment for age and race, females had more noncardiac causes of presumed SCD, including pulmonary emboli (8% versus 2%) and neurological causes (10% versus 3%; both $P<0.01$). Males had 3-fold higher rates of autopsy-proven sudden arrhythmic deaths (defined as cases in which no extracardiac cause of death or HF was noted on autopsy) compared with females, whereas more females had primary electric disease (4% versus 2%; $P=0.02$) and nonischemic causes (53% versus 39%; $P<0.01$).

CI, 0.31–0.85]; $P<0.01$). Among autopsy-proven sudden arrhythmic deaths, MI with nonobstructive coronary arteries was more common in Asian individuals than in White individuals (7% versus 1%; $P<0.05$).

HD, Cardiac Risk Factors, and Other

- Comorbidities** • Incidence of SCD was 0.10 per 100 patient-years (95% CI, 0.07–0.14) in a cohort of 3242 untreated patients with hypertension without evidence of coronary or cerebrovascular disease at

Race and Ethnicity

- In the ARIC study, 215 of 3832 Black participants (5.61%) and 332 of 11 237 White participants (2.95%) experienced SCD during 27.4 years of follow-up.¹³⁸ The sex-adjusted HR for SCD comparing Black participants with White participants was 2.12 (95% CI, 1.79–2.51), and the fully adjusted HR was 1.38 (95% CI, 1.11–1.71).
- In a prospective postmortem study in San Francisco County, all incident presumed SCDs in individuals 18 to 90 years of age were autopsied through active surveillance of consecutive out-of-hospital deaths between February 1, 2011, and March 1, 2014.¹³⁷ Among 525 autopsied presumed SCDs in San Francisco County, sudden arrhythmic death was defined as deaths for which no extracardiac cause or acute HF was noted on autopsy. After adjustment for age, Black females had higher incidence of sudden arrhythmic death than White females (IRR, 2.55 [95% CI, 1.38–4.71]; $P<0.01$), Asian males had a lower incidence than White males (IRR, 0.51 [95% CI, 0.36–0.73]; $P<0.01$), and Hispanic males had a lower incidence than White males (IRR, 0.51 [95%

the rate of SCD was 0.37 per 100 patient-years versus 0.05 per 100 patient-years for patients without electrocardiographic LVH (aHR, 2.99 [95% CI, 1.47–6.09] adjusted for age, sex, diabetes, and 24-hour ambulatory pulse pressure).

- In a cohort of 233 970 patients from the United Kingdom, resting heart rate >90 bpm was associated with an increased hazard of SCD or cardiac arrest as initial presentation of HD (aHR, 2.71 [95% CI, 1.90–3.83]).¹⁴⁰
- Among 7011 patients admitted to the hospital with acute HF, the 30-day rate of SCD, SCA, or VT/VF was 1.8% (n=121).¹⁴¹ Events were associated with male sex (aOR, 1.73 [95% CI, 1.07–2.49]), history of VT (aOR, 2.11 [95% CI, 1.30–3.42]), chronic obstructive pulmonary disease (aOR, 1.63 [95% CI, 1.07–2.49]), or prolonged QRS interval (aOR, 1.10 [95% CI, 1.03–1.17] per 10% increase from baseline).
- Analysis of 76 009 patients including 8401 with AF from 21 studies between 1991 and 2017 found that patients with AF had a higher risk of incident SCD/SCA or VF/VT (RR, 2.04 [95% CI, 1.77–2.35]).¹⁴² Among 21 105 patients with AF followed up for a median of 2.8 years, SCD accounted for 31.7% of all deaths, with an incidence of 12.9 per 1000 patient-years.¹⁴³
- A French database of all hospitalized patients in 2013 was queried. In total, 3 345 638 patients were categorized into having AF or not having AF.¹⁴⁴ The incidence (2.23%/y versus 0.56%/y) and risk (HR, 3.657 [95% CI, 3.604–3.711]) of ventricular arrhythmia and cardiac arrest were higher in patients with AF compared with patients without AF.
- Risk of SCD in the general population ≥45 years of age who were initially free of CVD when recruited in 1987 to 1993 and followed up for a subsequent 10 years was associated with male sex, Black race, diabetes, current smoking, and SBP.¹⁴⁵
- A logistical model incorporating age, sex, race, current smoking, SBP, use of antihypertensive medication, diabetes, serum potassium, serum albumin,

HDL-C, eGFR, and QTc adults. correctly stratified 10-separate cohort of 4207 ARIC and 0.745 in the

- In a registry of 2119 SCAs in 2002 to 2015. prior syncope of cases. and history of with increased risk of SCA graphically matched control CI. 1.68–4.85).¹⁴⁶

• In a cohort of 5211 Finnish people >30 years of age in 2000 to 2001 who were followed up for a median of 13.2 years, high baseline thyroid-stimulating hormone was independently associated with greater risk of SCD (HR, 2.28 [95% CI, 1.13–4.60]).¹⁴⁷ • In a meta-analysis that included 17 studies with 118 954 subjects, presence of depression or depressive symptoms was associated with increased risk of SCD (HR, 1.62 [95% CI, 1.37–1.92]), specifically for VT/VF (HR, 1.47 [95% CI, 1.23–1.76]).¹⁴⁸

• The interaction among CHD, PA, and SCD is complex. Analysis from a Finnish registry of 1946 patients with angiographically documented CHD found that risk of SCD was increased in patients with more advanced angina (Canadian Cardiovascular Society angina grade ≥ 2) and both active (HR, 7.46 [95% CI, 2.32–23.9]; $P < 0.001$) and inactive (HR, 3.64 [95% CI, 1.16–11.5]; $P < 0.05$) lifestyles, whereas risk of SCD was decreased in active patients with lesser grades of angina (Canadian Cardiovascular Society angina grade 1; HR, ≈ 0.5).¹⁴⁹

Electrocardiographic Abnormalities

• Age- and sex-adjusted prevalence of electrocardiographic abnormalities associated with SCD was 0.6% to 1.1% in a sample of 7889 Spanish citizens ≥ 40 years of age,

Social Determinants of

- In the ARIC study. 215 of 3832 (5.61%) and 332 of 11 237 (2.95%) experienced SCD low-up.¹³⁸ The sex-adjusted Black participants with White (95% CI, 1.79–2.51), and the 1.38 (95% CI, 1.11–1.71).
- Survival and neurological arrest are worse in White including Brugada syndrome in 0.13%, QTc <340 milliseconds in 0.18%, and QTc ≥ 480 milliseconds in 0.42%.¹⁵⁰
 - Among 12 241 ARIC study participants, of whom 346 had SCD during a median follow-up of 23.6 years, prolongation of the QT interval at baseline was associated with risk of SCD (HR, 1.49 [95% CI, 1.01–2.18]), and this association was driven specifically by the T-wave onset to T-peak component of the total interval.¹⁵¹
 - Among 20 177 participants in the ARIC study followed up for 14 years (median), the incidence of SCD was 1.86 per 1000 PY. Five global markers of electric heterogeneity measured on a standard 12-lead ECG at baseline and during follow-up demonstrated an independent predictor of risk for SCD.¹⁵²
 - In a cohort of 4176 individuals with no known HD, 687 (16.5%) had early repolarization with terminal J wave, but this pattern had no association with cardiac deaths (0.8%) over 6 years of follow-up compared with matched controls.¹⁵³

Black individuals, and Asian individuals compared with White individuals.¹⁵⁴ In this single-center, retrospective study of patients receiving targeted temperature management after cardiac arrest, survival and neurological recovery were worse in individuals from underrepresented racial and ethnic groups (self-identified or identified by family as being Black, Asian, or White Hispanic compared with NH White). White people had a higher chance of a good outcome than people from underrepresented racial and ethnic groups (34.4% versus 21.7%; $P=0.015$). The observed disparities were explained in part by delays in onset of medical care: White people were brought to medical attention more quickly, and individuals from underrepresented races and ethnicities were more likely to have anoxic brain injury on early CT scans or highly malignant electroencephalograms during the first 24 hours. People from under-represented racial and ethnic groups were more likely to have early severe electroencephalogram/ CT anoxic changes (25.0% versus 15.8%; $P=0.03$). There were no statistically significant differences in the number of invasive procedures.

Mortality (See Table 19-7)

- In 2022, primary-cause SCD mortality was 19 171, was 417 957 (Table 19-7). The any-mention age-SCDs per 100 000 population (unpublished NHLBI tabulation).¹⁵⁵
- Of 1 452 808 death certificates from 1999 to 2015 SCD (2%) as the cause of death, for an SCD rate of 1.32 per 100 000 individuals.¹⁵⁶
 - SCD rate varied by age, from 0.49 per 100 000 (1–10 years of age) to 2.76 per 100 000 (26–34 years of age)
 - The rate of SCD declined from 1999 to 2015, from 1.48 to 1.13 per 100 000 individuals.

Complications

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including impaired consciousness and cognitive deficit. Functional impairments are associated with reduced

function, reduced quality of life, and shortened life span.^{157,158}

- Serial testing in a cohort of 141 people who survived hospitalization after SCA revealed severe cognitive deficits in 14 (13%), anxiety and depression in 16 (15%), posttraumatic stress symptoms in 29 (28%), and severe fatigue in 55 (52%).¹⁵⁹ Subjective symptoms declined over time after SCA, although 10% to 22% had
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.¹⁵⁹ In a meta-analysis of 35 studies including 7186 survivors, the incidence of first recurrence of cardiac arrest was 15.24%

participation, estimated by the Sport and Fitness Industry Association, from 2007 to 2015 was 1.83 deaths per 10 million athlete-years.¹⁶⁸

- Studies that included >14 million participants in long-distance or marathon running events from 1976 to 2009 reported race-related incidence of SCA or SCD ranging from 0.6 to 1.9 per 100 000 runners (95% CI, 11.01%–19.95%; mean follow-up time, 41.3±29.3 months) and of second recurrence was 35.03% (95% CI, 19.65%–51.93%; mean follow-up, 161.1±54.3 months).¹⁶¹

marathons in Sweden from 2007 to 2016, yielding an estimated SCD incidence of 0.24 (95% CI, 0.04–0.79) per 100 000 runners.¹⁷⁰

- In a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes, adjudication revealed a cause of death in 50 cases (73%): idiopathic LVH or possible cardiomyopathy (26%), autopsy-negative sudden unexplained death (18%), HCM (14%), and myocarditis (14%).¹⁶⁶
Shockable initial rhythm increased the incidence of first recurrence of cardiac arrest ($P=0.01$).

Special Circumstances

Opioid-Associated Cardiac Arrest

- The incidence of opioid-associated OHCA has been increasing with the overall rise in prevalence of syn-

- Adjudication of cause of death in 179 cases of SCA in middle school, high school, college, and professional athletes from 2014 to 2016 identified a cause in 117 (65.4%): HCM (16.2%), coronary artery anomalies (13.7%), idiopathic cardiomyopathy (11.1%), autopsy-negative sudden unexplained death (6.8%), WPW syndrome (6.8%), and LQTS (6.0%).¹⁶²

- Most estimates are based on EMS-treated events and do not account for those individuals who were left untreated by EMS after opiate overdose.¹⁶² • Two publications from large North American data-sets estimate the incidence of opioid-associated OHCA at 2% of the total OHCA population; however, recent smaller studies with the benefit of greater depth of chart review estimate that this incidence is closer to 6% to 15% of all OHCA.^{131,163,164}
- among those 25 to 34 years of age in a prospective registry of 3775 SCAs in Portland, OR, between 2002 and 2015 that included 186 SCAs in young people (5–34 years of age).¹⁶⁵
 - Incidence of SCA or SCD was 1 per 44 832 athlete-years for males and 1 per 237 510 athlete-years for females according to a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes.¹⁶⁶
- Incidence of SCA during competitive sports in people 12 to 45 years of age was 0.76 per 100 000 athlete-years in a population-based registry of all paramedic responses in Toronto, ON, Canada, from 2009 to 2014.¹⁶⁷
 - Incidence of SCD, estimated from LexisNexis

Sports-Related Cardiac Arrest

- Sports-related SCAs accounted for 39% of SCAs among those ≤18 years of age, 13% among those 19 to 25 years of age, and 7%

- Among 55 patients admitted to 8 Spanish hospitals with SCA during or within 1 hour of vigorous sport activities between 2007 and 2016, 90.9% were male, mean±SD age was 47±15 years, and 96.4% presented with shockable rhythm. The cause of SCA varied by age: 25% cardiomyopathy, 63% idiopathic VF, and 13% AMI for those <35 years of age; and 9% cardiomyopathy, 18% idiopathic VF, 67% AMI, and 7% unknown for those ≥35 years of age.¹⁷²
- Preparticipation screening of 5169 middle and high school students (mean±SD age, 13.06±1.78 years) from 2010 to 2017 revealed high-risk cardiovascular conditions in 1.47%.¹⁷³ Anatomic findings included DCM (n=11), nonobstructive HCM (n=3), and anomalous coronary artery origins (n=23). Electrocardiographic findings included WPW syndrome (n=4), prolonged QT intervals (n=34), and Brugada pattern (n=1).
- In a population-based registry of all paramedic responses for SCA from 2009 to 2014, 43.8% of athletes with SCA during competitive sports survived to hospital discharge.¹⁶⁷

Maternal Cardiac Arrest

- Incidence of maternal cardiovascular collapse requiring CPR during childbirth was 10 in 250 719 (4.0 per 100 000 births) in a registry of births in and public media New York.¹⁷⁴ reports, during youth

Epilepsy and Cardiac Arrest

- In a global cohort of 271 172 the 30-day risk of cardiac seizure was 0.9%.¹⁷⁵

Specific Ventricular Channelopathies

Genetics and Family History

- Exome sequencing in younger decedents who had sudden suspected arrhythmic death genic variants in thv-related genes for 29% to 34%
- Screening of SCA survivors by sequencing for 185 clinically revealed a pathogenic variant with a 28% yield in patients

diac phenotype.¹⁷⁹

- Among 228 unexplained SCA, whole-exome sequencing of 184 genes associated with SCD or cardiomyopathy identified a pathogenic/likely pathogenic variant in 23 survivors (10%). Among the 23 pathogenic/likely pathogenic variants identified, 13 variants (57%) were present in cardiomyopathy genes but were not associated with a diagnosis of cardiomyopathy at the time of arrest.¹⁸⁰
- Genetic testing for *SCN5A* rare variants with a minor allele frequency <0.005 in 60 patients with SCA revealed that 5 (8.3%) carried an *SCN5A* rare variant.¹⁸¹ All 5 variants identified were categorized as variants of unknown significance.¹⁸¹ However, whole-cell patch clamp studies showed that the Asp872Asn *SCN5A* variant was associated with PR prolongation and early repolarization.¹⁸¹
- Multiple studies have attempted to quantify the

completing follow-up, 3.3% within 3 years, and 7.2% within 5 years.¹⁸⁴

- Prevalence of genetic HD is increasing age among a report on 180 patients rhythm clinic from 1999 to adults, diagnoses included arrhythmogenic bileaflet mitral acquired LOTS (9.4%), LOTS syndromes such as Brugada children, diagnoses included (20.8%), idiopathic VF triadin knockout syndrome
- Among 225 patients of (51%) had an inherited fied inherited cardiac HCM (24%), Brugada and arrhythmogenic yield of genetic screening in probands and their family members:
 - Screening of 398 first-degree relatives of 186 probands with unexplained SCA and 212 probands with unexplained SCD revealed cardiac abnormalities in 30.2%: LQTS (13%), CPVT (4%), arrhythmogenic cardiomyopathy (4%), and Brugada syndrome (3%).¹⁸²
 - In a registry of families of probands with unexplained SCD before 45 years of age from 2009 to 2014, screening of 230 people from 64 families revealed a presumptive diagnosis in 25% of families: Brugada syndrome in 11%, LQTS in

Genome-Wide Association Studies

- GWASs on cases of arrhythmic death attempt to identify previously unidentified common genetic variants and biological pathways associated with potentially lethal ventricular arrhythmias and risk of sudden death. Limitations of these studies are the small number of samples available for analysis and the heterogeneity of case definition. The number of loci uniquely associated with SCD is much smaller than for other complex diseases. For example, a GWAS of 3939 cases with SCA found no variants associated with SCD at genome-wide significance, which suggests that common genetic variations may not portend a significant risk factor for SCD.¹⁸⁷ However, the oligogenic nature of genetic determinants of SCA requires further evaluation.
- Although SCA GWASs are limited, investigations have been conducted with multiple electrocardiographic traits used as a phenotype (ie, QRS, QT duration), which have identified novel genetic variants associated with these traits that are also associated with cardiac conduction, arrhythmias, and other cardiovascular end points.¹⁸⁸
- A GWAS of T-peak-to-T-end interval on ECG, a predictor of increased arrhythmic risk, in the UK Biobank identified 32 genomic loci for resting T-peak-to-T-end interval, 3 for T-peak-to-T-end response to exercise, and 3 for T-peak-to-T-end response to recovery, but a GRS of these variants was not associated with arrhythmic risk.¹⁸⁹

7.8%, DCM in 3.1%, and HCM in 3.1%.¹⁸³

- Screening of 292 relatives of 56 probands with SCD revealed a diagnosis in 47 relatives (16.1%): LQTS in 12.7%, CPVT in 0.3%, DCM in 0.7%, arrhythmogenic cardiomyopathy in

Long QT Syndrome

0.3%, and thoracic aortic dilation in 0.3%. Among relatives

- Hereditary LQTS is a genetic channelopathy characterized by prolongation of the QT interval (QTc typically >460 milliseconds) and susceptibility to ventricular tachyarrhythmias that lead to syncope and SCD. Investigators have identified rare variants

in 15 genes leading to 17 different subtypes of LQTS phenotype.^{190,191} There is variability in pre-sentation, therapeutic approach, and prognosis by subtype.

- Approximately 5% of sudden infant death syndrome cases and some cases of intrauterine fetal death could be attributable to LQTS.¹⁹²
- Ancestry-specific LQTS variants exist: The S1103Y polymorphism in *SCN5A* is found and SCD in Black individuals with HF.^{193,194}
- Acquired prolongation of the QT interval is common. Prevalence of prolonged QTc was 115 of

suggesting that individuals with long QT who are variant negative could have a polygenic inheritance. • Common genetic variants may explain ≈15% of the susceptibility to LQTS. A 68-SNP PRS for the QT interval had a higher score in genotype-negative (no disease-causing rare variant identified) patients compared with genotype-positive patients, support-412 (27.9%) among adults admitted to an ICU from 2014 to 2016 in Brazil.¹⁹⁵ At least 1 drug known to prolong QT interval was present in 70.4% of these

$P=4.8 \times 10^{-11}$) quartiles of the PRS score were associated with the first quartile.²⁰⁴

- A randomized controlled multicenter trial of 665 patients with COVID-19 in Brazil treated with standard care, hydroxychloroquine alone or in combination with azithromycin, found a 14.6% incidence of cases.
- Prevalence of prolonged QTc interval was 50 of 712 patients (7%) admitted to a short-stay medical unit in the United Kingdom.¹⁹⁶

of QT interval prolongation >480 milliseconds in patients in the 2 active treatment groups versus 1.7% in the standard care group. No patient devel-

- Prevalence of prolonged QTc interval was 95 of 7522 patients (1.9%) with ECG in the ED from 2010 to 2011, and these prolongations were attributable individually or in combination to electrolyte disturbances (51%), QT-prolonging medical conditions (56%), or QT-prolonging medications (77%).¹⁹⁷• Among 65 654 patients on

oped TdP.²⁰⁵

hemodialysis, initiation of a selective serotonin reuptake inhibitor with higher (47.1% of patients) versus lower (52.9% of patients) QT-prolonging potential was associated with higher risk of SCD (aHR, 1.18 [95% CI,

- A prospective survey of 119 patients with COVID-19 treated in 3 New York hospitals who received both chloroquine or hydroxychloroquine and azithromycin and 82 patients treated with chloroquine or hydroxychloroquine alone revealed significant increases in QTc.²⁰⁶ Patients receiving both drugs demonstrated significantly greater increases in QTc than patients receiving monotherapy. A peak QTc >500 milliseconds was observed in 8.6% of patients receiving a single drug and 9.2% of patients receiving 2 drugs. 1.05–1.31]).¹⁹⁸
- Genetic testing for LQTS among 281 families had a diagnostic yield for genetic variants of 47%.¹⁹⁹

There was no difference in QT prolongation according to treatment group. Nearly a third of patients with acquired LQTS are reported to carry pathogenic congenital LQTS

ing to sex. No patients in this series developed TdP. • A retrospective analysis of 91 hospitalized patients with COVID-19 in Connecticut treated with hydroxy-chloroquine and azithromycin found QTC prolongation >500 milliseconds in 14% on treatment.²⁰⁷

- However, some studies have called into question whether previously identified LQTS genes are truly causative.^{201,202} The ClinGen Channelopathy Clinical Domain Working Group, leveraging large publicly available genetic databases, has shown

that only 3 genes (*KCNQ1*, *KCNH2*, *SCN5A*) have definitive gene-disease association for typical LQTS, with another 4 (*CALM1*, *CALM2*, *CALM3*, *TRDN*) having definitive evidence for association with disease onset

Almost half the patients with marked QTc prolongation were receiving other agents known to prolong the QT interval, most often propofol. Two patients developed VT: TdP in 1 patient and polymorphic VT leading to VF in the other.

- A retrospective analysis of 415 hospitalized patients with COVID-19 infection treated with hydroxychloroquine and azithromycin found QTc prolongation >500 milliseconds in 21%, but no TdP was observed.²⁰⁸
That group has found that *KCNE1* and *KCNE2*, which are commonly clinically tested, being used to assess the significance of novel variants and to understand mechanisms of action of modifier genes.²⁰³
had limited or disputed evidence for typical LQTS but showed strong evidence for association with acquired LQTS. Several induced pluripotent stem cell–cardiomyocytes models are now being used to understand mechanisms of action of modifier genes.²⁰³
- GWASs have identified additional rare and common variants in genes associated with QT interval.²⁰¹

- A retrospective cohort analysis of 170 patients in Wuhan, China, hospitalized with COVID-19 infection and evidence of myocarditis (elevated cardiac troponin I) found 6 patients with VT/VF, all of whom died.²⁰⁹ Patients treated with QT-prolonging agents had significantly longer QTc, but the increase in QTc was not associated with mortality independently.
- A common ion channel genetic variant, p.Ser1103Tyr-SCN5A, which predisposes to QT prolongation and

increased risk of TdP, is the Black population with a variant not only increases risk but also has the ability to the presence of hypoxemia from an increase in the late explain part of the increased individuals and their of COVID infection.^{.210}

• Reappraisal of the 17 LQTS genes (KCNQ1, KCNH2, SCN5A) as definitive genes causing LQTS and 4 genes (CALM1, CALM2, CALM3, TRDN) as having definitive or strong evidence for causality in LQTS with atypical features; 1 gene (CACNA1C) had moderate evidence for causing LQTS, and the other genes had limited evidence for causing LQTS.^{.211}

Short QT Syndrome

Prevalence and Incidence

- Short QT syndrome is an inherited mendelian condition characterized by shortening of the QT interval (typically QT <320 milliseconds) and predisposition to AF, ventricular tachyarrhythmias, and sudden death. Variants in 5 ion channel genes (*SQT1*–*SQT5*) have been described.^{.212}
- Prevalence of a QTc interval <320 milliseconds in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,^{.213} which was identical to the prevalence in a Portuguese sudden death registry.^{.214}
- Prevalence of QT interval ≤340 milliseconds in 99 380 unique patients ≤21 years of age at the Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.^{.215} Of these children, 15 of 45 (33%) were symptomatic.

and North America, higher in males (0.9%) than in

- Among 678 patients with 23 centers in 14 countries, documented arrhythmic event mean±SD age of 39±15 first documented arrhythmic prophylactic defibrillator years.^{.220}

- In a multicenter retrospective

Genetics

- The genes that have been associated with short QT syndrome are many of the same ones involved in LQTS but with opposite effects on channel function and include potassium channel genes and calcium channel genes. The yield of genetic testing in short QT syndrome is only 23% of 53 probands.^{.216}

Brugada Syndrome

Prevalence and Incidence

- Brugada syndrome is an acquired or inherited channelopathy characterized by persistent ST-segment elevation in the right precordial leads (V₁ and V₂), either at rest or with provocative testing, and susceptibility to ventricular arrhythmias and SCD.^{.217} Brugada syndrome is associated with variants in at least 12 ion channel–related genes.
- In a meta-analysis of 24 studies, prevalence was estimated at 0.4% worldwide, with regional prevalence of 0.9%, 0.3%, and 0.2% in Asia, Europe,

with Brugada syndrome, 177 (23%) were female.²²¹ At initial presentation, 85% were asymptomatic.

Females were less likely to have a type 1 electrocardiographic pattern (31% versus 55%), but females were more likely to have a family history of SCD (49.7% versus 29.8%). Genetic testing was positive in 19% of females versus 13.5% of males ($P=0.06$). During a mean follow-up of 122 months, 2.8% of females versus 7.1% of males ($P=0.04$) experienced appropriate ICD therapy or SCD. Two factors independently predicted arrhythmic events: a positive genetic test (OR, 18.71 [95% CI, 1.82–192.53]) and AF (OR, 21.12 [95% CI, 1.27–350.85]).

- Family history of SCD has not been helpful in risk prediction of patients with Brugada syndrome.

However, a meta-analysis of 22 studies involving 3386 patients found that history of SCD in family members <40 years of age doubled the risk for a major arrhythmic event.²²²

Genetics

- Brugada syndrome is considered primarily a monogenic mendelian disease with autosomal dominant inheritance and incomplete phenotypic penetrance. However, other forms of inheritance (X-linked) have also been suggested.²²³
- Rare genetic variants in *SCN5A* account for disease in 20% of patients with Brugada syndrome. Variants in additional genes have been reported but remain unclear.²²⁴
- Variants in the *PKP2* gene that causes arrhythmogenic cardiomyopathy have been reported to cause an arrhythmogenic phenotype in the absence of overt structural disease²²⁵ and may be implicated in Brugada syndrome.²²⁶
- Apart from identifying 10 new loci, a GWAS meta-analysis for Brugada syndrome supported by functional studies has elucidated the causal role of *MAPRE2* in the pathogenesis of Brugada syndrome.²²⁷
- The large proportion of sporadic cases and variable penetrance in *SCN5A* carriers has suggested a more complex pattern of penetrance. PRS-based analysis for Brugada syndrome supports that the disease threshold varies between individuals depending on the contributions of rare variants

of *SCN5A*, common risk alleles, and exposure to sodium channel blockade.^{.227}

- A reappraisal of 21 genes associated with Brugada syndrome for clinical validity led to the classification of only *SCN5A* as definitive evidence for causing Brugada syndrome, and the other 20 were classified as limited evidence for causing Brugada syndrome.^{.228}

Catecholaminergic Polymorphic VT Prevalence and Incidence

- CPVT is a familial condition characterized by adrenergically induced polymorphic ventricular arrhythmias associated with syncope and sudden death.

Arrhythmias include frequent ectopy, bidirectional VT, and polymorphic VT with exercise or catechol-aminergic stimulation (eg, emotion or medicines such as isoproterenol). Most patients present in childhood or adolescence. Variants in genes encoding *RYR2* (*CPVT1*) are found in the majority of patients and result in an autosomal dominant pattern of inheritance.^{.229} Variants in genes encoding *CASQ2* (*CPVT2*) are found in a small minority and result in an autosomal recessive pattern of inheritance. Other less common variants have also been described in *TRDN* and *TECRL* (autosomal recessive), as well as *CALM1*, *CALM2*, and *CALM3* (autosomal dominant).

- Analysis of 171 probands with CPVT who 58%. Genetic testing of 194 individuals identified variants in *RYR2* (60%), *CASQ2* (5%), and >1 gene in 17 cases (9%). For 23 cases (12%), no genetic variant was identified.

Complications

- In a cohort of 34 patients with CPVT, 20.6% developed fatal cardiac events during 7.4 years of follow-up.^{.231}
- Incidence of SCA in children with ≥ 2 CPVT gene variants was 11 of 15 (73%).^{.232} VT or exertional syncope occurred in 3 of the children (20%), and only 1 (7%) was asymptomatic.

- Clinical Genomics Resource reappraisal of 26 candidate *ARVC* genes found 6 to have strong definitive evidence and 2 to have moderate evidence supporting their role in arrhythmogenic cardiomyopathy.^{.235} Although the original descriptions localized the disease to the RV, more recent work has demonstrated that LV involvement may occur early in the course of the disease.^{.236}

Complications

- In a cohort of 301 patients with arrhythmogenic cardiomyopathy from a single center in Italy, the probability of a first life-threatening arrhythmic event was 14% at 5 years, 23% at 10 years, and 30% at 15 years.^{.237}
- In a pooled analysis examining 5485 patients, rates of SCD were 0.65 per 1000 (95% CI, 0.00–6.43; $I_2=0.00\%$) in those with an ICD placed and 7.21 (95% CI, 2.38–13.79; $I_2=0.0\%$) in the non-ICD cohort.^{.238} Patient characteristics identified individuals at a higher risk of life-threatening arrhythmia: age at presentation (aHR, 0.98 [95% CI, 0.97–0.99]), male sex

Arrhythmogenic RV Dysplasia/Arrhythmogenic Cardiomyopathy

- Arrhythmogenic RV dysplasia or arrhythmogenic cardiomyopathy is a form of genetically inherited structural HD that presents with fibrofatty replacement of the myocardium, which increases risk for palpitations, syncope, and sudden death attributable to VT.^{.233}
- Twelve arrhythmogenic cardiomyopathy loci have been described (*ARVC1*–*ARVC12*).^{.234}

Hypertrophic Cardiomyopathy

(Please refer to Chapter 22 [Cardiomyopathy and Heart Failure] for statistics on the general epidemiology of HCM.)

Complications

- SCA rates were 2.7%/y in a retrospective cohort of 106 patients with HCM treated medically and followed up for a mean of 7.7 years.²⁴⁰
- Among 1436 SCA cases in individuals 5 to 59 years of age between 2002 and 2015, HCM was present in 3.2% of those 5 to 34 years of age and 2.2% of those 35 to 59 years of age. This study noted the difficulty in distinguishing HCM from secondary LVH in older patients, who were excluded from the analysis.²⁴¹
- In a pooled analysis of 98 studies and N=70 510 patients (431 407 patient-years), contemporary SCD rates from 2015 to present were 0.32%/y and significantly lower compared with 2000 or earlier (incidence rate, 0.32% [95% CI, 0.20%–0.52%] versus incidence rate, 0.73% [95% CI,

0.53%–1.02%], rates for HCM were lowest in incidence rate, 0.28% [95% CI, 0.54%–0.84%]).

Early Repolarization Syndrome Prevalence and Incidence

- There had been no single definition or set of criteria for ERP have used a range of criteria, including ST-segment elevation, terminal QRS slurring, terminal QRS notching, J-point elevation, J waves, and other variations. Although the Brugada electrocardiographic pattern is considered an early repolarization variant, it is generally not included in epidemiological assessments of ERP or early repolarization syndrome.²⁴³ The problem with older definitions of ERP is the high prevalence of this electrocardiographic finding in the general population. Currently, the existence of the electrocardiographic pattern of early repolarization in asymptomatic people is called ERP, whereas early repolarization in patients with arrhythmic syncope or cardiac arrest is called early repolarization syndrome.²⁴⁴
- ERP was observed in 4% to 19% of the population (more commonly in young males and in athletes) and conventionally has been considered a benign finding.²⁴³
- Among 11 956 residents of rural Liaoning Province, China, who were ≥35 years of age, 1.3% had ERP, with a higher prevalence in males (2.6%) than females (0.2%).²⁴⁵
- In an Italian public health screening project, 24% of 13 016 students 16 to 19 years of age had at least 1 of the following electrocardiographic abnormalities: ventricular ectopic beats,

years of age in the Mini-1.72 [95% CI, 1.05–2.80]).²⁴⁹

- Shocks from an automatic ICD and earlier in survivors of lateral early repolarization CI, 1.4–11.0]; $P=0.01$).²⁵⁰

Premature Ventricular

- In a study of 1139 older adults HF or systolic dysfunction atrioventricular block, Brugada-like electrocardiographic pattern, left anterior/posterior fascicular block, LVH/RV hypertrophy, long/short QT interval, LA enlargement, right atrial enlargement, short PQ interval, and ventricular pre-excitation WPW syndrome.²⁴⁶

Complications

- Early repolarization had been considered a benign normal electrocardiographic variant until reports linked early repolarization in the inferior and lateral leads with idiopathic VF.²⁴⁷
- The consensus panel²⁴⁴ and others have identified certain electrocardiographic characteristics associated with increased risk for VF: ERP in the inferior and lateral electrocardiographic leads and J waves associated with horizontal or down-sloping ST segments (as opposed to rapidly ascending ST segments).²⁴⁸
- ERP was associated with increased age- and sex-adjusted hazard of SCD among people 30 to 50

tor (median duration, 22.2 hours), 0.011% of all heartbeats were premature ventricular contractions, and 5.5% of participants had nonsustained VT. Over follow-up, the highest quartile of ambulatory electrocardiographic premature ventricular contraction burden was associated with an adjusted odds of decreased LVEF (OR, 1.13 [95% CI, 1.05–1.21]) and incident HF (HR, 1.06 [95% CI, 1.02–1.09]) and death (HR, 1.04 [95% CI, 1.02–1.06]).²⁵¹ Although premature ventricular contraction ablation has been shown to improve cardiomyopathy, the association with death may be complex, representing both a potential cause and a noncausal marker for coronary or structural HD.

Tetralogy of Fallot

- Patients with repaired TOF are known to be at the true incidence is not clear. Prevalence estimates 14%.^{252–254}

risk for ventricular arrhythmias and SCD. However, estimates from multicenter studies range from 1% to

Cardiac Sarcoidosis

- Cardiac involvement in sarcoidosis is increasingly high risk for sudden death attributable to ventricular of cardiac involvement in sarcoidosis vary widely, from 3.7% to 54.9%.²⁵⁵
- A review of the NIS from 2012 to 2014 identified was recognized in 2.29% of all patients with sarcoidosis (P<0.001). VF also was recognized significantly versus 0.21% (P<0.001). Prevalence of cardiac

recognized as a cardiomyopathy with relatively low tachyarrhythmias. Estimates of the prevalence depending on the method of diagnosis, ranging

46 289 patients with a diagnosis of sarcoidosis. VT coidosis compared with 1.22% of control patients more frequently in patients with sarcoidosis: 0.25% arrest in patients with sarcoidosis was 0.72%.²⁵⁶

Monomorphic VT

Prevalence and Incidence

- Incidence of monomorphic VT in hospitalized patients to 1988 to 10.5% in 2009 to 2011.²⁵⁷
- Prevalence of sustained VT in patients with LV
- Monomorphic VT occurred in 9 of 342 patients

patients with AMI decreased from 14.6% in 1986

aneurysm after MI is reported at 10%.²⁵⁸ (2.6%) at a median of 1 day (interquartile range,

0.25–4.75 days) after PCI for chronic total occlusion of a coronary artery.²⁵⁹

- During a mean follow-up period of 85 months, sustained VT was observed in 13 of 250 patients (5.2%) and monomorphic VT in 9 of 250 patients (3.6%) with congenital LV aneurysms or diverticula.²⁶⁰

Polymorphic VT/VF

Prevalence and Incidence

- In the setting of AMI, the prevalence of polymorphic VT was 4.4%.²⁶¹
- Incidence of VF in hospitalized patients with AMI decreased from 8.2% in 1986 to

Complications

- In the setting of AMI, polymorphic VT is associated with increased mortality (17.8%).²⁶¹

Torsade de Pointes

Prevalence and Incidence

- Among 14 756 patients exposed to QT-prolonging drugs in 36 studies, 6.3% developed QT prolongation, and 0.33% developed TdP.²⁶²

Risk Factors

- An up-to-date list of drugs with the potential to cause TdP is

Table 19-1. Differences in Bystander Interventions and Survival After OHCA by Race, Ethnicity, Sex, and Neighborhood Characteristics, CARES, United States, 2023

	Nontraumatic pathogenesis survival	Bystander intervention rates	
	Overall survival to hospital	CPR	Public AED use
Total	14 299/139 822 (10.2%)	43 736/106 193 (41.2%)	2228/19 099 (11.7%)
Race and ethnicity			
American Indian/Alaska Native	37/546 (6.8%)	185/451 (41.0%)	10/82 (12.2%)
Asian	371/3880 (9.6%)	1330/3050 (43.6%)	65/477 (13.6%)
Black/African American	2750/30 286 (9.1%)	7646/22 026 (34.7%)	351/3723 (9.4%)
Hispanic/Latino	1209/12 177 (9.9%)	3879/9771 (39.7%)	173/2014 (8.6%)
Native Hawaiian/Pacific Islander	76/653 (11.6%)	229/533 (43.0%)	6/103 (5.8%)
White	7679/70 459 (10.9%)	23 164/53 257 (43.5%)	1260/9386 (13.4%)
Unknown	2177/21 821 (10.0%)	7303/17 105 (42.7%)	363/3314 (11.0%)
Sex			
Male	9403/88 079 (10.7%)	28 445/68 741 (41.4%)	1849/14 862 (12.4%)
Female	4891/51 700 (9.5%)	15 281/37 420 (40.8%)	379/4222 (9.0%)
Neighborhood racial composition			
≥70% White	6478/59 111 (11.0%)	20 121/45 269 (44.4%)	953/7503 (12.7%)
≥40% Black	1726/20 079 (8.6%)	5102/15 317 (33.3%)	193/2329 (8.3%)
Integrated	6095/60 632 (10.0%)	18 513/45 607 (40.6%)	1082/9267 (11.7%)
Neighborhood median household			
<\$40 000 annually	1434/15 617 (9.2%)	3866/11 867 (32.6%)	172/2325 (7.4%)
\$40 000–\$80 000 annually	6787/67 673 (10.0%)	20 499/51 026 (40.2%)	923/8980 (10.3%)
>\$80 000 annually	5657/52 756 (10.7%)	19 319/40 324 (45.4%)	893/52 756 (13.1%)

Bystander CPR rate excludes 9-1-1 responder–witnessed, nursing home, and health care facility arrests. Public AED use rate excludes 9-1-1 responder–witnessed, home/residence, nursing home, and health care facility arrests. Sex was missing for 38 cases. Race is unknown for 16.2% of CARES cases in the 2022 dataset because a number of communities do not collect this information.

AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; and OHCA, out-of-hospital cardiac arrest.

Source: Data derived from CARES.³

Table 19-2. Variation in EMS-Treated OHCA in Selected States, United States, 2023

	OHCA incidence					Nontraumatic cause survival rates
	CARES cases reported	CARES population	Total state population	% population covered	Incidence rate (per 100 000)	Over survival hosp
National	139 822	167 583 783	333 287 557	50.30%	83.4	10.2
State						
Alaska	519	610 324	733 583	83.2%	85.0	11.2
California	25 324	32 898 701	39 029 342	84.3%	77.0	8.4
Colorado	3542	4 800 582	5 839 926	82.2%	73.8	10.8
Connecticut	2387	2 851 771	3 626 205	78.6%	83.7	8.4
Delaware	1298	1 018 396	1 018 396	100.0%	127.5	10.8
Hawaii	1591	1 440 196	1 440 196	100.0%	110.5	12.6
Maine	1159	1 385 340	1 385 340	100.0%	83.7	8.7
Michigan	8671	8 832 727	10 034 113	88.0%	98.2	8.6
Minnesota	3408	4 777 014	5 717 184	83.6%	71.3	11.7
Mississippi	1596	2 257 986	2 940 057	76.8%	70.7	7.7
Missouri	3223	3 137 940	6 177 957	50.8%	102.7	9.0
Montana	692	1 002 301	1 122 867	89.3%	69.0	11.3
Nebraska	717	1 166 752	1 967 923	59.3%	61.5	14.8
Nevada	2288	2 967 081	3 177 772	93.4%	77.1	13.6
North Carolina	8989	9 673 545	10 698 973	90.4%	92.9	11.6
Oregon	3183	3 966 389	4 240 137	93.5%	80.2	13.7
Pennsylvania	7106	9 157 463	12 972 008	70.6%	77.6	8.8

Criteria for reporting: at least 50% population catchment in state; voluntarily reporting data. Utstein: witnessed by bystander and found in shockable rhythm. By-stander CPR rate excludes 9-1-1 responder–witnessed, nursing home, and health care facility arrests.

Public AED use rate excludes 9-1-1 responder–witnessed, home/residence, nursing home, and health care facility arrests.

AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

Source: Data derived from CARES.³

Table 19-3. Characteristics of and Outcomes for OHCA (CARES) and IHCA (GWTG-R), United States, 2023

	OHCA*			IHCA		
	Adults (>18 y)	Children (1–18 y)	Infants (<1 y)†	Adults (>18 y)	Children (1–18 y)	Infants (<1 y)
Females	37.0	40.0	43.9	40.6	47.4	47.2
Males	63.0	60.0	56.0	59.4	52.6	52.7
Survival to hospital	10.2	15.9	7.4	23.6	42.2	45.9
Good functional status at hospital	8.1	12.8	5.7	79.2	70.9	79.6
Initial pulseless						
VF/VT/shockable	17.8	9.5	2.5	14.4	8.8	1.9
PEA	22.1	16.8	13.5	55.4	39.1	21.2
Asystole	51.7	63.6	74.6	21.3	26.9	16.0
Unknown	...	...	...	7.6	7.7	7.9
Public setting	18.2	16.7	8.3	...	...	...
Home	71.0	83.0	91.7	...	...	...
Nursing home	10.7	0.3	0.0	...	...	...
Public AED usell	11.7	19.2	2.5	...	...	...
Arrest in ICU	...	...	...	41.1	47.5	57.4
Arrest in operating	...	...	...	2.2	5.8	4.5
Arrest in ED				17.8	19.8	4.7
Noncritical care				38.7	26.7	33.4

Values are percentages. AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; ED, emergency department; ellipses (...), data not available; EMS, emergency medical services; GWTG-R, Get With The Guidelines–Resuscitation; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital

cardiac arrest; PEA, pulseless electric activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Inclusion criteria: an OHCA for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=332).

†Stillborn neonates and perinatal newborns born without signs of life are not CARES cases and are not entered into the registry.

‡Good functional status is defined as discharge Cerebral Performance Category of 1 or 2 in adults or Pediatric Cerebral Performance Category of 1 or 2 in pediatric patients.

§Does not include initial rhythms of bradycardia with poor perfusion.

||Inclusion criteria: an OHCA. Public AED use rate excludes 9-1-1 responder–witnessed, home/residence, nursing home, and health care facility arrests.

Source: OHCA data derived from CARES₃ and are based on 135 723 EMS-treated OHCA adult cases, 2079 EMS-treated OHCA pediatric cases (1–18 years of age), and 1587 EMS-treated OHCA infant cases (<1 year of age) with known hospital outcome data in 2023. IHCA data are from GWTG-R (unpublished AHA tabulation) 2023 and are based on 40 837 adult IHCAs in 404 hospitals, 722 child (≥1–<18 years of age) IHCAs in 108 hospitals, and 1274 infant (<1 year of age) IHCAs in 104 hospitals.

Table 19-4. Outcomes of EMS-Treated Nontraumatic OHCA in Adults (>18 Years of Age), CARES, United States, 2023

Presenting characteristics (n)	Survival to hospital admission	Survival to hospital discharge	Survival to hospital discharge and good neurological function
All presentations (135 723)	26.1	10.2	8.1
Home/residence (96 429)	24.6	8.8	6.9
Nursing home (14 540)	15.8	3.9	1.6

Values are percentages.

Inclusion criteria: an OHCA for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=293).

AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

*Percentage of patients admitted to the hospital who died before hospital discharge.

†Excludes nursing home/health care facility events.

Source: Data derived from CARES.³

Table 19-5. Quality of Care of Patients With IHCA Among GWTG-R Hospitals, United States, 2023

	Adults (≥18 y)	Children (≥1y–<18 y)*	Infants (<1 y)*
Event outside critical care setting	38.7	26.7	33.4
Hospital survival to discharge for IHCA	16.6	22.2	23.6
End-tidal CO ₂ monitoring used	34.7	55.4	40.2

Values are mean percentages.

GWTG-R is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

GWTG-R indicates Get With The Guidelines–Resuscitation; ICU, intensive care unit; and IHCA, in-hospital cardiac arrest. Source: Unpublished American Heart Association tabulation, GWTG-Resuscitation.

*Includes children and infants with initial rhythms of bradycardia with poor perfusion.

Table 19-6. Outcomes of EMS-Treated Nontraumatic OHCA in Children and Infants, CARES, United States, 2023

Age group, y (n)	Survival to hospital admission	Survival to hospital discharge	Survival with good neurological function	In-hospital mortality*
<1 (1587)	18.5	7.4	5.7	60.2
1–12 (1225)	31.6	14.1	10.5	55.3
13–18 (854)	37.7	18.5	16.2	50.9

Values are percentages.

Inclusion criteria: an OHCA for which resuscitation is attempted by a 9-1-1 responder (CPR or defibrillation). This would also include patients who received an AED shock by a bystander before the arrival of 9-1-1 responders. Analysis excludes patients with missing hospital outcome (n=36). Stillborn neonates and perinatal newborns born without signs of life are not CARES cases and are not entered into the registry.

CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

*Percentage of patients admitted to the hospital who died before hospital discharge.

Source: Data derived from CARES.³

Table 19-7. SCA Mortality, United States, 2022 (ICD-10 I46.0, I46.1, I46.9, I49.0)

Population group	No. of deaths as underlying cause, 2022, all ages	Underlying cause age-adjusted mortality rates per 100 000	Any-mention mortality, 2022, all ages	Any-mention age-adjusted mortality rates per 100 000 (95% CI), 2022
Both sexes	19 171	4.6 (4.5–4.6)	417 957	99.6 (99.3–99.9)
Males	10 622	5.7 (5.5–5.8)	222 334	120.7 (120.2–121.2)
Females	8549	3.7 (3.6–3.7)	195 623	82.5 (82.1–82.8)
NH White males	7605	5.6 (5.4–5.7)	152 654	112.7 (112.1–113.3)
NH White females	6089	3.6 (3.5–3.7)	132 636	76.4 (76.0–76.8)
NH Black males	1913	10.9 (10.4–11.4)	31 415	183.1 (180.9–185.2)
NH Black females	1658	6.9 (6.6–7.2)	29 940	124.6 (123.2–126.0)
Hispanic males	712	3.4 (3.1–3.7)	24 714	130.0 (128.2–131.7)
Hispanic females	526	2.2 (2.0–2.4)	21 236	89.7 (88.5–90.9)
NH Asian males*	252	2.7 (2.4–3.0)	9577	104.5 (102.4–106.6)
NH Asian females*	191	1.5 (1.3–1.8)	8702	69.7 (68.2–71.2)
NH American Indian/Alaska Native*	74	2.8 (2.2–3.5)	2650	103.8 (99.7–107.8)
NH Native Hawaiian or Pacific Islander*	34	5.6 (3.8–7.8)	866	147.3 (137.2–157.3)

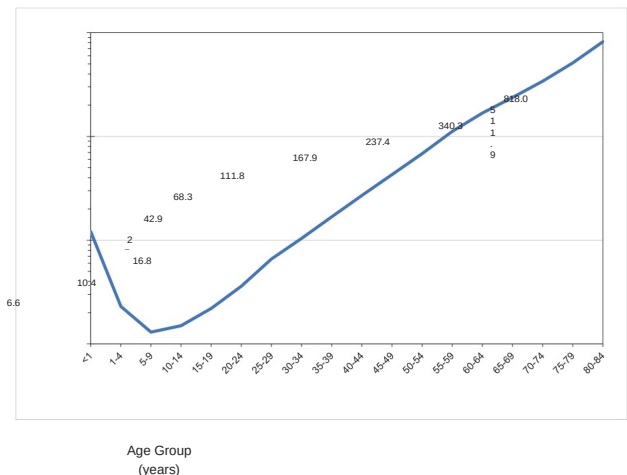
ICD-10 indicates *International Classification of Diseases, 10th Revision*; NH, non-Hispanic; and SCA, sudden cardiac arrest.

*Mortality for Hispanic people, NH American Indian or Alaska Native people, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown under-reporting on death certificates of American Indian or Alaska Native decedents, Asian decedents, Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

Sources: Any-mention cause and underlying cause data derived from the National Vital Statistics System²⁶⁴ and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database.¹⁵⁵



Chart 19-1. Temporal trends in survival to hospital discharge after IHCA in adults and children in GWTG-R from 2000 to 2023, United States.



GWTG-R indicates Get With The Guidelines–Resuscitation; IHCA, in-hospital cardiac arrest; and PEDS, pediatrics.

Source: GWTG-R; unpublished American Heart Association data.

SCD indicates sudden cardiac death.

Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database.¹⁵⁵

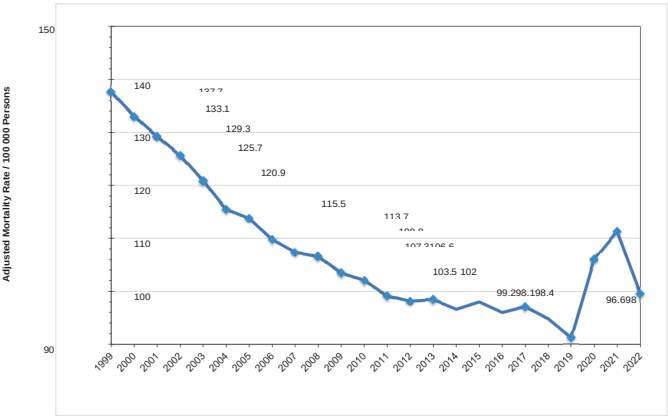
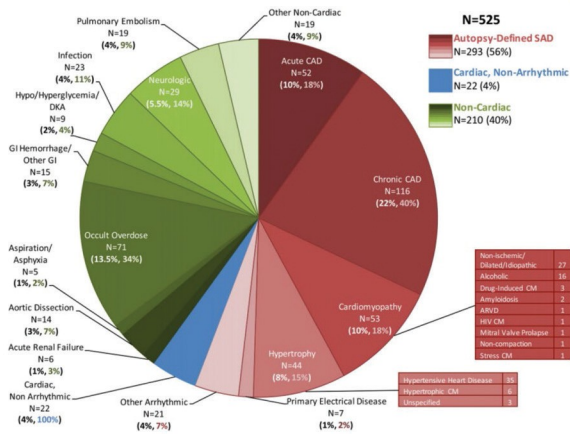
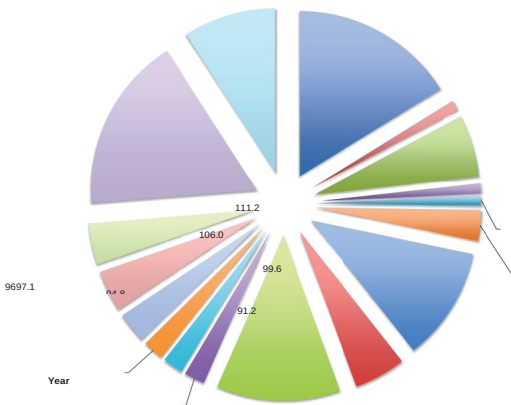


Chart 19-3. Age-adjusted mortality rates for any mention of SCD. United States. 1999 to 2022.

SCD indicates sudden cardiac death.

Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.¹⁵⁵



Non-ischemic/	27
Ischemic/Ischemic	16
Alcoholic	3
Drug-induced CM	3
Amphetamine	2
Alcohol	1
Myx CM	1
Mitral Valve Prolapse	1
Non-compact	1
Stress CM	1

Hypertensive Heart Disease	18
Hypertensive CM	18
Unspecified	1

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Chart 19-4. Adjudicated causes of autopsied WHO-defined SCDs.

Adjudicated causes of autopsied WHO-defined SCDs after review

IHCA indicates in-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest.

Source: Data derived from Chen et al.¹³¹

of comprehensive medical records, EMS records, complete autopsy, toxicology, and postmortem chemistries. Autopsy-defined SADs had no identifiable extracardiac (eg, PE, hemorrhage, lethal toxicology) or nonarrhythmic (tamponade, acute HF) cause of death. The first percent is of total WHO-defined SCDs; the second percent is of cause of death category. Overall, autopsy-defined SADs accounted for 56% of all WHO-defined SCDs; 4% were cardiac nonarrhythmic cause of death; and 40% were noncardiac cause of death. ARVD indicates arrhythmogenic right ventricular dysplasia; CAD,

coronary artery disease; CM, cardiomyopathy; DKA, diabetic ketoacidosis; EMS, emergency medical services; GI, gastrointestinal; HF, heart failure; PE, pulmonary embolism; SAD, sudden arrhythmic death; SCD, sudden cardiac death; and WHO, World Health Organization.

Source: Adapted from Tseng et al.²⁶⁵ Copyright © 2018 American Heart Association, Inc.

REFERENCES

1. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, et al; on behalf of the ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for health-care professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation*. 2004;110:3385–3397. doi: 10.1161/01.CIR.0000147236.85306.15
2. Utstein Collaborators. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for Australia (2002-2014): trends over time. *Emerg Med Australas*. 2019;31:813–820. doi: 10.1111/1742-6723.13353
15. Lee SY, Song KJ, Shin SD, Ro YS, Hong KJ, Kim YT, Hong SO, Park JH, Lee SC. A disparity in outcomes of out-of-hospital cardiac arrest by community socioeconomic status: a ten-year observational study. *Resuscitation*. 2018;126:130–136. doi: 10.1016/j.resuscitation.2018.02.025
16. Yoshimoto H, Fukui K, Nishimoto Y, Kuboyama K, Oishi Y, Sekine K, Hiraide A. Annual improvement trends in resuscitation outcome of patients defibrillated by laypersons after out-of-hospital cardiac arrests and compression-only resuscitation of laypersons. *Resuscitation*. 2023;183:109672. doi: 10.1016/j.resuscitation.2022.12.010
17. Faxén J, Jernberg T, Hollenberg J, Gadler F, Herlitz J, Szummer healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian

18. Kontos MC, Fordyce CB, Chen AY, Chiswell K, Enriquez JR, de Lemos J, Roe MT. Association of acute myocardial infarction cardiac arrest patient volume and in-hospital mortality in the United States: insights from the National Cardiovascular Data Registry Acute Coronary Treatment And Intervention Outcomes Network Registry. *Clin Cardiol*. 2019;42:352–357. doi: 10.1002/clc.23146
- and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation [published correction appears in *Circulation*. 2015;131:e168–e169]. *Circulation*. 2015;132:1286–1300. doi: 10.1161/cir.0000000000000144
3. Cardiac Arrest Registry to Enhance Survival. CARES website. Accessed

19. Shavelle DM, Bosson N, Thomas JL, Kaji AH, Sung G, French WJ, Niemann JT. Outcomes of ST elevation myocardial infarction complicated by out-of-hospital cardiac arrest (from the Los Angeles County regional system). *Am J Cardiol*. 2017;120:729–733. doi: 10.1016/j.amjcard.2017.06.010
20. Olgin JE, Pletcher MJ, Vittinghoff E, Wranicz J, Malik R, Morin DP, Zweibel S, Buxton AE, Elayi CS, Chung EH, et al. Wearable cardioverter-defibrillator after myocardial infarction. *N Engl J Med*. 2018;379:1205–1215. doi: 10.1056/NEJMoa1800781
4. Allan KS, Morrison LJ, Pinter A, Tu JV, Dorian P; RESCU Investigators. Unexpected high prevalence of cardiovascular disease risk factors and psychiatric disease among young people with sudden cardiac arrest. *J Am Heart Assoc*. 2019;8:e010330. doi: 10.1161/JAHA.118.010330
5. Lindqvist E, Hollenberg J, Ringh M, Nordberg P, Forsberg S. Out-of-hospital cardiac arrest caused by poisoning: a Swedish nationwide study over 15 years. *Resuscitation*. 2023;193:110012. doi: <https://doi.org/10.1016/j.resuscitation.2023.110012>
6. Wittwer MR, Zeitz C, Beltrame JF, Arstall MA. Aetiology of resuscitated out-of-hospital cardiac arrest treated at hospital. *Resuscitation*. 2022;170:178–183. doi: 10.1016/j.resuscitation.2021.11.035
7. Lai PH, Lancet EA, Weiden MD, Webber MP, Zeig-Owens R, Hall CB, Prezant DJ. Characteristics associated with out-of-hospital cardiac arrests and resuscitations during the novel coronavirus disease 2019 pandemic in New York City. *JAMA Cardiol*. 2020;5:1154–1163. doi: 10.1001/jamacardio.2020.2488
8. Chan PS, Girotra S, Tang Y, Al-Araji R, Nallamothu BK, McNally B. Outcomes for out-of-hospital cardiac arrest in the united states during the coronavirus disease 2019 pandemic. *JAMA Cardiol*. 2021;6:296–303. doi: 10.1001/jamacardio.2020.6210
9. Nickles AV, Oostema A, Allen J, O'Brien SL, Demel SL, Reeves

21. Zhao B, Johnston FH, Salimi F, Kurabayashi M, Negishi K. Short-term exposure to ambient fine particulate matter and out-of-hospital cardiac arrest: a nationwide case-crossover study in Japan. *Lancet Planet Health*. 2020;4:e15–e23. doi: 10.1016/S2542-5196(19)30262-1
22. Kranc H, Novack V, Shtein A, Sonkin R, Jaffe E, Novack L. Ambient air pollution and out-of-hospital cardiac arrest: Israel nation wide assessment. *Atmos Environ*. 2021;261:118567. doi: 10.1016/j.atmosenv.2021.118567
23. Gentile FR, Primi R, Baldi E, Compagnoni S, Mare C, Contri E, Reali F, Bussi D, Facchin F, Currao A, et al. Out-of-hospital cardiac arrest and ambient air pollution: a dose-effect relationship and an association with OHCA incidence. *PLoS One*. 2021;16:e0256526. doi: 10.1371/journal.pone.0256526
24. Bougouin W, Mustafic H, Marijon E, Murad MH, Dumas F, Barbouttis A, Jabre P, Beganton F, Empana JP, Celermajer DS, et al. Gender and survival after sudden cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2015;94:55–60. doi: 10.1016/j.resuscitation.2015.06.018
25. Ng YY, Wah W, Liu N, Zhou SA, Ho AF, Pek PP, Shin SD, Tanaka H, Khunkhlai N, Lin CH, et al; PAROS Clinical Research Network. Associations between gender and cardiac arrest outcomes in Pan-Asian out-of-hospital cardiac arrest patients. *Resuscitation*. 2016;102:116–121. doi: 10.1016/j.resuscitation.2016.03.002

MJ. Comparison of out-of-hospital cardiac arrests and fatal- 26. Dicker

ties in the metro Detroit area during the COVID-19 pandemic with previous-year events. *JAMA Netw Open*. 2021;4:e2032331. doi: 10.1001/jamanetworkopen.2020.32331

10. Rollman JE, Kloner RA, Bosson N, Niemann JT, Gausche-Hill M, Williams M, Clare C, Tan W, Wang X, Shavelle DM, et al. Emergency medical services responses to out-of-hospital cardiac arrest and suspected ST-segment-elevation myocardial infarction during the COVID-19 pandemic in Los Angeles County. *J Am Heart Assoc*. 2021;10:e019635. doi: 10.1161/jaha.120.019635

11. Lim ZJ, Ponnappa Reddy M, Afroz A, Billah B, Shekar K, Subramaniam A.

Incidence and outcome of out-of-hospital cardiac arrests in the COVID-19 era: a systematic review and meta-analysis. *Resuscitation*. 2020;157:248–258. doi: 10.1016/j.resuscitation.2020.10.025

12. Perrin N, Iglesias JF, Rey F, Benzakour L, Cimci M, Noble S, Degrauwe S, Tessitore E, Mach F, Roffi M. Impact of the COVID-19 pandemic on acute coronary syndromes. *Swiss Med Wkly*. 2020;150:w20448. doi: 10.4414/smw.2020.20448

13. Baldi E, Klersy C, Chan P, Elmer J, Ball J, Counts CR, Rosell Ortiz F, Fothergill R, Auricchio A, Paoli A, et al; OHCA-COVID Study Group. The impact of COVID-19 pandemic on out-of-hospital cardiac arrest: an individual patient data meta-analysis. *Resuscitation*. 2024;194:110043. doi:

- cardiac arrest: a New Zealand registry study. *Emerg Med J*. 2018;35:367–371. doi: 10.1136/emermed-2017-207176
27. Vogelsong MA, May T, Agarwal S, Cronberg T, Dankiewicz J, Dupont A, Friberg H, Hand R, McPherson J, Mlynash M, et al. Influence of sex on survival, neurologic outcomes, and neurodiagnostic testing after out-of-hospital cardiac arrest. *Resuscitation*. 2021;167:66–75. doi: 10.1016/j.resuscitation.2021.07.037
28. Bockler B, Preisner A, Bathe J, Rauch S, Ristau P, Wnent J, Grasner JT, Seewald S, Lefering R, Fischer M. Gender-related differences in adults concerning frequency, survival and treatment quality after out-of-hospital cardiac arrest (OHCA): an observational cohort study from the German resuscitation registry. *Resuscitation*. 2024;194:110060. doi: 10.1016/j.resuscitation.2023.110060
29. Rachoin JS, Olsen P, Gaughan J, Cerceo E. Racial differences in outcomes and utilization after cardiac arrest in the USA: a longitudinal study comparing different geographical regions in the USA from 2006-2018. *Resuscitation*. 2021;169:115–123. doi: 10.1016/j.resuscitation.2021.10.038
30. Monlezun DJ, Samura AT, Patel RS, Thannoun TE, Balan P. Racial and socioeconomic disparities in out-of-hospital cardiac arrest outcomes: artificial intelligence-augmented propensity score and geospatial cohort analysis of 3,952 patients. *Cardiol Res Pract*. 2021;2021:3180987. doi: 10.1016/j.resuscitation.2023.110043
14. Pemberton K, Bosley E, R CF, Watt K. Pre-hospital outcomes of adult out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland, 2011-2018. *Resuscitation*. 2021;169:115–123. doi: 10.1016/j.resuscitation.2021.10.038
31. Office of the Assistant Secretary for Planning and Evaluation. Prior HHS poverty guidelines and federal register references. Accessed April 24, 2024.

123. doi: 10.1016/j.resuscitation.2018.07.005
35. Hughes ZH, Shah NS, Tanaka Y, Hammond MM, Passman R, Khan SS. Rural-urban temporal trends for sudden cardiac death in the United States, 1999-2019. *JACC Clin Electrophysiol*. 2022;8:382–384. doi: 10.1016/j.jacep.2021.12.006
36. van Nieuwenhuizen BP, Tan HL, Blom MT, Kunst AE, van Valkengoed IGM. Association between income and risk of out-of-hospital cardiac arrest: a retrospective cohort study. *Circ Cardiovasc Qual Outcomes*. 2023;16:e009080. doi: 10.1161/CIRCOUTCOMES.122.009080
37. Blewer AL, Ibrahim SA, Leary M, Dutwin D, McNally B, Anderson ML, Morrison LJ, Aufderheide TP, Day M, Idris AH, et al. Cardiopulmonary resuscitation training disparities in the United States. *J Am Heart Assoc*. 2017;6:e006124. doi: 10.1161/JAHA.117.006124
38. Bakke HK, Steinvik T, Angell J, Wisborg T. A nationwide survey of first aid training and encounters in Norway. *BMC Emerg Med*. 2017;17:6. doi: 10.1186/s12873-017-0116-7
39. Bray JE, Smith K, Case R, Cartledge S, Straney L, Finn J. Public cardiopulmonary resuscitation training rates and awareness of hands-only cardio-pulmonary resuscitation: a cross-sectional survey of Victorians. *Emerg Med Australas*. 2017;29:158–164. doi: 10.1111/1742-6723.12720
40. Brooks B, Chan S, Lander P, Adamson R, Hodgetts GA, Deakin CD. Public knowledge and confidence in the use of public access defibrillation. *Heart*. 2015;101:967–971. doi: 10.1136/heartjnl-2015-307624
41. Cartledge S, Saxton D, Finn J, Bray JE. Australia's awareness of cardiac arrest and rates of CPR training: results from the Heart Foundation's HeartWatch survey. *BMJ Open*. 2020;10:e033722. doi: 10.1136/bmjopen-2019-033722
42. Gonzalez M, Leary M, Blewer AL, Cinousis M, Sheak K, Ward M, Merchant RM, Becker LB, Abella BS. Public knowledge of automatic external de-fibrillators in a large U.S. urban community. *Resuscitation*. 2015;92:101–106. doi: 10.1016/j.resuscitation.2015.04.022
43. Duber HC, McNellan CR, Wollum A, Phillips B, Allen K, Brown JC, Bryant M, Guptam RB, Li Y, Majumdar P, et al. Public knowledge of cardiovascular disease and response to acute cardiac events in three cities
50. Shekhar A, Narula J. Globally, GDP per with rates of bystander CPR. *Ann*. 10.5334/aandh.3624
51. Alhaeni A, Bevdoun MA, Bevdoun HA, Chandra-Strobos N, Eid SM. Regional nitalized patients having out-of- 2017;120:421–427. doi:
52. Andrew E, Nehme Z, Wolfe R, Bernard lowing out-of-hospital cardiac arrest. 10.1136/heartjnl-2016-310485
53. Pane M, Raian S, Hansen SM. Karlsson L, Linnert F, Kohler L. hospital cardiac arrest in nursing in China and India. *Heart*. 2018;104:67–72. doi: 10.1136/heartjnl-2017-311388
44. Krammel M, Schnaubelt S, Weidenauer D, Winnisch M, Steininger M, Eichelher J, Hamp T, van Tulder R, Sulzgruber P. Gender and age-specific aspects of awareness and knowledge in basic life support. *PLoS One*. 2018;13:e0198918. doi: 10.1371/journal.pone.0198918
45. Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, Ko PC, Leong BS, Khunkhlai N, Naroo GY, et al. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the Pan Asian Resuscitation Outcomes Study (PAROS). *Resuscitation*. 2015;96:100–108. doi: 10.1016/j.resuscitation.2015.07.026
46. Okubo M, Matsuyama T, Gibo K, Komukai S, Izawa J, Kiyohara K, Nishiyama C, Kiguchi T, Callaway CW, Iwami T, et al. Sex differences in receiving layperson cardiopulmonary resuscitation in pediatric out-of-hospital cardiac arrest: a nationwide cohort study in Japan. *J Am Heart Assoc*. 2019;8:e010324. doi: 10.1161/JAHA.118.010324
47. Sasson C, Magid DJ, Chan P, Root ED, McNally BF, Kellermann AL, Haukoos JS. Association of neighborhood characteristics with bystander-initiated CPR. *N Engl J Med*. 2012;367:1607–1615. doi: 10.1056/NEJMoa1110700
48. Moon S, Bobrow BJ, Vadeboncoeur TF, Kortuem W, Kisakye M, Sasson C, Stolz U, Spaite DW. Disparities in bystander CPR provision and survival from out-of-hospital cardiac arrest according to neighborhood ethnicity. *Am J Emerg Med*. 2014;32:1041–1045. doi: 10.1016/j.ajem.2014.06.019
49. Garcia RA, Spertus JA, Girotra S, Nallamothu BK, Kennedy KF, McNally BF, Breathett K, Del Rios M, Sasson C, Chan PS. Racial and ethnic differences in bystander CPR for witnessed cardiac arrest. *N Engl J Med*. 2022;387:1569–1578. doi: 10.1056/NEJMoa2200798

- 2018;125:90–98. doi: 10.1016/j.resuscitation.2018.02.004
54. Branch KRH, Strote J, Gunn M, Maynard C, Kudenchuk PJ, Brusen R, Petek BJ, Sayre MR, Edwards R, Carlborn D, et al. Early head-to-pelvis computed tomography in out-of-hospital circulatory arrest without obvious etiology. *Acad Emerg Med*. 2021;28:394–403. doi: 10.1111/acem.14228
55. Amacher SA, Bohren C, Blatter R, Becker C, Beck K, Mueller J, Loretz N, Gross S, Tisljar K, Sutter R, et al. Long-term survival after out-of-hospital cardiac arrest: a systematic review and meta-analysis. *JAMA Cardiol*. 2022;7:633–643. doi: 10.1001/jamacardio.2022.0795
56. Elfvärn L, Lagedal R, Rubertsson S, James S, Oldgren J, Olsson J, Hollenberg J, Jensen U, Ringh M, Svensson L, et al. Post-resuscitation myocardial dysfunction in out-of-hospital cardiac arrest patients randomized to immediate coronary angiography versus standard of care. *Int J Cardiol Heart Vasc*. 2020;27:100483. doi: 10.1016/j.ijcha.2020.100483
57. Song H, Kim HJ, Park KN, Kim SH, Kim WY, Lee BK, Cho IS, Lee JH, Youn CS; Korean Hypothermia Network Investigators. Which out-of-hospital cardiac arrest patients without ST-segment elevation benefit from early coronary angiography? Results from the Korean Hypothermia Network prospective registry. *J Clin Med*. 2021;10:439. doi: 10.3390/jcm10030439
58. Desch S, Freund A, Akin I, Behnes M, Preusch MR, Zelniker TA, Skurk C, Landmesser U, Graf T, Eitel I, et al. Angiography after out-of-hospital cardiac arrest without ST-segment elevation. *N Engl J Med*. 2021;385:2544–2553. doi: 10.1056/NEJMoa2101909
59. Herzog N, Laager R, Thommen E, Widmer M, Vincent AM, Keller A, Becker C, Beck K, Perrig S, Bernasconi L, et al. Association of taurine with in-hospital mortality in patients after out-of-hospital cardiac arrest: results from the prospective, observational communicate study. *J Clin Med*. 2020;9:1405. doi: 10.3390/jcm9051405
60. Rafecas A, Bañeras J, Sans-Roselló J, Ortiz-Pérez JT, Rueda-Sobella F, Santamarina E, Milà L, Sionis A, Gaig C, García-García C, et al. Change in neuron-specific enolase levels in out-of-hospital cardiopulmonary arrest survivors as a simple and useful tool to predict neurological prognosis. *Rev Esp Cardiol (Engl Ed)*. 2020;73:232–240. doi: 10.1016/j.rec.2019.01.007
61. Ryoo SM, Kim YJ, Sohn CH, Ahn S, Seo DW, Kim WY. Prognostic abilities of serial neuron-specific enolase and lactate and their combination in cardiac arrest survivors during targeted temperature management. *J Clin Med*. 2020;9:159. doi: 10.3390/jcm9010159
62. Lascarrrou JB, Mialhe AF, le Gouge A, Cariou A, Dequin PF, Reignier J, Coupez E, Quenot JP, Legriel S, Pichon N, et al. NSE as a predictor of death or poor neurological outcome after non-shockable cardiac arrest due to any cause: ancillary study of HYPERION trial data. *Resuscitation*. 2021;158:193–200. doi: 10.1016/j.resuscitation.2020.11.035
63. Panchal AR, Bartos JA, Cabanas JG, Donnino MW, Drennan IR, Hirsch KG, Kudenchuk PJ, Kurz MC, Lavonas EJ, Morley PT, et al; on behalf of the Advanced Life Support Writing Group. Part 3: adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142:S366–S468. doi: 10.1161/CIR.0000000000000916
64. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, Rylander C, Wise MP, Oddo M, Cariou A, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med*. 2021;384:2283–2294. doi: 10.1056/NEJMoa2100591
65. Osman M, Munir MB, Regner S, Osman K, Benjamin MM, Kheiri B, Agrawal P, McCarthy P, Balla S, Bianco CM. Induced hypothermia in patients with cardiac arrest and a non-shockable rhythm: meta-analysis and trial sequential analysis. *Neurocrit Care*. 2021;34:279–286. doi: 10.1007/s12028-020-01034-x
66. Sandroni C, Natalini D, Nolan JP. Temperature control after cardiac arrest. *Crit Care*. 2022;26:361. doi: 10.1186/s13054-022-04238-z
67. Meyer MAS, Wiberg S, Grand J, Meyer ASP, Obilling LER, Frydland M, Thomsen JH, Josiassen J, Møller JE, Kjaergaard J, et al. Treatment effects of

- interleukin-6 receptor antibodies for modulating the systemic inflammatory response after out-of-hospital cardiac arrest (the IMICA trial): a double-blind-ed, placebo-controlled, single-center, randomized, clinical trial. *Circulation*. 2021;143:1841–1851. doi: 10.1161/circulationaha.120.053318
68. Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Borregaard B, Venø S, Sarkisian L, Mamaev D, Jensen LO, et al. Blood-pressure targets in comatose survivors of cardiac arrest. *N Engl J Med*. 2022;387:1456–1466. doi: 10.1056/NEJMoa2208687
69. Schmidt H, Kjaergaard J, Hassager C, Molstrom S, Grand J, Borregaard B, Roelsgaard Obling LE, Veno S, Sarkisian L, Mamaev D, et al. Oxygen targets in comatose survivors of cardiac arrest. *N Engl J Med*. 2022;387:1467–1476. doi: 10.1056/NEJMoa2208686
- Bernard S, Skrifvars MB, Stub D, Taccone FS, et al; Tame Study Investigators. Mild hypercapnia or normocapnia after out-of-hospital cardiac arrest. *N Engl J Med*. 2023;389:45–57. doi: 10.1056/NEJMoa2214552
71. Belohlavek J, Smalcova J, Rob D, Franek O, Smid O, Pokorna M, Horak J, Mrazek V, Kovarnik T, Zemanek D, et al. Effect of intra-arrest trans- port, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2022;327:737–747. doi: 10.1001/jama.2022.1025
72. Silverstein FS, Slomine BS, Christensen J, Holubkov R, Page K, Dean JM, Moler FW. Functional outcome trajectories after out-of-hospital pediatric cardiac arrest. *Crit Care Med*. 2016;44:e1165–e1174. doi: 10.1097/ccm.0000000000002003
73. Tong JT, Eyngorn I, Mlynash M, Albers GW, Hirsch KG. Functional neurologic outcomes change over the first 6 months after cardiac arrest. *Crit Care Med*. 2016;44:e1202–e1207. doi: 10.1097/ccm.0000000000001963
74. Lilja G, Nielsen N, Bro-Jeppesen J, Dunford H, Friberg H, Hofgren C, Horn J, Insorsi A, Kjaergaard J, Nilsson F, et al. Return to work and participation in society after out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes*. 2018;11:e003566. doi: 10.1161/CIRCOUTCOMES.117.003566
75. Descatha A, Dumas F, Bougouin W, Cariou A, Geri G. Work factors
85. Australia and New Zealand Cardiac Arrest Outcome and Determinants of ECMO Investigators. The epidemiology of in-hospital cardiac arrests in Australia: a prospective multicentre observational study. *Crit Care Resusc*. 2019;21:180–187.
86. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024.
87. Hessulf F, Karlsson T, Lundgren P, Aune S, Stromsoe A, Sodersved Kallestedt ML, Djarv T, Herlitz J, Engdahl J. Factors of importance to 30-day survival after in-hospital cardiac arrest associated with return to work in out-of-hospital cardiac arrest survivors. *Resuscitation*. 2018;128:170–174. doi: 10.1016/j.resuscitation.2018.05.021
76. Tiainen M, Vaahersalo J, Skrifvars MB, Hastbacka J, Gronlund J, Pettila V. Surviving out-of-hospital cardiac arrest: the neurological and functional outcome and health-related quality of life one year later. *Resuscitation*. 2018;129:19–23. doi: 10.1016/j.resuscitation.2018.05.011
77. van Wijnen HG, Rasquin SM, van Heugten CM, Verbunt JA, Moulaert VR. The impact of cardiac arrest on the long-term wellbeing and care-giver burden of family caregivers: a prospective cohort study. *Clin Rehabil*. 2017;31:1267–1275. doi: 10.1177/0269215516686155
78. Yaow CYL, Teoh SE, Lim WS, Wang RSQ, Han MX, Pek PP, Tan BY, Ong MEH, Ng QX, Ho AFW. Prevalence of anxiety, depression, and post-traumatic stress disorder after cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2022;170:82–91. doi: 10.1016/j.resuscitation.2021.11.023
79. Hsu Chen C, Chang CY, Yang MC, Wu JH, Liao CH, Su CP, Chen YC, Ho SY, Huang CC, Lee TH, et al. The impact of emergency interventions and patient characteristics on the risk of heart failure in patients with nontraumatic OHCA. *Emerg Med Int*. 2019;2019:6218389. doi: 10.1155/2019/6218389
80. Nishiyama C, Brown SP, May S, Iwami T, Koster RW, Beesems SG, Kuisma M, Salo A, Jacobs I, Finn J, et al. Apples to apples or apples to oranges? International variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:1599–1609. doi: 10.1016/j.resuscitation.2014.06.031
81. Grasner JT, Lefering R, Koster RW, Masterson S, Bottiger BW, Herlitz J, Whent J, Tjelmeland IB, Ortiz FR, Maurer H, et al; EuReCa ONE

- Medicare beneficiaries. *JAMA Netw Open*. 2022;5:e2148485. doi: 10.1001/jamanetworkopen.2021.48485
89. Flam B, Andersson Franko M, Skrifvars MB, Djarv T, Cronhjort M, Jonsson Fagerlund M, Martensson J. Trends in incidence and outcomes of cardiac arrest occurring in Swedish ICUs. *Crit Care Med*. 2024;52:e11–e20. doi: 10.1097/CCM.0000000000006067
90. Costa YC, Rafaelli A, Mauro V, Charask A, Tajer C, Gagliardi J; Investigators of the ARGEN-IAM-ST Registry. Cardiac arrest within the first 24 hours af-ter hospital admission in ST-segment elevation acute coronary syndromes: the ARGEN-IAM-ST registry. *Rev Argent Cardiol*. 2019;87:227–229.
91. Abe T, Olanipekun T, Igwe J, Ndausung U, Amah C, Chang A, Effoe V, Egbuche O, Ogunbayo G, Onwuanyi A. Incidence and predictors of sudden cardiac arrest in the immediate post-percutaneous coronary intervention period for ST-elevation myocardial infarction: a single-center study. *Coron Artery Dis*. 2022;33:261–268. doi: 10.1097/mca.0000000000001119
92. Li H, Wu TT, Liu PC, Liu XS, Mu Y, Guo YS, Chen Y, Xiao LP, Huang JF. Characteristics and outcomes of in-hospital cardiac arrest in adults hospitalized with acute coronary syndrome in China. *Am J Emerg Med*. 2019;37:1301–1306. doi: 10.1016/j.ajem.2018.10.003
93. Fielding-Singh V, Willingham MD, Fischer MA, Grogan T, Benharash P, Neelankavil JP. A Population-based analysis of intraoperative cardiac arrest in the United States. *Anesth Analg*. 2020;130:627–634. doi: 10.1213/ane.0000000000004477
94. Heller AR, Mees ST, Lauterwald B, Reeps C, Koch T, Weitz J. Detection of deteriorating patients on surgical wards outside the ICU by an automated MEWS-based early warning system with paging functionality. *Ann Surg*. 2020;271:100–105. doi: 10.1097/sla.0000000000002830
95. Hogan H, Hutchings A, Wulff J, Carver C, Holdsworth E, Nolan J, Welch J, Harrison D, Black N. Type of track and trigger system and incidence of in-hospital cardiac arrest: an observational registry-based study. *BMC Health Serv Res*. 2020;20:885. doi: 10.1186/s12913-020-05721-5
96. Ko BS, Lim TH, Oh J, Lee Y, Yun I, Yang MS, Ahn C, Kang H. The effectiveness of a focused rapid response team on reducing the incidence of cardiac arrest in the general ward. *Medicine (Baltimore)*. 2020;99:e19032. doi: 10.1097/md.00000000000019032
97. Mankidy B, Howard C, Morgan CK, Valluri KA, Giacomino B, Marfil E, Voore P, Ababio Y, Razjouyan J, Naik AD, et al. Reduction of in-hospital cardiac arrest with sequential deployment of rapid response team and medical emergency team to the emergency department and acute care wards. *PLoS One*. 2020;15:e0241816. doi: 10.1371/journal.pone.0241816
98. Parikh PB, Malhotra A, Qadeer A, Patel JK. Impact of sex on survival and neurologic outcomes in adults with in-hospital cardiac arrest. *Am J Cardiol*. 2020;125:309–312. doi: 10.1016/j.amjcard.2019.10.039
99. Hayek SS, Brenner SK, Azam TU, Shadid HR, Anderson E, Berlin H, Pan M, Meloche C, Feroz R, O'Hayer P, et al. In-hospital cardiac arrest in critically ill patients with COVID-19: multicenter cohort study. *BMJ*. 2020;371:m3513. doi: 10.1136/bmj.m3513
- Collaborators. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: a prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation*. 2016;105:188–195. doi: 10.1016/j.resuscitation.2016.06.004
82. Gowens P, Smith K, Clegg G, Williams B, Nehme Z. Global variation in the incidence and outcome of emergency medical services witnessed out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2022;175:120–132. doi: 10.1016/j.resuscitation.2022.03.026
83. Holmberg MJ, Ross CE, Fitzmaurice GM, Chan PS, Duval-Arnould J, Grossestreuer AV, Yankama T, Donnino MW, Andersen LW; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Annual incidence of adult and pediatric in-hospital cardiac arrest in the United States. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005580.
84. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. *JAMA*. 2019;321:1200–1210. doi: 10.1001/jama.2019.1696

100. Edwards JM, Nolan JP, Soar J, Smith GB, Reynolds E, Carnall J, Rowan KM, Harrison DA, Doidge JC. Impact of the COVID-19 pandemic on in-hospital cardiac arrests in the UK. *Resuscitation*. 2022;173:4–11. doi: 10.1016/j.resuscitation.2022.02.007
101. Andersen LW, Kim WY, Chase M, Berg KM, Mortensen SJ, Moskowitz A, Novack V, Cocchi MN, Donnino MW. The prevalence and significance of abnormal vital signs prior to in-hospital cardiac arrest. *Resuscitation*. 2016;98:112–117. doi: 10.1016/j.resuscitation.2015.08.016
102. Smith GB, Prytherch DR, Jarvis S, Kovacs C, Meredith P, Schmidt PE, Briggs J. A Comparison of the ability of the physiologic components of medical emergency team criteria and the U.K. national early warning score to discriminate patients at risk of a range of adverse clinical outcomes. *Crit Care Med*. 2016;44:2171–2181. doi: 10.1097/ccm.0000000000002000
103. Green M, Lander H, Snyder A, Hudson P, Churpek M, Edelson D. Comparison of the Between the Flags calling criteria to the MEWS, NEWS

- and the electronic Cardiac Arrest Risk
tification of deteriorating ward patients.
doi: 10.1016/j.resuscitation.2017.10.028
104. Kim M, Li G. Postoperative complications
arrest in general surgery patients. *Anesth*
10.1213/ane.0000000000002460
 105. Canino LM, Moskowitz A, Nallamothu BK.
American Heart Association's Get With The
Investigators. Trends in return of
hospital discharge for in-intensive care unit
Soc. 2023;20:1012–1019. doi:
106. Nolan JP, Soar J, Smith GB, Gwinnutt C,
Nixon F, Rowan K. National Cardiac Arrest
in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest
Audit.
Resuscitation. 2014;85:987–992. doi:
10.1016/j.resuscitation.2014.04.002
 107. Al-Dury N, Rawshani A, Israelsson
J, Stromsoe A, Aune S, Agerstrom J, Karlsson T, Ravn-Fischer A,
Herlitz J. Characteristics and outcome among 14,933 adult cases of
in-hospital cardiac arrest: a nationwide study with the emphasis on
gender and age. *Am J Emerg Med*. 2017;35:1839–1844.
doi: 10.1016/j.ajem.2017.06.012
 108. Dolmatova EV, Moazzami K, Klapholz M, Kothari N, Feurdean M,
Waller AH. Impact of hospital teaching status on mortality, length of stay
and cost among patients with cardiac arrest in the United States. *Am J*
Cardiol.
2016;118:668–672. doi: 10.1016/j.amjcard.2016.05.062
 109. Evans E, Swanson MB, Mohr N, Boulos N, Vaughan-Sarrazin M, Chan
PS, Girotra S. Epinephrine before defibrillation in patients with shock-
able in-hospital cardiac arrest: propensity matched analysis. *BMJ*.
2021;375:e066534. doi: 10.1136/bmj-2021-066534
 110. Andersen LW, Isbye D, Kjærgaard J, Kristensen CM, Darling S,
Zwisler ST, Fisker S, Schmidt JC, Kirkegaard H, Grejs AM, et al.
Effect of vasopressin and methylprednisolone vs placebo on return
of spontaneous circulation in patients with in-hospital cardiac arrest: a
randomized clinical trial. *JAMA*.
2021;326:1586–1594. doi: 10.1001/jama.2021.16628
 111. Bucy RA, Hanisko KA, Kamphuis LA, Nallamothu BK, Iwashyna TJ,
Pfeiffer PN. Suicide risk management protocol in post-cardiac
arrest survivors: development, feasibility, and outcomes. *Ann Am*
Thorac Soc. 2017;14:363–367. doi: 10.1513/AnnalsATS.201609-694BC
 112. Doherty ZB, Fletcher JA, Fuzzard KL, Leach MJ, O'Sullivan BG,
Panozzo LE, Pound GM, Saka E, Kippen RJ. Functional outcomes
following an in-hospital cardiac arrest: a retrospective cohort study.
Aust Crit Care.
2022;35:424–429. doi: 10.1016/j.aucc.2021.07.002
 113. Shao F, Li CS, Liang LR, Qin J, Ding N, Fu Y, Yang K, Zhang GQ,
Zhao L, Zhao B, et al. Incidence and outcome of adult in-hospital car-diac
arrest in Beijing, China. *Resuscitation*. 2016;102:51–56. doi:
10.1016/j.resuscitation.2016.02.002
 120. Tham LP, Wah W, Phillips R,
KD, Ko PC, Khunklai N, et al.
out-of-hospital cardiac arrests: a
Resuscitation Outcomes Study
117. doi:
121. Albrecht M, de Jonge RCJ, Nadkarni
JAE, Moors XRJ, van Zelle L.
rhythms and long-term outcome after
in Rotterdam, the Netherlands: an 18-
2021;166:110–120. doi:
122. Berg RA, Nadkarni VM, Clark AE,
Sutton RM, Wessel DL, Berner JT, et
pulmonary resuscitation in PICHs. *Crit*
114. Ngunga LM, Yonga G, Wachira B, Ezekowitz JA. Initial
rhythm and resus-citation outcomes for patients developing
cardiac arrest in hospital: data from low-middle income
country. *Glob Heart*. 2018;13:255–260. doi:
10.1016/j.gheart.2018.07.001
 115. Inoue M, Tohira H, Williams T, Bailey P, Borland M,
McKenzie N, Brink D, Finn J. Incidence, characteristics and
survival outcomes of out-of-hospital cardiac arrest in children
and adolescents between 1997 and 2014 in Perth, Western
Australia. *Emerg Med Australas*. 2017;29:69–76. doi:
10.1111/1742-6723.12657
 116. Nehme Z, Namachivayam S, Forrest A, Butt W,
Bernard S, Smith K. Trends in the incidence and outcome of
paediatric out-of-hospital cardiac ar-rest: a 17-year
observational study. *Resuscitation*. 2018;128:43–50. doi:
10.1016/j.resuscitation.2018.04.030
 117. Albargi H, Mallett S, Berhane S, Booth S, Hawkes C,
Perkins GD, Norton M, Foster T, Scholefield B. Bystander
cardiopulmonary resus-citation for paediatric out-of-hospital
cardiac arrest in England: an ob-servational registry cohort
study. *Resuscitation*. 2022;170:17–25. doi:
10.1016/j.resuscitation.2021.10.042
 118. Matsui S, Kurosawa H, Hayashi T, Takei H, Tanizawa
N, Ohnishi Y, Murata S, Ohnishi M, Henry Yoshii T,
Miyawaki K, et al. Annual patterns in the outcomes and post-
arrest care for pediatric out-of-hospital cardiac ar-rest: a
nationwide multicenter prospective registry in Japan.
Resuscitation.
2023;191:109942. doi: 10.1016/j.resuscitation.2023.109942
 119. Murasaka K, Yamashita A, Owada H, Wato Y, Inaba
H. Association be-tween the types of bystander
cardiopulmonary resuscitation and the sur-vival with good
neurologic outcome of preschool pediatric out-of-hospital
cardiac arrest cases in Japan: a propensity score matching
analysis using an extended nationwide database. *Front*
Pediatr. 2022;10:1075983. doi: 10.3389/fped.2022.1075983

- 10.1097/ccm.0000000000001484
123. Alten JA, Klugman D, Raymond TT, Cooper DS, Donohue JE, Zhang W, Pasquali SK, Gaies MG. Epidemiology and outcomes of cardiac arrest in pediatric cardiac ICUs. *Pediatr Crit Care Med*. 2017;18:935–943. doi: 10.1097/pcc.0000000000001273
124. Sperotto F, Daverio M, Amigoni A, Gregori D, Dorste A, Allan C, Thiagarajan RR. Trends in in-hospital cardiac arrest and mortality among children with cardiac disease in the intensive care unit: a systematic review and meta-analysis. *JAMA Netw Open*. 2023;6:e2256178. doi: 10.1001/jamanetworkopen.2022.56178
125. Morgan RW, Reeder RW, Ahmed T, Bell MJ, Berger JT, Bishop R, Bochkoris M, Burns C, Carcillo JA, Carpenter TC, et al. Outcomes and characteristics of cardiac arrest in children with pulmonary hypertension: a secondary analysis of the ICU-RESUS clinical trial. *Resuscitation*. 2023;190:109897. doi: 10.1016/j.resuscitation.2023.109897
126. Esangbedo ID, Byrnes J, Brandewie K, Ebraheem M, Yu P, Zhang S, Raymond T. Risk factors for peri-intubation cardiac arrest in pediatric cardiac intensive care patients: a multicenter study. *Pediatr Crit Care Med*. 2020;21:e1126–e1133. doi: 10.1097/pcc.0000000000002472
127. Holmberg MJ, Wiberg S, Ross CE, Kleinman M, Hoeyer-Nielsen AK, Donnino M, Andersen LW; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Trends in survival after pediatric in-hospital cardiac arrest in the United States. *Circulation*. 2019;140:1398–1408. doi: 10.1161/CIRCULATIONAHA.119.041667
128. Morgan RW, Wolfe HA, Reeder RW, Alvey JS, Frazier AH, Friess SH, Maa T, McQuillen PS, Meert KL, Nadkarni VM, et al. The temporal association of the COVID-19 pandemic and pediatric cardiopulmonary resuscitation quality and outcomes. *Pediatr Crit Care Med*. 2022;23:908–918. doi: 10.1097/pcc.0000000000003073
129. Abate SM, Nega S, Basu B, Tamrat K. Global mortality of children after perioperative cardiac arrest: a systematic review, meta-analysis, and meta-regression. *Ann Med Surg (Lond)*. 2022;74:103285. doi: 10.1016/j.amsu.2022.103285
130. Fernandez-Vazquez D, Ferrero-Gregori A, Alvarez-Garcia J, Gomez-Otero I, Vazquez R, Delgado Jimenez J, Worner Diz F, Bardaji A, Garcia-Pavia P, Bayes-Genis A, et al. Changes in causes of death and influence of therapeutic improvement over time in patients with heart failure and reduced ejection fraction. *Rev Esp Cardiol (Engl Ed)*. 2020;73:561–568. doi: 10.1016/j.rec.2019.09.030
131. Chen N, Callaway CW, Guyette FX, Rittenberger JC, Doshi AA, Dezfulian C, Elmer J; Pittsburgh Post-Cardiac Arrest Service. Arrest etiology among patients resuscitated from cardiac arrest. *Resuscitation*. 2018;130:33–40. doi: 10.1016/j.resuscitation.2018.06.024
132. Merlo M, Gentile P, Artico J, Cannata A, Paldino A, De Angelis G, Barbati G, Alonge M, Gigli M, Pinamonti B, et al. Arrhythmic risk stratification in patients with dilated cardiomyopathy and intermediate left ventricular dysfunction. *J Cardiovasc Med (Hagerstown)*. 2019;20:343–350. doi: 10.2459/JCM.0000000000000792
133. Boas R, Thune JJ, Pehrson S, Kober L, Nielsen JC, Videbaek L, Haarbo J, Korup E, Bruun NE, Brandes A, et al. Prevalence and prognostic association of ventricular arrhythmia in non-ischaemic heart failure patients: results from the DANISH trial. *Europace*. 2021;23:587–595. doi: 10.1093/europace/euaa341
134. Haukilahti MAE, Holmstrom L, Vahatalo J, Kentta T, Tikkanen J, Pakanen L, Kortelainen ML, Perkiomaki J, Huikuri H, Myerburg RJ, et al. Sudden cardiac death in women. *Circulation*. 2019;139:1012–1021. doi: 10.1161/CIRCULATIONAHA.118.037702
135. Cunningham JW, Vaduganathan M, Claggett BL, John JE, Desai AS, Lewis EF, Zile MR, Carson P, Jhund PS, Kober L, et al. Myocardial infarction in heart failure with preserved ejection fraction: pooled analysis of 3 clinical trials. *JACC Heart Fail*. 2020;8:618–626. doi: 10.1016/j.jchf.2020.02.007

136. Tu SJ, Gallagher C, Elliott AD, Linz D, Pittman BM, Hendriks JML, Lau DH, Sanders P, Wong CX. Alcohol consumption and risk of ventricular arrhythmias and sudden cardiac death: an observational study of 408,712 individuals. <i>Heart Rhythm</i> . 2022;19:177–184. doi: 10.1016/j.hrthm.2022.05.018	an early repolarization/J wave electrocardiographic pattern. <i>Am J Cardiol</i> . 2017;120:2073–2077. doi: 10.1016/j.amjcard.2017.08.028	
	154. Jacobs CS, Beers L, Park S, Scirica B, Henderson GV, Hsu L, Bevers M, Dworetzky BA, Lee JW. Racial and ethnic disparities in postcardiac arrest targeted temperature management outcomes. <i>Crit Care Med</i> . 2020;48:56–63. doi: 10.1097/ccm.0000000000004001	
	155. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.	
	156. El-Assaad I, Al-Kindi SG, Aziz PF. Trends of out-of-hospital sudden cardiac death among children and young adults. <i>Pediatrics</i> . 2017;140:e20171438. doi: 10.1542/peds.2017-1438	
	157. Geri G, Dumas F, Bonnetain F, Bougouin W, Champigneulle B, Arnaout M, Carli P, Marijon E, Varenne O, Mira JP, et al. Predictors of long-term functional outcome and health-related quality of life after out-	
	of-hospital cardiac arrest. <i>Resuscitation</i> . 2017;113:77–82. doi: 10.1016/j.resuscite.2017.07.018	
	Hemingway H. Clinically recorded heart rate and incidence of 12 coronary, cardiac, cerebrovascular and peripheral arterial diseases in 233,970 men and women: a linked electronic health record study. <i>Eur J Prev Cardiol</i> . 2018;25:1485–1495. doi: 10.1177/2047487318785228	
	141. Pokorney SD, Al-Khatib SM, Sun JL, Schulte P, O'Connor CM, Teerlink JR, Armstrong PW, Ezekowitz JA, Starling RC, Voors AA, et al. Sudden cardiac death after acute heart failure hospital admission: insights from ASCEND-HF. <i>Eur J Heart Fail</i> . 2018;20:525–532. doi: 10.1002/ehf.1078	

158. Elmer J, Rittenberger JC, Coppler PJ, Guyette FX, Doshi AA, Callaway CW. Long-term survival benefit from treatment at a specialty center after cardiac arrest. *Resuscitation*. 2016;108:48–53. doi: 10.1016/j.resuscitation.2016.09.008
159. Moulaert VRM, van Heugten CM, Gorgels TPM, Wade DT, Verbunt JA. Long-term outcome after survival of a cardiac arrest: a prospective longitudinal cohort study. *Neurorehabil Neural Repair*. 2017;31:530–539. doi: 10.1177/1545968317697032
142. Rattana Wong P, Upala S, Riangwiwat T, Jaruvongvanich V, Sanguankeo A, Vutthikraivit W, Chung EH. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2018;51:91–104. doi: 10.1007/s10840-017-0308-9
143. Eisen A, Ruff CT, Braunwald E, Nordio F, Corbalan R, Dalby A, Dorobantu M, Mercuri M, Lanz H, Rutman H, et al. Sudden cardiac death in patients with atrial fibrillation: insights from the ENGAGE AF-TIMI 48 trial. *J Am Heart Assoc*. 2016;5:e003735. doi: 10.1161/JAHA.116.003735
144. Fawzy AM, Bisson A, Bodin A, Herbert J, Lip GYH, Fauchier L. Atrial fibrillation and the risk of ventricular arrhythmias and cardiac arrest: a nationwide population-based study. *J Clin Med*. 2023;12:1075. doi: 10.3390/jcm12031075
145. Deo R, Norby FL, Katz R, Sotoodehnia N, Adabag S, DeFilippi CR, Kestenbaum B, Chen LY, Heckbert SR, Folsom AR, et al. Development and validation of a sudden cardiac death prediction model for the general population. *Circulation*. 2016;134:806–816. doi: 10.1161/circulationaha.116.023042
146. Aro AL, Rusinaru C, Uy-Evanado A, Reinier K, Phan D, Gunson K, Jui J, Chugh SS. Syncope and risk of sudden cardiac arrest in coronary artery disease. *Int J Cardiol*. 2017;231:26–30. doi: 10.1016/j.ijcard.2016.12.021
147. Langen VL, Niiranen TJ, Puukka P, Lehtonen AO, Hernesniemi JA, Sundvall J, Salomaa V, Jula AM. Thyroid-stimulating hormone and risk of sudden cardiac death, total mortality and cardiovascular morbidity. *Clin Endocrinol (Oxf)*. 2018;88:105–113. doi: 10.1111/cen.13472
148. Shi S, Liu T, Liang J, Hu D, Yang B. Depression and risk of sudden cardiac death and arrhythmias: a meta-analysis. *Psychosom Med*. 2017;79:153–161. doi: 10.1097/psy.0000000000000382
149. Tulppo MP, Kiviniemi AM, Lahtinen M, Ukkola O, Toukola T, Perkiömäki J, Junttila MJ, Huikuri HV. Physical activity and the risk for sudden cardiac death in patients with coronary artery disease. *Circ Arrhythm Electrophysiol*. 2020;13:e007908. doi: 10.1161/circep.119.007908
150. Awamleh Garcia P, Alonso Martin JJ, Graupner Abad C, Jimenez Hernandez RM, Curcio Ruigomez A, Talavera Calle P, Cristobal Varela C, Serrano Antolin J, Muniz J, Gomez Doblas JJ, et al. Prevalence of electrocardiographic patterns associated with sudden cardiac death in the Spanish population aged 40 years or older. results of the OFRECE study. *Rev Esp Cardiol (Engl Ed)*. 2017;70:801–807. doi: 10.1016/j.rec.2016.11.039
151. O'Neal WT, Singleton MJ, Roberts JD, Tereshchenko LG, Sotoodehnia N, Chen LY, Marcus GM, Soliman EZ. Association between QT-interval components and sudden cardiac death: the ARIC study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol*. 2017;10:e005485. doi: 10.1161/arrhythm.116.005485

160. Steinbusch CVM, van Heugten CM, Rasquin SMC, Verbunt JA, Moulaert VRM. Cognitive impairments and subjective cognitive complaints after survival of cardiac arrest: a prospective longitudinal cohort study. *Resuscitation*. 2017;120:132–137. doi: 10.1016/j.resuscitation.2017.08.007
161. Lam TJR, Yang J, Poh JE, Ong MEH, Liu N, Yeo JW, Gräsner JT, Masuda Y, Ho AFW. Long term risk of recurrence among survivors of sudden cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2022;176:30–41. doi: 10.1016/j.resuscitation.2022.04.027
162. Dezfulian C, Orkin AM, Maron BA, Elmer J, Girotra S, Gladwin MT, Merchant RM, Panchal AR, Perman SM, Starks MA, et al; on behalf of the American Heart Association Council on Cardiopulmonary Critical Care, Perioperative Resuscitation, Council on Arteriosclerosis Thrombosis and Vascular Biology, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes and Research Council on Clinical Cardiology. Opioid-associated out-of-hospital cardiac arrest: distinctive clinical features and implications for health care and public responses: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e836–e870. doi: 10.1161/CIR.0000000000000958
163. Smith G, Beger S, Vadeboncoeur T, Chikani V, Walter F, Spaite DW, Bobrow B. Trends in overdose-related out-of-hospital cardiac arrest in Arizona. *Resuscitation*. 2019;134:122–126. doi: 10.1016/j.resuscitation.2018.10.019
164. Elmer J, Lynch MJ, Kristan J, Morgan P, Gerstel SJ, Callaway CW, Rittenberger JC; Pittsburgh Post-Cardiac Arrest Service. Recreational drug overdose-related cardiac arrests: break on through to the other side. *Resuscitation*. 2015;89:177–181. doi: 10.1016/j.resuscitation.2015.01.028
165. Jayaraman R, Reinier K, Nair S, Aro AL, Uy-Evanado A, Rusinaru C, Stecker EC, Gunson K, Jui J, Chugh SS. Risk factors of sudden cardiac death in the young: multiple-year community-wide assessment. *Circulation*. 2018;137:1561–1570. doi: 10.1161/circulationaha.117.031262
166. Harmon KG, Asif IM, Maleszewski JJ, Owens DS, Prutkin JM, Salerno JC, Zigman ML, Ellenbogen R, Rao AL, Ackerman MJ, et al. Incidence and etiology of sudden cardiac arrest and death in high school athletes in the United States. *Mayo Clin Proc*. 2016;91:1493–1502. doi: 10.1016/j.mayocp.2016.07.021
167. Landry CH, Allan KS, Connelly KA, Cunningham K, Morrison LJ, Dorian P. Sudden cardiac arrest during participation in competitive sports. *N Engl J Med*. 2017;377:1943–1953. doi: 10.1056/NEJMoa1615710
168. Endres BD, Kerr ZY, Stearns RL, Adams WM, Hosokawa Y, Huggins RA, Kucera KL, Casa DJ. Epidemiology of sudden death in organized youth sports in the United States, 2007–2015. *J Athl Train*. 2019;54:349–355. doi: 10.1161/circep.117.005485
152. Waks JW, Sitlani CM, Soliman EZ, Kabir M, Ghafoori E, Biggs ML, Henrikson CA, Sotoodehnia N, Biering-Sørensen T, Agarwal SK, et al. Global electric heterogeneity risk score for prediction of sudden cardiac death in the general population: the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) studies. *Circulation*. 2016;133:2222–2234. doi: 10.4085/1062-6050-358-18

169. Waite O, Smith A, Madge L, Spring H, Noret N. Sudden cardiac death in marathons: a systematic review. *Phys Sportsmed*. 2016;44:79–84. doi: 10.1080/00913847.2016.1135036
170. Nilsson F, Borjesson M. Mortality in long-distance running races in Sweden: 2007-2016. *PLoS One*. 2018;13:e0195626. doi: 10.1371/journal.pone.0195626
153. Lanza GA, Argiro A, Mollo R, De Vita A, Spera F, Golino M, Rota E, Filice Crea F. Six-year outcome of subjects without overt heart disease with
171. Peterson DF, Siebert DM, Kucera KL, Thomas LC, Maleszewski JJ, M, Lopez-Anderson M, Suchsland MZ, Harmon KG, Drezner JA. Etiology

- of sudden cardiac arrest and death in US prospective surveillance study. *Clin J Sport* 10.1097/ism.0000000000000598
172. Vicent L, Ariza-Sole A, Gonzalez-Juanatev Lopez de Sa E, Sans-Rosello J, Querol CT, I. et al. Exercise-related severe cardiac: 2018;28:1404–1411. doi:
 173. Angelini P, Cheong BY, Lennie De Rosen Ali SW, Davis BR, Muthunillai R, Willerson ditions in sports-related sudden death: screened via cardiac magnetic resonance. 213. doi: 10.14503/thii-18-6645
 174. Goffman D, Ananth CV, Fleischer A, D'Alton Zielinski K, Chazotte C; Safe Motherhood Initiative Obstetric Hemorrhage Work Group. The New York State Safe Motherhood Initiative: early im-pact of obstetric hemorrhage bundle implementation. *Am J Perinatol*. 2019;36:1344–1350. doi: 10.1055/s-0038-1676976
 175. Bucci T, Mbizvo GK, Rivera-Caravaca JM, Mayer J, Marson AG, Abdul-Rahim AH, Lip GYH. Epilepsy-heart syndrome: incidence and clinical outcomes of cardiac complications in patients with epilepsy. *Curr Probl Cardiol*. 2023;48:101868. doi: 10.1016/j.cpcardiol.2023.101868
 - cardiac electrophysiology and 10.1038/s41467-019-12682-9
 189. Ramirez J, van Duijvenhoden S, PB, Tinker A. Common genetic ic Tneak-to-Tend interval. *Am J Hum* 10.1016/j.ajhm.2020.04.009
 190. Bezzina CR, Lahrouchi N, Priori SG. *Res*. 2015;116:1919–1936. doi:
 191. Nakano Y, Shimizu W. Genetics of 2016;61:51–55. doi:
 192. Tester DJ, Wond LCH, Chanana P, MJ, Fleming P, Jeffrev I, Cohen MC. in sudden infant death syndrome. 176. Bagnall RD, Weintraub RG, Ingles J, Dufflou J, Yeates L, Lam L, Davis AM, Thompson T, Connell V, Wallace J, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med*. 2016;374:2441–2452. doi: 10.1056/NEJMoa1510687
 177. Christiansen SL, Hertz CL, Ferrero-Miliani L, Dahl M, Weeke PE, Lu C, Ottesen GL, Frank-Hansen R, Bundgaard H, Morling N. Genetic investigation of 100 heart genes in sudden unexplained death victims

- doi: 10.1016/j.jacc.2018.01.030
193. Sun AY, Koontz JI, Shah SH, Piccini JP, Nilsson KR Jr., Craig D, Haynes C, Gregory SG, Hranitzky PM, Pitt GS. The S1103Y cardiac sodium channel variant is associated with implantable cardioverter-defibrillator events in blacks with heart failure and reduced ejection fraction. *Circ Cardiovasc Genet*. 2011;4:163–168. doi: 10.1161/CIRCGENETICS.110.958652
 194. Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, Cappuccio FP, Sagnella GA, Kass RS, Keating MT. Variant of *SCN5A* sodium channel implicated in risk of cardiac arrhythmia. *Science*. 2002;297:1333–1336. doi: 10.1126/science.1073569
 195. Fernandes FM, Silva EP, Martins RR, Oliveira AG. QTc interval prolongation in critically ill patients: prevalence, risk factors and associated medications. *PLoS One*. 2018;13:e0199028. doi: 10.1371/journal.pone.0199028
 196. Mahmud R, Gray A, Nabeebaccus A, Whyte MB. Incidence and outcomes of long QTc in acute medical admissions. *Int J Clin Pract*. 2018;72:e13250. doi: 10.1038/ejhg.2016.118
 197. Anderson HN, Bos JM, Haugaa KH, Morlan BW, Tarrell RF, Caraballo Prevalence and electrophysiological phenotype of rare *SCN5A* genetic variants identified in unexplained sudden cardiac arrest survivors. *Europace*. 2020;22:622–631. doi: 10.1093/europace/euz337
 182. Steinberg C, Padfield GJ, Champagne J, Sanatani S, Angaran P, Andrade JG, Roberts JD, Healey JS, Chauhan VS, Birnie DH, et al. Cardiac abnormalities in first-degree relatives of unexplained cardiac arrest victims: a report from the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry. *Circ Arrhythm Electrophysiol*. 2016;9:e004274. doi: 10.1161/circep.115.004274
 183. Quenin P, Kyndt F, Mabo P, Mansourati J, Babuty D, Thollet A, Guyomarch
 178. Nunn LM, Lopes LR, Syrris P, Murphy C, Plagnol V, Firman E, Dalageorgou C, Zorio E, Domingo D, Murday V, et al. Diagnostic yield of molecular autopsy in patients with sudden arrhythmic death syndrome using targeted exome sequencing. *Europace*. 2016;18:888–896. doi: 10.1093/europace/euv285
 179. Asatryan B, Schaller A, Seiler J, Servatius H, Noti F, Baldinger SH, Tanner H, Roten L, Dillier R, Lam A, et al. Usefulness of genetic testing in sudden cardiac arrest survivors with or without previous clinical evidence of heart disease. *Am J Cardiol*. 2019;123:2031–2038. doi: 10.1016/j.amjcard.2019.02.061
 180. Grondin S, Davies B, Cadrin-Tourigny J, Steinberg C, Cheung CC, Jorda P, Healey JS, Green MS, Sanatani S, Alqarawi W, et al. Importance of genetic testing in unexplained cardiac arrest. *Eur Heart J*. 2022;43:3071–3081. doi: 10.1093/eurheartj/ehac145
 181. Giudicessi JR, Ye D, Stutzman MJ, Zhou W, Tester DJ, Ackerman MJ.

PJ, Ackerman MJ. Prevalence and outcome of high-risk QT prolongation recorded in the emergency department from an institution-wide QT alert system. *J Emerg Med*. 2018;54:8–15. doi: 10.1016/j.jemermed.2017.08.073

198. Assimon MM, Brookhart MA, Flythe JE. Comparative cardiac safety of selective serotonin reuptake inhibitors among individuals receiving maintenance hemodialysis. *J Am Soc Nephrol*. 2019;30:611–623. doi: 10.1681/ASN.2018101032

199. Hofman N, Tan HL, Alders M, Kolder I, de Haij S, Mannens MM, Lombardi MP, Dit Deprez RH, van Langen I, Wilde AA. Yield of molecular and clinical testing for arrhythmia syndromes: report of 15 years' experience. *Circulation*. 2013;128:1513–1521. doi: 10.1161/CIRCULATIONAHA.112.000091

200. Itoh H, Crotti L, Aiba T, Spazzolini C, Denjoy I, Fressart V, Hayashi K, Nakajima T, Ohno S, Makiyama T, et al. The genetics underlying acquired long QT syndrome: impact for genetic screening. *Eur Heart J*. 2016;37:1456–1464. doi: 10.1093/eurheartj/ehv695

201. Bihlmeyer NA, Brody JA, Smith AV, Warren HR, Lin H, Isaacs A, Liu CT, Marten J, Radmanesh F, Hall LM, et al. ExomeChip-Wide Analysis of 95 626 Individuals Identifies 10 Novel Loci Associated With QT and JT Intervals. *Circ Genom Precis Med*. 2018;11:e001758. doi: 10.1161/CIRCGEN.117.001758

202. Roberts JD, Asaki SY, Mazzanti A, Bos JM, Tuleta I, Muir AR, Crotti L, Krahn AD, Kutiyafa V, Shoemaker MB, et al. An international multi-center evaluation of type 5 long QT syndrome: a low penetrant primary arrhythmic condition. *Circulation*. 2020;141:429–439. doi: 10.1161/CIRCULATIONAHA.119.045000

ter sudden death in young subjects: the French experience. *Circ Arrhythm Electrophysiol*. 2017;10:e005236. doi: 10.1161/circep.117.005236

184. Mullertz KM, Christiansen MK, Broendberg AK, Pedersen LN, Jensen HK. Outcome of clinical management in relatives of sudden cardiac death victims. *Int J Cardiol*. 2018;262:45–50. doi: 10.1016/j.ijcard.2018.03.022

185. Giudicessi JR, Ackerman MJ. Role of genetic heart disease in sentinel sudden cardiac arrest survivors across the age spectrum. *Int J Cardiol*. 2018;270:214–220. doi: 10.1016/j.ijcard.2018.05.100

186. Rucinski C, Winbo A, Marcondes L, Earle N, Stiles M, Stiles R, Hooks

D, Neas K, Hayes I, Crawford J, et al. A population-based registry of patients with inherited cardiac conditions and resuscitated cardiac arrest. *J Am Coll Cardiol*. 2020;75:2698–2707. doi: 10.1016/j.jacc.2020.04.004

187. Ashar FN, Mitchell RN, Albert CM, Newton-Cheh C, Brody JA, Muller-Nurasyid M, Moes A, Meitinger T, Mak A, Huikuri H, et al. A comprehensive evaluation of the genetic architecture of sudden cardiac arrest. *Eur Heart J*. 2018;39:3961–3969. doi: 10.1093/eurheartj/ehy474

- 10.1161/CIRCULATIONAHA.119.043114
203. Schwartz PJ. 1970-2020: 50 years of research on the long QT syndrome-from almost zero knowledge to precision medicine. *Eur Heart J*. 2021;42:1063–1072. doi: 10.1093/eurheartj/ehaa769
204. Lahrouchi N, Tadros R, Crotti L, Mizusawa Y, Postema PG, Beekman L, Walsh R, Hasegawa K, Barc J, Ernsting M, et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. *Circulation*. 2020;142:324–338. doi: 10.1161/CIRCULATIONAHA.120.045956
205. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med*. 2020;383:2041–2052. doi: 10.1056/NEJMoa2019014
206. Saleh M, Gabriels J, Chang D, Kim BS, Mansoor A, Mahmood E, Makker P, Ismail H, Goldner B, Willner J, et al. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. *Circ Arrhythm Electrophysiol*. 2020;13:e008662.
188. Norland K, Sveinbjornsson G, Thorolfsson RB, Davidsson roquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. *Circ Arrhythm Electrophysiol*. 2020;13:e008662.
- van Setten J, Asselbergs FW, et al. Sequence variants with large effects on . doi: 10.1161/CIRCEP.120.008662

207. Maraj I, Hummel JP, Taoutel R, Chamoun R, Workman V, Li C, Tran L, DelVecchio A, Howes C, Akar JG. Incidence and determinants of QT interval prolongation in COVID-19 patients treated with hydroxychloroquine and azithromycin. *J Cardiovasc Electrophysiol*. 2020;31:1904–1907. doi: 10.1111/jce.14594
208. O'Connell TF, Bradley CJ, Abbas AE, Williamson BD, Rusia A, Tawney AM, Gaines R, Schott J, Dmitrienko A, Haines DE. Hydroxychloroquine/azithromycin therapy and QT prolongation in hospitalized patients with COVID-19. *JACC Clin Electrophysiol*. 2021;7:16–25. doi: 10.1016/j.jacep.2020.07.016
209. Si D, Du B, Ni L, Yang B, Sun H, Jiang N, Liu G, Massé S, Jin L, Nanthakumar J, et al. Death, discharge and arrhythmias among patients with COVID-19 and cardiac injury. 210. Giudicessi JR, Roden DM, Wilde AAM, Ackerman MJ. Genetic susceptibility for COVID-19-associated sudden cardiac death in African Americans. *Heart Rhythm*. 2020;17:1487–1492. doi: 10.1016/j.hrthm.2020.04.045
211. Adler A, Novelli V, Amin AS, Abiusi E, Care M, Nannenber EA, Feilotter H, Amenta S, Mazza D, Bikker H, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. *Circulation*. 2020;141:418–428. doi: 10.1161/CIRCULATIONAHA.119.043132
212. Cross B, Homoud M, Link M, Foote C, Garlitski AC, Weinstock J, Estes NAM, Weinstock J, Estes NA 3rd. The short QT syndrome. *J Interv Card Electrophysiol*. 2011;31:25–31. doi: 10.1007/s10840-011-9566-0
213. Kobza R, Roos M, Niggli B, Abacherli R, Lupi GA, Frey F, 226. Cerrone M, Lin X, Zhang M, Agullo-Pascual E, Pfenniger A, Chkourko Guskys H, Novelli V, Kim C, Tirasawadichai T, Judge DP, et al. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada syndrome phenotype. *Circulation*. 2014;129:1092–1103. doi: 10.1161/CIRCULATIONAHA.113.003077
227. Barc J, Tadros R, Glinge C, Chiang DY, Jouni M, Simonet F, Jurgens SJ, Baudic M, Nicastro M, Potet F, et al; Nantes Referral Center for Inherited Cardiac Arrhythmias. Genome-wide association analyses identify new Brugada syndrome risk loci and highlight a new mechanism of sodium
- Schmid JJ, Erne P. Prevalence of long and short QT in a young population of 41,767 pre-dominantly male Swiss conscripts. *Heart Rhythm*. 2009;6:652–657. doi: 10.1016/j.hrthm.2009.01.009
214. Providencia R, Karim N, Srinivasan N, Honarbakhsh S, Vidigal Ferreira MJ, Goncalves L, Marijon E, Lambiase PD. Impact of QTc formulae in the prevalence of short corrected QT interval and impact on probability and diagnosis of short QT syndrome. *Heart*. 2018;104:502–508. doi: 10.1136/heartjnl-2017-311673
215. Guerrier K, Kwiatkowski D, Czošek RJ, Spar DS, Anderson JB, Knillans TK. Short QT interval prevalence and clinical outcomes in a pediatric population. *Circ Arrhythm Electrophysiol*. 2015;8:1460–1464. doi: 10.1161/circep.115.003256
216. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, Probst V, Blanc JJ, Sbragia P, Dalmasso P, et al. Long-term follow-up of patients with short QT syndrome. *J Am Coll Cardiol*. 2011;58:587–595. doi:

- Clinical Genome Resource Consortium. Reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for Brugada syndrome. *Circulation*. 2018;138:1195–1205. doi: 10.1161/CIRCULATIONAHA.118.035070
229. Walsh R, Adler A, Amin AS, Abiusi E, Care M, Bikker H, Amenta S, Feilottter H, Nannenber EA, Mazzarotto F, et al. Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. *Eur Heart J*. 2022;43:1500–1510. doi: 10.1093/eurheartj/ehab687
230. Roston TM, Yuchi Z, Kannankeril PJ, Hathaway J, Vinocur JM, Etheridge SP, Potts JE, Maginot KR, Salerno JC, Cohen MI, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. *Europace*. 2018;20:541–547. doi: 10.1093/europace/euw389
231. Kawata H, Ohno S, Aiba T, Sakaguchi H, Miyazaki A, Sumitomo N, Kamakura T, Nakajima I, Inoue YY, Miyamoto K, et al. Catecholaminergic polymorphic ventricular tachycardia (CPVT) associated with ryanodine receptor (RyR2) gene mutations: long-term prognosis after initiation of medical treatment. *Circ J*. 2016;80:1907–1915. doi: 10.1253/circj.CJ-16-0250
232. Roston TM, Haji-Ghassemi O, LaPage MJ, Batra AS, Bar-Cohen Y, Anderson C, Lau YR, Maginot K, Gebauer RA, Etheridge SP, et al. Catecholaminergic polymorphic ventricular tachycardia patients with multiple genetic variants in the PACES CPVT Registry. *PLoS One*. 2018;13:e0205925. doi: 10.1371/journal.pone.0205925
233. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, et al. Diagnosis of arrhythmic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533–1541. doi: 10.1093/eurheartj/ehq025
217. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:1046–1059. doi: 10.1016/j.jacc.2018.06.037
218. Quan XQ, Li S, Liu R, Zheng K, Wu XF, Tang Q. A meta-analytic review of prevalence for Brugada ECG patterns and the risk for death. *Medicine (Baltimore)*. 2016;95:e5643. doi: 10.1097/md.0000000000005643
219. Benito B, Brugada J, Brugada R, Brugada P. Brugada syndrome. *Rev Esp Cardiol*. 2009;62:1297–1315. doi: 10.1016/s1885-5857(09)73357-2
220. Milman A, Andorin A, Gourraud JB, Postema PG, Sacher F, Mabo P, Kim SH, Juang JJM, Maeda S, Takahashi Y, et al. Profile of patients with Brugada syndrome presenting with their first documented arrhythmic event: data from the Survey on Arrhythmic Events in BRUGADA Syndrome (SABRUS). *Heart Rhythm*. 2018;15:716–724. doi: 10.1016/j.hrthm.2018.01.014
221. Rodríguez-Mañero M, Jordá P, Hernandez J, Muñoz C, Grima EZ, García-Fernández A, Cañadas-Godoy MV, Jiménez-Ramos V, Oloriz T, Basterra N, et al. Long-term prognosis of women with Brugada syndrome and electrophysiological study. *Heart Rhythm*. 2021;18:664–671. doi: 10.1016/j.hrthm.2020.12.020
222. Rattanawong P, Kewcharoen J, Kanitsoraphan C, Barry T, Shanbhag A, Ko

234. Mattesi G, Zorzi A, Corrado D, Cipriani A. Natural history of arrhythmogenic cardiomyopathy. *J Clin Med*. 2020;9:878. doi: 10.3390/jcm9030878
235. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, Pilichou K, Domingo AM, Murray B, Cadrin-Tourigny J, et al. International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the clinical genome resource framework. *Circ Genom Precis Med*. 2021;14:e003273. doi: 10.1161/CIRCGEN.120.003273
236. Miles C, Finocchiaro G, Papadakis M, Gray B, Westaby J, Ensam B, Basu J, Parry-Williams G, Papatheodorou E, Paterson C, et al. Sudden death and left ventricular involvement in arrhythmogenic cardiomyopathy. *Circulation*. 2019;139:1786–1797. doi: 10.1161/CIRCULATIONAHA.118.037230
237. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, Monteforte N, Memmi M, Gambelli P, Novelli V, et al. Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol*. 2016;68:2540–2550. doi: 10.1016/j.jacc.2016.09.951
238. Agbaedeng TA, Roberts KA, Colley L, Noubiap JJ, Oxborough D. Incidence and predictors of sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy: a pooled analysis. *Europace*. 2022;24:1665–1674. doi: 10.1093/europace/euac014
- NL, Vutthikraivit W, Home M, Agasthi P, Ashraf H, et al. Does the age of sudden cardiac death in family members matter in Brugada syndrome? *J Am Heart Assoc*. 2021;10:e019788. doi: 10.1161/jaha.120.019788
223. David JP, Lisewski U, Crump SM, Jepps TA, Bocksteins E, Wilck N, Lossie J, Roepke TK, Schmitt N, Abbott GW. Deletion in mice of X-linked, Brugada syndrome- and atrial fibrillation-associated *Kcne5* augments ventricular KV currents and predisposes to ventricular arrhythmia. *FASEB J*. 2019;33:2537–2552. doi: 10.1096/fj.201800502R
224. Offerhaus JA, Bezzina CR, Wilde AAM. Epidemiology of inherited arrhythmias. *Nat Rev Cardiol*. 2020;17:205–215. doi: 10.1038/s41569-019-0266-2
225. Ingles J, Bagnall RD, Yeates L, McGrady M, Berman Y, Whalley D, Dufflou J, Semsarian C. Concealed arrhythmogenic right ventricular cardiomyopathy in sudden unexplained cardiac death events. *Circ Genom Precis Med*. 2018;11:e002355. doi: 10.1161/CIRCGEN.118.002355

239. Bhonsale A, Te Riele ASJM, Sawant AC, Groeneweg JA, James CA, Murray B, Tichnell C, Mast TP, van der Pols MJ, Cramer MJM, et al. Cardiac phenotype and long-term prognosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with late presentation. *Heart Rhythm*. 2017;14:883–891. doi: 10.1016/j.hrthm.2017.02.013
240. Hoedemakers S, Vandenberk B, Liebrechts M, Bringmans T, Vriesendorp P, Willems R, Van Cleemput J. Long-term outcome of conservative and invasive treatment in patients with hypertrophic obstructive cardiomyopathy. *Acta Cardiol*. 2019;74:253–261. doi: 10.1080/00015385.2018.1491673 241. Aro AL, Nair SG, Reinier K, Jayaraman R, Stecker EC, Uy-Evanado A, Rusinaru C, Jui J, Chugh SS. Population burden of sudden death associated with hypertrophic cardiomyopathy. *Circulation*. 2017;136:1665–1667. doi: 10.1161/CIRCULATIONAHA.117.030616

242. Abdelfattah OM, Martinez M, Sayed A, A. Masri A. Winters SL, Kanadia SR, Maron global trends of the incidence of sudden cardiomyopathy. *JACC Clin Electrophysiol*. 10.1016/j.jacep.2022.07.012
243. Patton KK, Ellinor PT, Ezekowitz M, Kowey Turakhia M, Wann P, Viskin S; on behalf of Electrocardiography and Arrhythmias Cardiology and Council on Functional Electrocardiographic early repolarization: a American Heart Association. *Circulation*. 10.1161/cir.0000000000000388
244. Antzelevitch C, Yan GX, Ackerman MJ, Gussak I, Hasdemir C, Horie M, Huikuri H, et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. patients with repaired tetralogy of *Heart*. 2014;100:247–253. doi: 10.1093/eurheartj/ehu001
254. Gatzoulis MA, Balaji S, Webb SA, Rosenthal M, Nakazawa M, Moller JH. tors for arrhythmia and sudden onv of Fallot: a multicentre study. 10.1016/s0140-6736(00)02714-8
255. Birnie DH, Sauer WH, Booun F, Judson MA, Kron J, Mehta D. Cosedis sus statement on the diagnosis and ated with cardiac sarcoidosis. *Heart* 10.1016/j.hrthm.2014.03.043
256. Salama A, Abdullah A, Wahab A. *Europace*. 2017;19:665–694. doi: 10.1093/europace/euw235

sarcoidosis and ventricular arrhythmias: a rare association of a rare dis-ease: a retrospective cohort study from the National Inpatient Sample and current evidence for management. *Cardiol J*. 2020;27:272–277. doi:

245. Sun GZ, Ye N, Chen YT, Zhou Y, Li Z, Sun YX. Early repolarization pattern in the general population: prevalence and associated factors. *Int J Cardiol*. 2017;230:614–618. doi: 10.1016/j.ijcard.2016.12.045
246. De Lazzari C, Genuini I, Gatto MC, Cinque A, Mancone M, D'Ambrosi A, Silvetti E, Fusto A, Pisanelli DM, Fedele F. Screening high school students in Italy for sudden cardiac death prevention by using a telecardiology device: a retrospective observational study. *Cardiol Young*. 2017;27:74–81. doi: 10.1017/s1047951116000147
247. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquie JL, Nogami A, Babuty D, Yli-Mayry S, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med*. 2008;358:2016–2023. doi: 10.1056/NEJMoa071968
248. Rosso R, Glikson E, Belhassen B, Katz A, Halkin A, Steinvil A, Viskin S. Distinguishing “benign” from “malignant early repolarization”: the value of the ST-segment morphology. *Heart Rhythm*. 2012;9:225–229. doi: 10.5603/CJ.a2018.0104
249. Holkeri A, Eranti A, Haukilahti MAE, Kerola T, Kentta TV, Tikkanen JT, Rissanen H, Heliövaara M, Knekt P, Junttila MJ, et al. Impact of age and sex on the long-term prognosis associated with early repolarization in the general population. *Heart Rhythm*. 2020;17:621–628. doi: 10.1016/j.hrthm.2019.10.026
250. Siebermair J, Sinner MF, Beckmann BM, Laubender RP, Martens E, Sattler S, Fichtner S, Estner HL, Kaab S, Wakili R. Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. *Europace*. 2016;18:718–725. doi: 10.1093/europace/euv301
251. Dukes JW, Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK, Psaty BM, Sotoodehnia N, Gottdiener JS, et al.

257. Tran HV, Ash AS, Gore JM, Darling CE, Kiefe CI, Goldberg RJ. Twenty-five year trends (1986-2011) in hospital incidence and case-fatality rates of ventricular tachycardia and ventricular fibrillation complicating acute myocardial infarction. *Am Heart J*. 2019;208:1–10. doi: 10.1016/j.ahj.2018.10.007
258. Ning X, Ye X, Si Y, Yang Z, Zhao Y, Sun Q, Chen R, Tang M, Chen K, Zhang X, et al. Prevalence and prognosis of ventricular tachycardia/ventricular fibrillation in patients with post-infarction left ventricular aneurysm: analysis of 575 cases. *J Electrocardiol*. 2018;51:742–746. doi: 10.1016/j.jelectrocard.2018.03.010
259. Konig S, Boudriot E, Arya A, Lurz JA, Sandri M, Erbs S, Thiele H, Hindricks G, Dinov B. Incidence and characteristics of ventricular tachycardia in patients after percutaneous coronary revascularization of chronic total occlusions. *PLoS One*. 2019;14:e0225580. doi: 10.1371/journal.pone.0225580
260. Haegeli LM, Ercin E, Steffel J, Wolber T, Tanner FC, Jenni R, Gamperli O, Saguner AM, Luscher TF, Brunckhorst C, et al. Incidence and prognosis of ventricular arrhythmias in patients with congenital left ventricular aneurysms or diverticula. *Am J Med*. 2015;128:653.e1–653.e6. doi: 10.1016/j.amjmed.2015.01.001
261. Hai JJ, Un KC, Wong CK, Wong KL, Zhang ZY, Chan PH, Lau CP, Siu CW, Tse HF. Prognostic implications of early monomorphic and non-monomorphic tachyarrhythmias in patients discharged with acute coronary syndrome. *Heart Rhythm*. 2018;15:822–829. doi: 10.1016/j.hrthm.2018.02.016
262. Arunachalam K, Lakshmanan S, Maan A, Kumar N, Dominic P. Impact of drug induced long QT syndrome: a systematic review. *J Clin Med Res*. 2018;10:384–390. doi: 10.14740/jocmr3338w
263. Arizona Center for Education and Research on Therapeutics. QTDrugs list: CredibleMeds website. Accessed April 22, 2024.
- Ventricular ectopy as a predictor of heart failure and death. *J Am Coll Cardiol*. 2015;66:101–109. doi: 10.1016/j.jacc.2015.04.062
252. Khairy P, Aboulhosn J, Gurvitz MZ, Opatowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation*. 2010;122:868–875. doi: 10.1161/circulationaha.109.928481
253. Valente AM, Gauvreau K, Assenza GE, Babu-Narayan SV, Schreier J, Gatzoulis MA, Groenink M, Inuzuka R, Kilner PJ, Koyak Z, et al. Contemporary predictors of death and sustained ventricular tachycardia in

264. Centers for Disease Control and Prevention and National Center for Health
tion: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.

265. Tseng ZH, Olgin JE, Vittinghoff E, Ursell PC, Kim AS, Sporer K, Yeh C, Colburn
sy characterization of sudden cardiac death: POST SCD study. *Circulation*.
2018;137:2689–2700. doi: 10.1161/CIRCULATIONAHA.117.033427

Statistics. National Vital Statistics System: public use data file documenta-

B, Clark NM, Khan R, et al. Prospective countywide surveillance and autop-

20. SUBCLINICAL
ATHEROSCLEROSIS *See Charts 20-1*

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Multiple complementary imaging modalities facilitate the detection and quantification of atherosclerosis at different stages and within various vascular beds. Early identification of subclinical atherosclerosis can guide preventive treatment (eg, aspirin, antihypertensives, lipid-lowering therapy, GLP1-RA) to prevent clinical manifestations of atherosclerosis such as MI, stroke, or PAD. Several modalities can be used for assessing atherosclerosis, including noncontrast chest CT, CCTA, B-mode ultrasound, brachial artery reactivity testing, aortic and carotid MRI, and tonometric measurement of vascular compliance. Among these modalities, the role of CAC in assessing cardiovascular risk is particularly well established. The 2018 Cholesterol Clinical Practice

Coronary Atherosclerosis
Background

- CAC quantifies the calcified within the coronary arteries using noncontrast CT and correlates strongly with the total plaque reported with an Agatston score based on the total area of calcium deposits and the density of coronary calcium.
 - CCTA is a contrasted CT scan that can visualize calcified and noncalcified atherosclerotic and assesses for coronary
- Guideline¹ and the 2019 CVD Primary Prevention Clinical Practice Guide-lines² recommend using a CAC score to guide decisions on statin therapy in intermediate-risk or selected border-line-risk adults (10-year ASCVD risk, 5%–19%). This approach is advised if statin therapy decisions remain uncertain after 10-year ASCVD risk is estimated and risk enhancers are considered. The US-based National Lipid Association³ also recommends the use of CAC to guide preventive strategies for ASCVD risk reduction, as do professional organizations around the globe such as those in Europe, Canada, China, Australia, and the United

Prevalence and Risk Factors

(See Charts 20-1 through 20-4)

- The NHLBI's MESA, a study of White adults, Black adults, Chinese adults, and Hispanic adults, measured CAC in 6814 participants 45 to 84 years of age (mean, 63 years), including White men and women (n=2619), Black men and women (n=1898), Hispanic men and women (n=1494), and Chinese men and women (n=803).⁵

- The overall prevalence of CAC in these 4 ethnic groups was 70.4%, 52.1%, 56.5%, and 59.2%, respectively, among males and 44.6%, 36.5%, 34.9%, and 41.9%, respectively, among females.

- The prevalence and 75th percentile levels of CAC were highest in White males and lowest in Black females and Hispanic females. Ethnic differences persisted after adjustment for risk factors, with a CAC prevalence that was 22% lower in Black people, 15% lower in Hispanic people, and 8% lower in Chinese people than in White

Kindgom.⁴

people.

This chapter begins with a focus on coronary atherosclerosis followed by statistics on carotid atherosclerosis and includes statistics on other

subclinical atherosclerosis imaging studies. The chapter prioritizes discussion of

- On average, the prevalence of CAC among women is comparable to that among men who are 10 to 15 years younger (Chart 20-1).⁶
- The prevalence of atherosclerosis increases with social determinants of health and health equity in relation to subclinical atherosclerosis. Furthermore, the last section of the chapter provides statistics on subclinical atherosclerosis in relation to healthy lifestyle behaviors and preventive medications.

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups

age:

very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- In a harmonized dataset analysis of 19 725 Black individuals and White individuals 30 to 45 years of age from CARDIA, the CAC Consortium, and the Walter Reed Cohort, the prevalence of CAC >0 among White males, Black males, White females, and Black females was 26%, 16%, 10%, and 7%, respectively (Chart 20-2).
- Among MESA participants 60 to 70 years of age, the prevalence of CAC was ≈44% for women and 68% for men (unpublished tabulation using MESA data⁷).
- Among MESA and ARIC participants ≥75 years of age, the prevalence of CAC was 85% for women and 90% to 95% for men, and for participants ≥90 years of age, there was a >95% prevalence of CAC regardless of sex.⁸

- To illustrate the variability of CAC habits, a forager-individuals living in the lowest reported levels of CAC recorded to date.⁹
 - Overall, in the population 50% female), 85% of CAC, and even in 65% remained free of CAC, emphasize the importance tors and that coronary can be avoided by den of CAD risk factors.⁹
- In US adults who are free of CAC at baseline, sub-
 - In 937 apparently healthy members of individuals with high lipoprotein(a) levels CAC ≥ 100 (OR, 1.79 [95% CI, 1.08–1.38]).¹⁵
 - In a study-level meta-participants (6699 living with HIV; mean age, 52 Black), the prevalence of 49% (95% CI, 47%–52%) in with HIV versus 20% (95% CI, 17%–23%) in individuals not living with HIV.

- The 10-year trends in CAC progression among individuals without clinical CVD in MESA were assessed (Chart 20-4).
 - The duration of risk factor exposure is associated with CAC, as exemplified in an analysis of exposure to diabetes and prediabetes in 3628 participants in
 - The 10-year trends in CAC progression among individuals without clinical CVD in MESA were assessed (Chart 20-4).
 - The duration of risk factor exposure is associated with CAC, as exemplified in an analysis of exposure to diabetes and prediabetes in 3628 participants in
- sequent development of CAC is strongly correlated with a person's risk factor profile. In 3116 MESA participants (58±9 years of age; 63% women) who had no detectable CAC at baseline and were followed up over 10 years, 53%, 36%, and 8% of individuals had CAC >0, CAC >10, and CAC >100, respectively, at 10 years.¹⁰ A rescanning interval of 3 years was suggested for high-risk individuals and 6 to 7 years for low-risk individuals.

- The mean age at the baseline examination was 67 years; 47.4% were men. Detectable CAC was evaluated in White participants, Black participants, Hispanic participants, and Chinese participants, with >50% prevalence at baseline.
- CAC severity was also evaluated at baseline and 10 years. After adjustment for age, gender, ethnicity, and type of CT scanner, the proportion of participants with no CAC decreased over time from 40.7% to 32.6% ($P=0.007$). The proportions increased from 29.9% to 37.0% ($P=0.01$)

CARDIA.¹¹

 - For each additional 5 years of exposure to diabetes and prediabetes, the aHR for CAC was 1.15 (95% CI, 1.06–1.25) and 1.07 (95% CI, 1.01–1.13), respectively.

for those with CAC 1 to 99 and from 14.7%
 • In 2359 asymptomatic adults (including 47%

to 17.7% ($P=0.14$) for those with CAC 100 to 399, whereas the proportion with CAC ≥ 400 decreased from 9.1% to 7.2% ($P=0.11$).

CAC and Incidence of ASCVD Events (CHD and

Hispanic) of the Miami Heart Study who underwent *Stroke)*

CCTA, 49% of participants had coronary plaque, 6% had stenosis $\geq 50\%$, and 7% had plaques with high-risk features (Chart 20-3).

- In SCAPIS, among 25 182 middle-aged individuals without known CHD who underwent

CCTA, 42% had coronary atherosclerosis and 5.2% had $\geq 50\%$ stenosis.¹² Among those with CAC=0, 5.5% had noncalcified atherosclerosis and 0.4% had $\geq 50\%$

(See Charts 20-5 and 20-6)

- The NHLBI's MESA reported the association follow-up of 3.9 years among a population-based 27% Black participants, 22% Hispanic participants,
 - Chart 20-5 shows the HRs associated with stenosis.
- Studies have identified APO, obesity, elevated lipoprotein(a), and inflammatory disorders as being associated with calcified or noncalcified

of CAC with incident CHD events over a median sample of 6722 individuals (39% White participants, and 12% Chinese participants).¹⁶

CAC scores of 1 to 100, 101 to 300, and coronary atherosclerosis:

- Among 10 528 females in Sweden with ≥ 1 deliv-

>300 compared with CAC=0 after adjustment for standard risk factors. People with CAC 1 to 100 had ≈4 times greater risk, and those with CAC scores >100 were 7 to 10 times more likely to experience a CHD event than those without CAC.

eries in 1973 or later who later participated in an imaging study at a median of 57.3 years of age in 2013 to 2018, atherosclerosis was present by CCTA in 32.1% (95% CI, 30.0%–34.2%) of females with a history of any APO.¹³ This preva-

- CAC provided similar predictive value for CHD events in White individuals, Chinese individuals, Black individuals, and Hispanic individuals (HRs ranging from 1.15–1.39 for each doubling of CAC).
Prevalence was higher compared with females without any history of APO (prevalence difference, 3.8% [95% CI, 1.6%–6.1%]; PR, 1.14 [95% CI,

- In an analysis of 66 636 participants from the CAC Consortium, higher CAC scores were associated with an increased risk of SCD with a nearly 5-fold
1.06–1.22]).

increased risk for individuals with CAC ≥ 1000 (sub-distribution HR, 4.9 [95% CI, 2.6–9.9]).¹⁷

- In 13 397 low-risk younger adults 30 to 49 years of age of the Walter Reed Cohort, a CAC score >100 was associated with an HR of 5.16 (95% CI, 3.29–8.10) for MI, 3.14 (95% CI, 2.26–4.36) for MACEs (MI, stroke, or CVD death), 1.73 (95% CI, 1.01–2.97) for stroke, and 2.08 (95% CI, 1.13–3.82) for all-cause mortality.¹⁸
- In analysis of 4511 participants without known CAD who were compared with 438 individuals with a prior ASCVD event in the CONFIRM international registry, there was a similar MACE event rate of ≈ 53 per 1000 PY for individuals with CAC >300 and those with a history of ASCVD. Over a median of 4 years follow-up, there was a similar cumulative incidence of MACEs for individuals with CAC >300 or a prior ASCVD event ($P=0.329$; Chart 20-6).
- In MESA, individuals with a very high CAC score ≥ 1000 ($n=257$) had a MACE rate of 3.4 per 100 PY, which was similar to the secondary prevention population in the FOURIER trial who had a prior ASCVD event plus at least 1 additional major or 2 minor ASCVD risk factors.¹⁹ After adjustment for age, sex, and traditional cardiovascular risk factors, individuals with CAC ≥ 1000 had a 5-fold greater risk of CVD mortality compared with those with CAC=0.²⁰
- During 13.2 years of follow-up in asymptomatic individuals from the MESA study ($n=4512$; 61.9 years of age; 52.5% women; 36.8% White, 29.3% Black, 22.2% Hispanic, and 11.7% Chinese), an independent association with ASCVD risk was observed for elevated lipoprotein(a) levels (HR, 1.29 [95% CI, 1.04–1.61]) and elevated CAC scores (score of ≥ 100 versus 0: HR, 2.66 [95% CI, 2.07–3.43]).²¹ No lipoprotein(a)-by-CAC interaction was observed. This study noted similar findings when the same analyses were performed with the following:
 - 2.2 Agatston units per year. Among MESA participants with CAC >0 at baseline, 85% had progression of CAC with an average CAC progression of 29 Agatston units/y over a median follow-up of 7.6 years. Among those with CAC >0 at baseline, there was a

prevalent CAC, an association emerged between sex hormones and CAC progression over a median of 4.7 years.²³

Social Determinants of Health/Health Equity in CAC and Coronary Atherosclerosis

In addition to the differences by race and ethnicity detailed previously, differences in CAC or associations with CAC have been described by factors such as sex, unemployment, and exposure to air pollution:

- In 1125 Black participants in the CARDIA study, exposure to a low versus high level of neighborhood-level racial residential segregation in young adulthood was associated with a lower risk of developing midlife CAC (rate ratio, 0.52 [95% CI, 0.28–0.98]).²⁴ This association was attenuated and lost significance after adjustment for cardiovascular risk factor burden (rate ratio, 0.56, [95% CI, 0.29–1.09]).
- In 1429 participants from the MESA study, insomnia symptoms were independently associated with an 18% higher prevalence of CAC (PR, 1.18 [95% CI, 1.04–1.33]) among women but not men (PR, 1.00 [95% CI, 0.91–1.08]).²⁵
- In 312 females (mean age, 50.8 years), after adjustment for potential confounders, depression, health behaviors, and CVD risk factors, psychosocial well-being was not significantly associated with CAC progression.²⁶ However, among the 134 females with baseline CAC >0 , well-being was associated with less CAC progression (RR, 0.921 [95% CI, 0.852–0.995]; $P=0.037$)
- stepwise increased cumulative incidence of CHD with higher annual CAC progression, and for every 100–Agatston units annual increase, there was a 1.3 (95% CI, 1.1–1.5) higher adjusted hazard for total CHD events.²²
- In a MESA study of 2759 postmenopausal women, despite no association between sex hormones and

CAC, Carotid IMT, CT Angiography, and Risk

Prediction

- In MESA, the investigators reported the follow-up of 6779 men and women in 4 ethnic groups over 9.5 years and compared the predictive utility of carotid IMT, carotid plaque, and CAC (presence and burden).²⁹
 - For CVD and CHD prediction: Compared with traditional risk factors, C statistics for CVD (C=0.756) and CHD (C=0.752) increased the most by the addition of CAC presence (CVD, C=0.776; CHD, C=0.784; $P<0.001$) followed by

carotid plaque presence
($C=0.757$; $P<0.05$). Mean
(for age, gender, and race)
events.

- For stroke/TIA prediction:
factors ($C=0.782$), carotid
($C=0.787$; $P=0.045$), but not
 $P=0.438$), added to risk

- In 4724 participants of the
aged to older adults with

of whom had follow-up ultrasounds, prevalent and
incident common carotid artery plaque was
associ- ated with incident CVD (incident plaque
HR, 1.95 [95% CI, 1.14–3.3]) for CVD and HR,
2.01 [95% CI, 1.01–3.99] for stroke].³⁰

- In the CONFIRM study, coronary atherosclerosis

Carotid IMT is thought to be
of atherosclerosis because
development of

- Carotid IMT methods may vary
measured (common carotid,
measurement of near and far
average (more common) or
- Accurate measurement of
skilled ultrasonographer
for middle-aged patients are
presence, extent, and severity
quantified by CT angi- ography
improved risk prediction over
traditional risk factors (C statistic,
0.64 versus 0.73; $P=0.008$).³¹

vary during the cardiac cycle.³⁹

• Carotid IMT is greater with older age and in men compared with women of the same age. Thus, a ≥ 75 th percentile carotid IMT thickening is commonly considered to identify high ASCVD risk.⁴⁰ • Stroke risk was higher with greater degrees of asymptomatic carotid stenosis (OR, 2.5 for stenosis 80%–99% versus 50%–79% [95% CI, 1.8–3.5]; $P < 0.0001$) in a large meta-analysis of 11 cohort

studies.⁴¹

• Although CT angiography can measure coronary artery stenosis, the total burden of atherosclerosis is the primary predictor of CVD risk. In a study of 23 759 patients from the Western Denmark Heart Registry, patients with obstructive coronary artery stenosis did not have a higher risk compared with those with nonobstructive coronary artery stenosis and a similar CAC score.³² For example, the CVD and mortality event rate per 1000-PY follow-up for patients with CAC ≥ 100 to 399 and obstructive CAD was 17.3 (95% CI, 14.5–20.6) compared with 17.9 (95% CI, 14.8–21.7) for patients with CAC ≥ 100 to 399 and nonobstructive CAD.

• In 4184 young to middle-aged asymptomatic individuals in the PESA cohort in whom carotid ultrasound and CAC were performed, elastic net machine-learning models identified a score based on age, HbA1c, TC/HDL, leukocyte volume, and hemoglobin predicting prevalent

and progression of subclinical atherosclerosis and CVD risk.³³ This score was externally validated in the AWHs of males of similarly age.

• Conversely, a number of studies have demonstrated that the absence of atherosclerosis is strongly predictive of low CVD risk.^{34–36} In a study of 6814 participants from the MESA cohort, CAC=0 was associated with the lowest risk for CVD and had the greatest downward change in net reclassification index of 13.8 compared with the next largest net reclassification index of 4.9 for carotid IMT < 25 th percentile.³⁷

Carotid IMT and Carotid Atherosclerosis

Prevalence and Risk Factors

• Gender and race differences have been demonstrated in carotid IMT. In 518 healthy Black males and females and White males and females in the Bogalusa Heart Study, males had significantly higher carotid IMT in all segments than females ($P<0.05$), and Black participants had higher common carotid and carotid bulb IMT than White participants ($P<0.001$).⁴² In MESA and a large cross-continent cohort of individuals of African, Asian, White European, and Hispanic ancestry, Black people had the thickest carotid IMT (particularly common carotid, 0.91 mm) of all 4 ethnic groups.⁴³ Chinese participants had the lowest carotid IMT (0.83 mm), in particular in the internal carotid, of the 4 ethnic groups. • Adverse risk factors in early childhood and young adulthood are implicated in the early development of atherosclerosis. In the Bogalusa Heart Study (mean, 32±3 years of age), carotid IMT was significantly and positively associated with WC, SBP, DBP, and LDL-C and inversely correlated with HDL-C levels. Participants with greater numbers of adverse risk factors (0, 1, 2, 3, or more) had stepwise increases in mean carotid IMT levels.⁴² Higher BMI and LDL-C levels measured at 4 to 7 years of age were associated with increased risk for carotid IMT >75th percentile in young adulthood.⁴⁴ Higher SBP and LDL-C and lower HDL-C in young adulthood also were associated with high carotid IMT. A large Finnish cohort study showed similar findings.⁴⁵

Background

Increased trajectory of lipids from 5 to 45 years

of

- Carotid IMT measures the thickness of 2 layers of the intima and media) of the wall of the carotid arteries, the largest conduits of blood going to the brain.

age measured in 1201 individuals in the Bogalusa Heart Study was also associated with midlife IMT compared with stable low lipid levels.⁴⁶

- In 9388 US and Finnish individuals with longitudinal measurement of CVD risk factors and carotid IMT, CVH declined from childhood to adulthood and was associated with IMT thickening.⁴⁷

Social Determinants of Health/Health Equity in Carotid IMT and Vascular Disease

- In the FAMILIA trial of 436 socioeconomically challenged young adults who underwent carotid and femoral vascular ultrasound, subclinical atherosclerosis was present in 12.6% of NH Black individuals versus 6.6% of Hispanic individuals, ($P=0.026$) in analyses adjusted for CVD risk factors, as well as lifestyle and SES factors.⁴⁸
- In the biracial HANDLS study of 2270 adults, interaction analyses demonstrated a race-by-SES effect whereby individuals who self-identified as Black race with high (rather than low) SES had higher carotid IMT (0.71 versus 0.67 in White individuals) and aortic stiffness than other groups, suggesting a group with greater subclinical CVD.⁴⁹
- In 2903 participants of the Cardiovascular Risk in Young Finns Study of individuals initially examined in youth, in adulthood, urban-dwelling (compared with rural-dwelling) residents had lower cardiovascular risk factors and lower IMT (-0.01 mm), lower vascular stiffness (PWV, -0.22 m/s), and higher carotid artery compliance ($0.07\%/10$ mm Hg).⁵⁰
- The IMPROVE study of 3703 European people assessed the relationship between SES and carotid IMT. Manual laborers had higher carotid IMT than white collar workers, a finding that was independent of sex, age groups, and education and was only partially mediated by risk factors ($+7.7\%$, $+5.3\%$, $+4.6\%$ for IMT_{max} , $IMT_{mean-max}$, and IMT_{mean} , respectively; all $P<0.0001$).⁵¹
- In the Cardiovascular Risk in Young Finns Study of 1813 adults 27 to 39 years of age followed up for >20 years, individuals with higher education had lower progression of IMT in follow-up ($P=0.002$).⁵²
- Several studies from cohorts including ELSA-Brasil, Mexican-Teachers Cohort, and an urban US cohort suggest that psychosocial well-being is associated with lower IMT, whereas serious financial difficulty, psychosocial stress, and racial discrimination are associated with subclinical vascular disease, including stroke.⁵⁶
- In MESA⁵⁶ and CHS participants,⁵⁷ the upper quartile and quintile were associated with 2- to 3-fold increased risks for CVD, respectively, including MI and stroke. Among >13 000 participants in ARIC, carotid IMT was associated with incident HF⁵⁸ and CHD and, with carotid plaque, was able to improve risk reclassification ($0.742-0.755$ [95% CI for difference in adjusted AUC, $0.008-0.017$]).⁵⁹
- The presence of carotid plaque is a strong risk factor for incident CVD.

Genetics and Family History

- Substantial evidence demonstrates the heritability of subclinical atherosclerosis. Studies leveraging twin data and family cohorts indicate that genetic factors significantly influence the development of both carotid artery IMT and CAC. Heritability estimates for carotid artery IMT range up to 59%, whereas $\approx 40\%$ to 50% of the variation in CAC quantity is attributable to genetic influences.^{60,61} Even the progression of CAC has a heritable component, albeit at a smaller magnitude ($h^2=14\%$).⁶²
- There is evidence for genetic control of subclinical atherosclerosis, with several loci identified that are associated with CAC and carotid artery IMT in multi-ancestry and racial populations.^{63–67} The identified genes and variants indicated that there are considerable shared genetic components with subclinical disease and other risk factors.^{68–70}
- CHARGE Consortium investigators identified 8 unique genetic loci that contributed to carotid IMT in 71 128 individuals and 1 novel locus for carotid plaque in 48 434 individuals.⁶⁵ A parallel GWAS in the UK Biobank (N=45 185) identified 7 novel loci for carotid IMT (*ZNF385D*, *ADAMTS9*, *EDNRA*, *HAND2*, *MYOCD*, *ITCH/EDEM2/MMP24*, and *MRTFA*).⁶⁷ When the CHARGE Consortium and UK Biobank data were meta-analyzed, an additional 3 novel loci were identified at *APOB*, *FIP1L1*, and *LOXL4*.⁶⁷ Positive genetic correlations with CHD, PAD, SBP, and stroke and negative genetic correlations with HDL-C using linkage disequilibrium score regression analysis were observed. These observations suggest connections between genetic susceptibility to subclinical atherosclerosis and overt CVD and CVD risk factors.
- ing elevated IMT.^{53–55}

- Ancestrally diverse populations can enable identification of novel subclinical atherosclerosis loci. In a

Risk Prediction

- Carotid IMT has been associated with incident CVD in multiple large cohorts. In MESA, an IMT rate of change of 0.5 mm/y was associated with an HR of 1.23 (95% CI, 1.02–1.48) for incident

Saharan Africa, a carotid IMT GWAS identified 2 novel loci for mean-maximum carotid IMT (*SIRPA* and *FBXL17*) and sex-specific loci at *SNX29*, *LARP6*, and *PROK1*.⁷¹ These loci may influence

macrophage activity (*SIRPA*), **Flow-Mediated Dilation** and growth (*PROK1*), and collagen

- A 48-SNP GRS for type 2 diabetes was associated with carotid plaque and $\approx 160\,000$ individuals, between genetic and ASCVD.⁷²
- In a meta-analysis of 13 individuals without follow-up duration of 2 to 7.2 years, age, sex, and risk factors, a (95% CI, 0.90–0.96) for CVD

- The combination of GWASs and brachial flow-mediated dilation was associated with incident CVD.

identified novel biomarkers of subclinical atherosclerosis, including circulating C-type lectin domain family 1 member B and platelet-derived growth factor receptor- β .⁷³

Arterial Stiffness and CVD

- In a study of 12 170 patients hospitalized with SARS-CoV-2 in the SEMI-COVID-19 network in Spain, arterial stiffness, defined as pulse pressure ≥ 60 mm Hg, conferred a 27% greater odds of in-hospital mortality after multivariable adjustment for comorbidities.⁷⁴

- A study from Denmark of 1678 individuals 40 to 70 years of age found that each 1-SD increment in aortic PWV (3.4 m/s) increased CVD risk by 16% to 20%.⁷⁵

- In the FHS, higher PWV was associated with a 48% increased risk of incident CVD events, and PWV improved CVD risk prediction (integrated discrimination improvement, 0.7%; $P < 0.05$).⁷⁶

- In 440 Black participants in the JHS (mean age 57 years), higher PWV was associated with higher risk of CVD.⁷⁷

- Evidence suggests that arterial stiffness has negative impacts on brain health across the life spectrum.

- In 5853 children in the Generation R Study, higher DBP was related to nonverbal intelligence, and

- In 5187 adults in the Rotterdam Study, cognition was linearly related to SBP, PWV, and pulse pressure and nonlinearly related to DBP.⁷⁸

- In the ARIC-NCS and ARIC-PET studies, higher arterial stiffness measured by heart-carotid PWV was associated with greater β -amyloid deposition in the

Comparison of Measures of Subclinical Atherosclerosis

- CAC provides a particularly strong prognostic value in predicting CHD and CVD events among markers of subclinical atherosclerosis. In 1330 intermediate-risk individuals in MESA, CAC provided the highest incremental improvement over the FRS (0.784 for both CAC and FRS versus 0.623 for FRS alone), as well as the greatest NRI (0.659) compared with other subclinical markers, including family history, ABI, IMT, and CRP.⁸⁵ Similar findings also were noted in the Rotterdam Study, in which addition of CAC score had the largest improvement in risk prediction among 12 CHD risk markers.⁸⁶

- In addition, in MESA, the values of 12 negative markers were compared for all and hard CHD and for all CVD events over the 10-year follow-up.³⁷

- After accounting for CVD risk factors, absence of CAC had the strongest negative predictive value with an adjusted mean $\pm$ SD diagnostic likelihood

- In the Rotterdam Study, brain defined by positron emission tomography imaging, and carotid femoral PWV was associated with lower brain volumes and with higher WMH burden.⁷⁹

- FHS investigators also previously demonstrated that arterial stiffness is related to brain aging, with structural brain abnormalities and progression of these abnormalities as occur in AD.^{80–83}

Subclinical Atherosclerosis and Healthy Lifestyle/ Preventive Medications

- CAC has been examined in multiple studies for its potential to identify those most likely and not likely to benefit from pharmacological treatment for the primary prevention of CVD.
- CAC identifies those most likely to benefit from statin treatment across the spectrum of risk profiles with an appropriate 5-year NNT: The estimated 5-year NNT for preventing 1 CVD event across dyslipidemia categories in the MESA cohort ranged from 23 to 30 in those with CAC ≥ 100 .³⁵ A very high 5-year NNT of 186 and 222 was estimated to prevent 1 CHD event in the absence of CAC among those with 10-year FRS of 11% to 20% and >20%, respectively. The respective estimated 5-year NNT was as low as 36 and 50 with the presence of a very high CAC score (>300) among those with a 10-year FRS of 0% to 6% and 6% to 10%, respectively.⁸⁷

-
- Similarly, CAC testing has identified individuals who might derive the highest net benefit with aspirin therapy: In MESA, among aspirin-naïve participants <70 years of age who were not at high risk for bleeding (n=3540), CAC ≥ 100 and CAC ≥ 400 identified individuals with a 5-year NNT lower than the number needed to harm (for CAC ≥ 100 , 5-year NNT, 140 versus 518).⁸⁸ In individuals with CAC=0, Similarly, in the Dallas Heart Study, among individuals at lower bleeding risk, CAC ≥ 100 identified individuals who would tend to have and DHS cohorts who had diabetes without prior CVD, the NNT with a GLP1-RA to prevent 1 CVD event over 5 years was 3-fold higher for participants with CAC=0 (NNT, 280) compared with those with CAC >100 (NNT, 85).⁹¹
 - Optimal lifestyle habits in youth and adulthood are associated with lower subclinical atherosclerosis: – net benefit, but only if 10-year ASCVD risk were $\geq 5\%$.⁸⁹ In individuals at higher bleeding risk, net harm from aspirin was observed regardless of CAC and

$P=0.009$).⁹²

- In a cohort of older females, a diet high in vegetables associated with lower carotid IMT.⁹³ Consuming with a $\approx 5\%$ lower amount of carotid atherosclerosis risk.
- In a microsimulation model of 1083 individuals with a family history of premature CAD, compared with traditional risk factor-based prediction alone, use of CAC scanning was more costly (\$145) and more effective (0.0097 QALY) with an incremental cost-effective ratio of \$15 014/QALY.⁹⁰ The incremental cost-effective ratio improved in the male, >60 years

etables, particularly cruciferous vegetables, was ≥ 3 servings of vegetables each day was associated

sclerosis compared with consuming <2 servings of vegetables.

of age, and $\geq 7.5\%$ 10-year risk subgroups, whereas CAC was not cost-effective in individuals with <5% 10-year risk or those 40 to 50 years of age.

- Measurement of CAC has the potential to inform the use of GLP1-RA therapy. In a study pooling 1125 participants from the MESA, CARDIA,

– In SWAN, healthier lifestyle, including self-PA, in females during midlife was associated with lower subclinical atherosclerosis in nearly 2000 individuals in the Spanish AWHS.⁹⁵ In the FHS, higher midlife-estimated cardiorespiratory fitness was associated with lower carotid-femoral PWV measured by carotid-femoral PWV (B=−0.12 mm [SE, 0.05 mm]) and aortic stiffness (B=−11.13 ms/m [SE, 1.33 ms/m]).⁹⁶

reported abstinence from smoking, healthy diet, and with lower carotid IMT.⁹⁴ Similar results of lifestyle habits, including Mediterranean diet, abstinence from smoking, and moderate alcohol intake, were associated with lower subclinical atherosclerosis in nearly 2000 individuals in the Spanish AWHS.⁹⁵ In the FHS, higher midlife-estimated cardiorespiratory fitness was associated with lower carotid-femoral PWV measured by carotid-femoral PWV (B=−0.12 mm [SE, 0.05 mm]) and aortic stiffness (B=−11.13 ms/m [SE, 1.33 ms/m]).⁹⁶

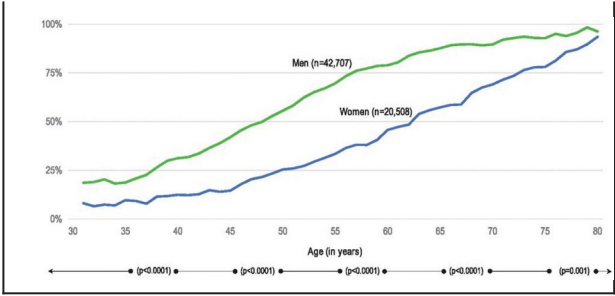
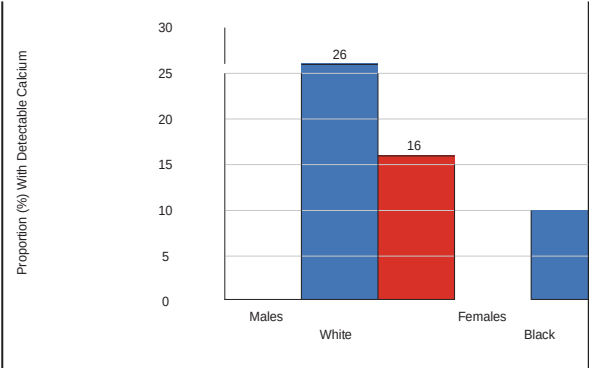


Chart 20-1. Proportion of women and men with detectable CAC (score >0) across 30 to ≥80 years of age from the CAC Consortium, 1991 to 2010.

CAC indicates coronary artery calcium.



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Chart 20-2. Prevalence (percent) of detectable CAC by sex and race among 19 725 asymptomatic individuals 30 to 45 years of age without known ASCVD pooled from CARDIA (1995–2001), the CAC Consortium (1992–2011), and the Walter Reed Cohort (1997–2009).

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcification; and CARDIA, Coronary Artery Risk Development in Young Adults.

Source: Data derived from Javaid et al.⁹⁷

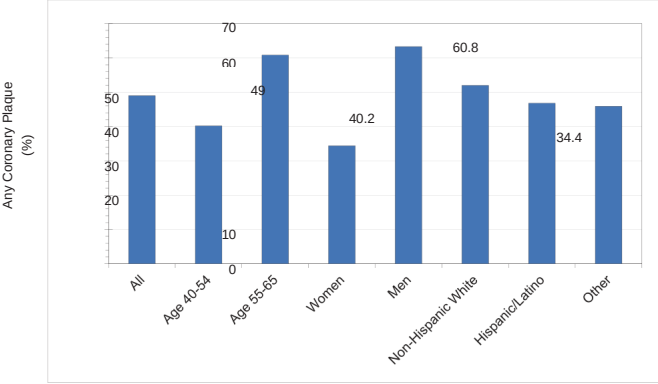
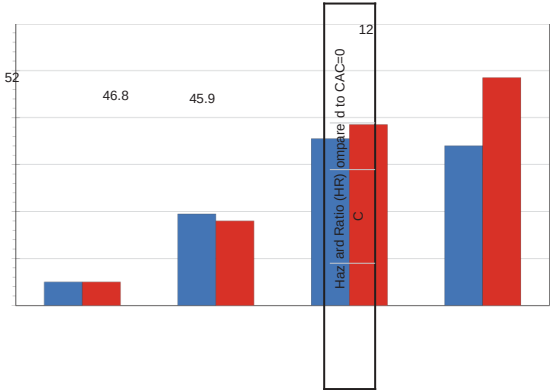


Chart 20-3. Presence of any coronary plaque by CCTA in an asymptomatic US population of 2359 individuals in the Miami Heart Study at Baptist Health South Florida, 2015 to 2018.



CCTA indicates coronary CT angiography.
Source: Reprinted from Nasir et al,⁹⁸ Copyright 2022, with permission from American College of Cardiology Foundation.

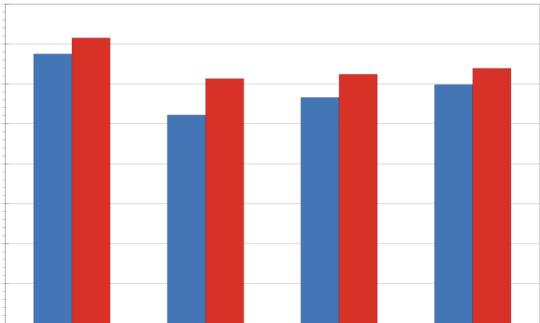


Chart 20-5. HRs for CHD events associated with CAC scores: US adults 45 to 84 years of age (reference group, CAC=0) in MESA, baseline examination 2000 to 2002.

Baseline examination in 2000 to 2002 with a median of 3.9 years of follow-up (maximum, 5.3 years). All HRs, $P<0.0001$. Major CHD events included MI and death attributable to CHD; any CHD events included major CHD events plus definite angina or definite or probable angina followed by revascularization.

CAC indicates coronary artery calcification; CHD, coronary

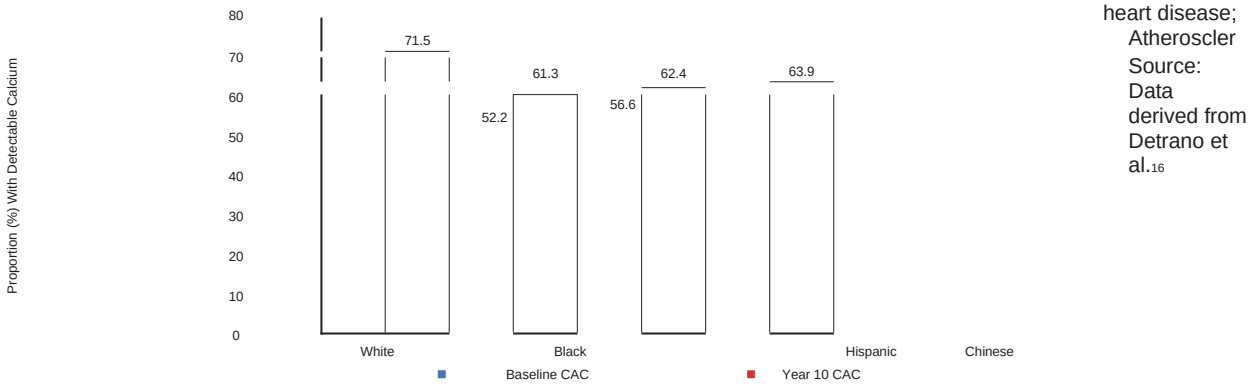


Chart 20-4. Prevalence by ethnicity of detectable CAC at baseline (2000–2002) and year 10 (2010–2012) among US adults 55 to 84 years of age without CVD in MESA.

CAC indicates coronary artery calcification; CVD, cardiovascular disease; and MESA, Multi-Ethnic Study of Atherosclerosis. Source: Data derived from Bild et al.^{5,99}

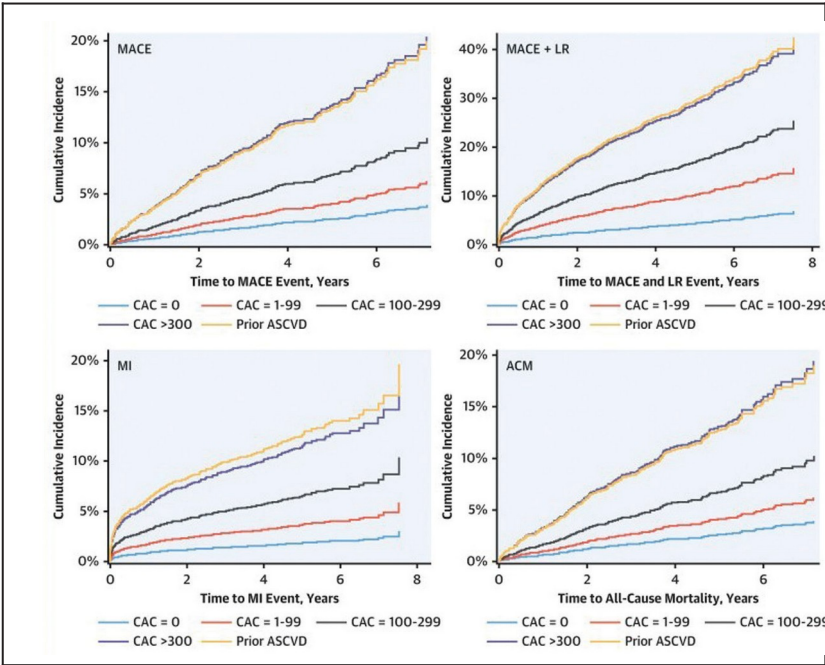


Chart 20-6. Cumulative incidence of MACEs by CAC score compared with patients with a prior ASCVD event in the CONFIRM registry, 2005 to 2009.

cardiovascular disease; CAC, coronary artery calcium; CONFIRM, Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry; LR, likelihood ratio; MACE, major adverse cardiovascular events; and MI, myocardial infarction. Source: Reprinted from Budoff et al.¹⁰⁰ Copyright © 2023, with permission from the American College of Cardiology Foundation.

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol [published corrections appear in *Circulation*. 2019;139:e1182–e1186 and *Circulation*. 2023;148:e5]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625

2. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published corrections appear in *Circulation*. 2019;140:e649–e650, *Circulation*. 2020;141:e60, and *Circulation*. 2020;141:e774]. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678

3. Orringer CE, Blaha MJ, Blankstein R, Budoff MJ, Goldberg RB, Gill EA, Maki KC, Mehta L, Jacobson TA. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *J Clin Lipidol*. 2021;15:33–60. doi: 10.1016/j.jacl.2020.12.005

4. Golub IS, Termeie OG, Kristo S, Schroeder LP, Lakshmanan S, Shafter AM, Hussein L, Verghese D, Aldana-Bitar J, Manubolu VS, et al. Major coronary artery calcium guidelines. *JACC Cardiovasc Imaging*. 2023;16:98–117. doi: 10.1016/j.jcmg.2022.06.018

5. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2005;111:1313–1320. doi: 10.1161/01.CIR.0000157730.94423.4B

6. Shaw LJ, Min JK, Nasir K, Xie JX, Berman DS, Miedema MD, Whelton SP, Dardari ZA, Rozanski A, Rumberger J, et al. Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC Consortium. *Eur Heart J*. 2018;39:3727–3735. doi: 10.1093/eurheartj/ehy534

7. The Multi-Ethnic Study of Atherosclerosis website. Accessed June 30, 2024.

8. Wang FM, Cainzos-Achirica M, Ballew SH, Coresh J, Folsom AR, Howard CM, Post WS, Wagenknecht LE, Budoff MJ, Blaha MJ, et al. Defining

10. Dzaye O, Razavi AC, Michos ED, Mortensen MB, Dardari ZA, Nasir K, Osei AD, Peng AW, Blankstein R, Page JH, et al. Coronary artery calcium scores indicating secondary prevention level risk: findings from the CAC consoCrtium and FOURIER trial. *Atherosclerosis*. 2022;347:70–76. doi: 10.1016/j.atherosclerosis.2022.02.006
11. Reis JP, Allen NB, Bancks MP, Carr JJ, Lewis CE, Lima JA, Rana JS, Gidding SS, Schreiner PJ. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age: the CARDIA study. *Diabetes Care*. 2018;41:731–738. doi: 10.2337/dc17-2233
12. Bergstrom G, Persson M, Adiels M, Bjornson E, Bonander C, Ahlstrom H, Alfredsson J, Angeras O, Berglund G, Blomberg A, et al. Prevalence of subclinical coronary artery atherosclerosis in the general population. *Circulation*. 2021;144:916–929. doi: 10.1161/CIRCULATIONAHA.121.055340
13. Sederholm Lawesson S, Swahn E, Pihlgård M, Andersson T, Angerås O, Bacsovcics Brolin E, Bergdahl E, Blomberg M, Christersson C, Gonçalves I, et al. Association between history of adverse pregnancy outcomes and coronary artery disease assessed by coronary computed tomography angiography. *JAMA*. 2023;329:393–404. doi: 10.1001/jama.2022.24093
14. Verweij SL, de Ronde MWJ, Verbeek R, Boekholdt SM, Planken RN, Stroes ESG, Pinto-Sietsma SJ. Elevated lipoprotein(a) levels are associated with coronary artery calcium scores in asymptomatic individuals with a family history of premature atherosclerotic cardiovascular disease. *J Clin Lipidol*. 2018;12:597–603.e1. doi: 10.1016/j.jacl.2018.02.007
15. Soares C, Samara A, Yuyun MF, Echouffo-Tcheugui JB, Masri A, Samara A, Morrison AR, Lin N, Wu WC, Erqou S. Coronary artery calcification and plaque characteristics in people living with HIV: a systematic review and meta-analysis. *J Am Heart Assoc*. 2021;10:e019291. doi: 10.1161/jaha.120.019291
16. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336–1345. doi: 10.1056/NEJMoa072100
17. Razavi AC, Uddin SMI, Dardari ZA, Berman DS, Budoff MJ, Miedema MD, Osei AD, Obisesan OH, Nasir K, Rozanski A, et al. Coronary artery calcium for risk stratification of sudden cardiac death: the Coronary Artery Calcium Consortium. *JACC Cardiovasc Imaging*. 2022;15:1259–1270. doi: 10.1016/j.jcmg.2022.02.011
9. Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim demographic-specific coronary artery calcium percentiles in the population aged ≥ 75 : the ARIC study and MESA. *Circ Cardiovasc Imaging*. 2023;16:e015145. doi: 10.1161/CIRCIMAGING.122.015145

18. Javadi A, Mitchell JD, Villines TC. Predictors of coronary artery calcium and long-term risks of death, myocardial infarction, and stroke in young adults. *J Am Heart Assoc.* 2021;10:e022513. doi:

B, Frohlich B, Sutherland ML, Sutherland JD, Stieglitz J, et al.

10.1161/JAHA.121.022513

Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet.* 2017;389:1730–1739. doi: 10.1016/S0140-6736(17)30752-3

19. Peng AW, Dardari ZA, Blaha MJ. Response by Peng et al to letter regarding article, "Very high coronary artery calcium (≥ 1000) and association with cardiovascular disease events, non-cardiovascular disease outcomes,

Circulation. 2025;151:e41–e660. DOI:

February 25, 2025 e513

- and mortality: results from MESA." 10.1161/CIRCULATIONAHA.121.056534
20. Peng AW, Mirbolouk M, Orimolove OA, Osei MJ, Shaw L, Miedema MD, Rumberger J. cause-specific mortality in asymptomatic subjects from the CAC Consortium. *JACC* 93. doi: 10.1016/j.jacc.2019.02.005
 21. Mehta A, Vasquez N, Avers CR, Patel J, RS, Shapiro MD, Rodriguez CJ, Tsai MY. tion of lipoprotein(a) and coronary artery atherosclerotic cardiovascular risk. *J Am Coll Cardiol*. 10.1016/j.jacc.2021.11.058
 22. Budoff MJ, Young R, Lopez VA, Kronmal RA, Detrano RC, Bild DE, Guerci AD, Liu K, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2013;61:1231–1239. doi: 10.1016/j.jacc.2012.12.035
 23. Subramanya V, Zhao D, Ouyang P, Ying W, Vaidya D, Ndumele CE, Heckbert SR, Budoff MJ, Post WS, Michos ED. Association of endogenous sex hormone levels with coronary artery calcium progression among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Cardiovasc Comput Tomogr*. 2019;13:41–47. doi: 10.1016/j.jcct.2018.09.010
 24. Reddy NM, Mayne SL, Pool LR, Gordon-Larsen P, Carr JJ, Terry JG, Kershaw KN. Exposure to neighborhood-level racial residential segregation in young adulthood to midlife and incident subclinical atherosclerosis in Black adults: the Coronary Artery Risk Development in Young Adults study. *Circ Cardiovasc Qual Outcomes*. 2022;15:e007986. doi: 10.1161/circoutcomes.121.007986
 25. Bertisch SM, Reid M, Lutsey PL, Kaufman JD, McClelland R, Patel SR, Redline S. Gender differences in the association of insomnia symptoms and coronary artery calcification in the Multi-Ethnic Study of Atherosclerosis. *Sleep*. 2021;44:zsab116. doi: 10.1093/sleep/zsab116
 26. Janssen I, Powell LH, Everson-Rose SA, Hollenberg SM, El Khoudary SR, Matthews KA. Psychosocial well-being and progression of coronary management guidelines: MESA (Multi-*Am Coll Cardiol*. 2015;66:1657–1668.
 35. Martin SS, Blaha MJ, Blankstein R, P, Jones SR, Blumenthal RS, Budoff calcium, and incident atherosclerotic for statin therapy from the Multi-Ethnic 2014;129:77–86. doi:
 36. Blaha MJ, Cainzos-Achirica M, Dardari A, Rumberger JA, Dzave O, Michos cause-specific mortality in individuals artery calcium: a long-term, competing Artery Calcium Consortium. 10.1016/j.atherosclerosis.2019.11.008 artery calcification in midlife women. *J Am Heart Assoc*. 2022;11:e023937. doi: 10.1161/jaha.121.023937
 27. Mamudu HM, Jones A, Paul TK, Osedeme F, Stewart D, Alamian A, Wang L, Orimaye S, Bledsoe J, Poole A, et al. The co-existence of diabetes and subclinical atherosclerosis in rural central Appalachia: do residential characteristics matter? *J Diabetes Complications*. 2021;35:107851. doi: 10.1016/j.jdiacomp.2021.107851
 28. Huynh Q, Marwick TH, Venkataraman P, Knibbs LD, Johnston FH, Negishi K. Long-term exposure to ambient air pollution is associated with coronary artery calcification among asymptomatic adults. *Eur Heart J Cardiovasc Imaging*. 2021;22:922–929. doi: 10.1093/ehjci/jeaa073
 29. Gepner AD, Young R, Delaney JA, Tattersall MC, Blaha MJ, Post WS, Gottesman RF, Kronmal R, Budoff MJ, Burke GL, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8:e002262. doi:

37. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, Dardari Z, Sibley CT, Burke GL, Kronmal RA, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2016;133:849–858. doi: 10.1161/CIRCULATIONAHA.115.018524
38. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med*. 2011;365:213–221. doi: 10.1056/NEJMoa1012592
39. Polak JF, Meisner A, Pencina MJ, Wolf PA, D'Agostino RB. Variations in common carotid artery intima-media thickness during the cardiac cycle: implications for cardiovascular risk assessment. *J Am Soc Echocardiogr*. 2012;25:1023–1028. doi: 10.1016/j.echo.2012.05.007
40. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS; American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. *J Am Soc Echocardiogr*. 2008;21:93–111; quiz 189. doi: 10.1016/j.echo.2007.11.011
41. Howard DPJ, Gaziano L, Rothwell PM; Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. *Lancet Neurol*. 2021;20:193–202. doi: 10.1016/S1474-4422(20)30484-1
42. Urbina EM, Srinivasan SR, Tang R, Bond M, Kieltyka L, Berenson GS. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (the Bogalusa Heart Study). *Am J Cardiol*. 2002;90:953–958. doi: 10.1016/s0002-9149(02)02660-7
43. Manolio TA, Arnold AM, Post W, Bertoni AG, Schreiner PJ, Sacco RL, Saad MF, Detrano RL, Szklo M. Ethnic differences in the relationship of carotid atherosclerosis to coronary calcification: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2008;197:132–138. doi: 10.1016/j.atherosclerosis.2007.02.030
44. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study [published correction appears in *JAMA*. 2003;290:2943]. *JAMA*. 2003;290:2271–2276. doi: 10.1161/circimaging.114.002262
30. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Nakamura F, Miyamoto Y. Impact of intima-media thickness progression in the common carotid arteries on the risk of incident cardiovascular disease in the Suita study. *J Am Heart Assoc*. 2018;7:e007720. doi: 10.1161/JAHA.117.007720.
31. Cho I, Al'Aref SJ, Berger A, B OH, Gransar H, Valenti V, Lin FY, Achenbach S, Berman DS, Budoff MJ, et al. Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study. *Eur Heart J*. 2018;39:934–941. doi: 10.1093/eurheartj/ehx774
32. Mortensen MB, Dzaye O, Steffensen FH, Botker HE, Jensen JM, Ronnow Sand NP, Kragholm KH, Sorensen HT, Leipsic J, Maeng M, et al. Impact of plaque burden versus stenosis on ischemic events in patients with coronary atherosclerosis. *J Am Coll Cardiol*. 2020;76:2803–2813. doi: 10.1001/jama.290.17.2271

45. Juonala M, Viikari JS, Kahonen M, Taittonen L, Laitinen T, Hutri-Kahonen N, Lehtimäki T, Jula A, Pietikainen M, Jokinen E, et al. Life-time risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular Risk in Young Finns study. *Eur Heart J*. 2010;31:1745–1751. doi: 10.1093/eurheartj/ehq141

46. Yan Y, Li S, Liu Y, Guo Y, Fernandez C, Bazzano L, He J, Chen W. Associations between life-course lipid trajectories and subclinical atherosclerosis in midlife. *JAMA Netw Open*. 2022;5:e2234862. doi: 10.1001/jamanetworkopen.2022.34862

47. Allen NB, Krefman AE, Labarthe D, Greenland P, Juonala M, Kähönen M, Lehtimäki T, Day RS, Bazzano LA, Van Horn LV, et al. Cardiovascular health trajectories from childhood through middle age and their association with subclinical atherosclerosis. *JAMA Cardiol*. 2020;5:557–566. doi: 10.1016/j.jacc.2020.10.021

33. Sánchez-Cabo F, Rossello X, Fuster V, Benito F, Manzano JP, Silla JC, Fernández-Alvira JM, Oliva B, Fernández-Friera L, López-Melgar B, et al. Machine learning improves cardiovascular risk definition for young, asymptomatic individuals. *J Am Coll Cardiol*. 2020;76:1674–1685. doi: 10.1016/j.jacc.2020.08.017

34. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ,

48. Iglesias-Grau J, Fernandez-Jimenez R, Diaz-Munoz R, Jaslow R, de Cos-Gandoy A, Santos-Beneit G, Hill CA, Turco A, Kadian-Dodov D, Kovacic JC, et al. Subclinical atherosclerosis in young, socioeconomically vulnerable Hispanic and non-Hispanic Black adults. *J Am Coll Cardiol*. 2022;80:219–229. doi: 10.1016/j.jacc.2022.04.054
49. Wendell CR, Waldstein SR, Evans MK, Zonderman AB. Distributions of subclinical cardiovascular disease in a socioeconomically and racially diverse sample. *Stroke*. 2017;48:850–856. doi: 10.1161/STROKEAHA.116.015267
- Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol

-
50. Nuotio J, Vahamurto L, Pakkala K, Magnussen CG, Hutri-Kahonen N, Kahonen M, Laitinen T, Taittonen L, Tossavainen P, Lehtimäki T, et al. CVD risk factors and surrogate markers: urban-rural differences. *Scand J Public Health*. 2020;48:752–761. doi: 10.1177/1403494819869816
51. Tedesco CC, Veglia F, de Faire U, Kurl S, Smit AJ, Rauramaa R, Giral P, Amato M, Bonomi A, Ravani A, et al; IMPROVE Study Group. Association of lifelong occupation and educational level with subclinical atherosclerosis in different European regions: results from the IMPROVE study. *Atherosclerosis*. 2018;269:129–137. doi: 10.1016/j.atherosclerosis.2017.12.023
52. Kestila P, Magnussen CG, Viikari JS, Kahonen M, Hutri-Kahonen N, Taittonen L, Jula A, Loo BM, Pietikainen M, Jokinen E, et al. *Vasc Biol*. 2012;32:815–821. doi: 10.1161/ATVBAHA.111.241182
53. Cundiff JM, Kamarck TW, Muldoon MF, Marsland AL, Manuck SB.
68. Nelson CP, Goel A, Butterworth AS, Kanoni S, Webb TR, Marouli E, Zeng L, Ntalla I, Lai FY, Hopewell JC, et al; EPIC-CVD Consortium. Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet*. 2017;49:1385–1391. doi: 10.1038/ng.3913
69. Klarin D, Zhu QM, Emdin CA, Zekavat SM, Sadee W, Samani NJ. Genetic analysis of venous thromboembolism identifies new risk loci and drug targets. *Nat Commun*. 2017;8:1–12.
70. van Setten J, Isgum I, Smolonska J, Ripke S, de Jong PA, Oudkerk M, de Koning H, Lammers JW, Zanen P, Groen HJ, et al. Genome-wide associations of respect and appreciation in daily life and associations with subclinical cardiovascular disease. *Health Psychol*. 2023;42:53–62. doi:

- G, Asiki G, Micklesfield L, Choma S, Gomez-Olive FX, et al; the H3Africa Consortium. Genetic associations with carotid intima-media thickness link to atherosclerosis with sex-specific effects in sub-Saharan Africans. *Nat Commun*. 2022;13:855. doi: 10.1038/s41467-022-28276-x 10.1037/hea0001255
54. Connors K, Flores-Torres MH, Cortés-Valencia A, Barrientos-Gutiérrez T, Cantú-Brito C, Rodríguez B, Lajous M, Valdimarsdóttir U, Catzin-Kuhlmann A. Serious financial difficulties, psychological stress, and subclinical cardiovascular disease in Mexican women. *Ann Epidemiol*. 2022;71:38–43. doi: 10.1016/j.annepidem.2022.03.001
55. Camelo LV, Machado AV, Chor D, Griep RH, Mill JG, Brant LCC, Barreto SM. Racial discrimination is associated with greater arterial stiffness and carotid intima-media thickness: the ELSA-Brasil study. *Ann Epidemiol*. 2022;72:40–47. doi: 10.1016/j.annepidem.2022.03.009
56. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2011;42:3017–3021. doi: 10.1161/STROKEAHA.111.625186
57. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22. doi: 10.1056/NEJM199901073400103
58. Effoe VS, Rodriguez CJ, Wagenknecht LE, Evans GW, Chang PP, Mirabelli MC, Bertoni AG. Carotid intima-media thickness is associated with incident heart failure among middle-aged Whites and Blacks: the Atherosclerosis Risk in Communities study. *J Am Heart Assoc*. 2014;3:e000797. doi: 10.1161/JAHA.114.000797
59. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*. 2010;55:1600–1607. doi: 10.1016/j.jacc.2009.11.075
60. Devan WJ, Falcone EL, Anderson CD, Akers SR, Ehrlich E. Heritability of carotid intima-media thickness: an update from the Boston Area Stroke Genetics study. *Arterioscler Thromb Vasc Biol*. 2022;42:442–447.

- J, Bian Z, Bennett D, et al; China Kadoorie Biobank Collaborative Group. Genetic predisposition to type 2 diabetes and risk of subclinical athero-sclerosis and cardiovascular diseases among 160,000 Chinese adults. *Diabetes*. 2019;68:2155–2164. doi: 10.2337/db19-0224
73. Mosley JD, Benson MD, Smith JG, Melander O, Ngo D, Shaffer CM, Ferguson JF, Herzig MS, McCarty CA, Chute CG, et al. Probing the virtual proteome to identify novel disease biomarkers. *Circulation*. 2018;138:2469–2481. doi: 10.1161/CIRCULATIONAHA.118.036063
74. Rodilla E, Lopez-Carmona MD, Cortes X, Cobos-Palacios L, Canales S, Saez MC, Campos Escudero S, Rubio-Rivas M, Diez Manglano J, Freire Castro SJ, et al; SEMI-COVID-19 Network. Impact of arterial stiffness on all-cause mortality in patients hospitalized with COVID-19 in Spain. *Hypertension*. 2021;77:856–867. doi: 10.1161/HYPERTENSIONAHA.120.16563
75. Willum Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006;113:664–670. doi: 10.1161/circulationaha.105.579342
76. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121:505–511. doi: 10.1161/CIRCULATIONAHA.109.886655
77. Tripathi A, Benjamin EJ, Musani SK, Hamburg NM, Tsao CW, Saraswat A, Vasan RS, Mitchell GF, Fox ER. The association of endothelial function and tone by digital arterial tonometry with MRI left ventricular mass in African Americans: the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:258–264. doi: 10.1016/j.jash.2017.03.005
78. Lamballais S, Sajjad A, Leening MJG, Gaillard R, Franco OH, Mattace-Raso FUS, Jaddoe VVW, Roza SJ, Tiemeier H, Ikram MA. Association of blood pressure and arterial stiffness with cognition in 2 population-based child and adult cohorts. *J Am Heart Assoc*. 2018;7:e009847. doi: 10.1161/JAHA.118.009847
61. Wang JG, Staessen JA, Franklin SS, Fagard R, Gueyffier F. Genetic heritability of common carotid artery intima-media thickness and its relation to cardiovascular risk factors. *J Hum Hypertens*. 2005;19:443–447. doi: 10.1161/JAHA.118.009847
63. Natarajan P, Bis J, Bielak L, Cox A, Dorr M, Feitosa M, Franceschini N, Guo X, Hwang SJ, Isaacs A, et al. Multiethnic exome-wide association study of subclinical atherosclerosis. *Circ Cardiovasc Genet*. 2016;9:511–520. doi: 10.1161/JAHA.118.009847
62. Cassidy-Bushrow AE, Bielak LF, Sheedy PF 2nd, Turner ST, Kullo IJ, Lin X, Peyser PA. Coronary artery calcification progression is heritable. *Circulation*. 2007;116:25–31. doi: 10.1161/CIRCULATIONAHA.106.658583

79. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, Wong D, Zhou Y, Knopman D, Mosley TH, et al. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. *Neurology*. 2018;90:e1248–e1256. doi: 10.1212/WNL.0000000000005259
80. Cooper LL, Himali JJ, Torjesen A, Tsao CW, Beiser A, Hamburg NM, DeCarli C, Vasani RS, Seshadri S, Pase MP, et al. Inter-relations of orthostatic blood pressure change, aortic stiffness, and brain structure and function in young adults. *J Am Heart Assoc*. 2017;6:e006206. doi: 10.1161/CIRCGENETICS.116.001572
64. Divers J, Palmer ND, Langefeld CD, Brown WM, Lu L, Hicks PJ, Smith SC, Xu J, Terry JG, Register TC, et al. Genome-wide association study of coronary artery calcified atherosclerotic plaque in African Americans with type 2 diabetes. *BMC Genet*. 2017;18:105. doi: 10.1186/s12863-017-0572-9
65. Wojczynski MK, Li M, Bielak LF, Kerr KF, Reiner AP, Wong ND, Yanek LR, Qu L, White CC, Lange LA, et al. Genetics of coronary artery calcification among African Americans, a meta-analysis. *BMC Med Genet*. 2013;14:75. doi: 10.1186/1471-2350-14-75
66. Vargas JD, Manichaikul A, Wang XQ, Rich SS, Rotter JI, Post WS, Polak JF, Budoff MJ, Bluemke DA. Common genetic variants and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2016;245:230–236. doi: 10.1016/j.atherosclerosis.2015.11.034
67. Wai Yeung M, Wang S, van de Vegte YJ, Borisov O, van Setten J, Snieder H, Verweij N, Said MA, van der Harst P. Twenty-five novel loci for carotid intima-media thickness: a genome-wide association study in >45 000 individuals and meta-analysis of >100 000 individuals. *Arterioscler Thromb*

81. Maillard P, Mitchell GF, Himali JJ, Beiser A, Fletcher E, Tsao CW, Pase MP, Satizabal CL, Vasán RS, Seshadri S, et al. Aortic stiffness, increased white matter free water, and altered microstructural integrity: a continuum of injury. *Stroke*. 2017;48:1567–1573. doi: 10.1161/STROKEAHA.116.016321
82. Maillard P, Mitchell GF, Himali JJ, Beiser A, Tsao CW, Pase MP, Satizabal CL, Vasán RS, Seshadri S, DeCarli C. Effects of arterial stiffness on brain integrity in young adults from the Framingham Heart Study. *Stroke*. 2016;47:1030–1036. doi: 10.1161/STROKEAHA.116.012949
83. Tsao CW, Himali JJ, Beiser AS, Larson MG, DeCarli C, Vasán RS, Mitchell GF, Seshadri S. Association of arterial stiffness with progression of sub-clinical brain and cognitive disease. *Neurology*. 2016;86:619–626. doi: 10.1212/WNL.0000000000002368
84. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, Rigatto C, Komenda P, Sood MM, Tangri N. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2014;15:736–746. doi: 10.1093/ehjci/et256

85. Yeboah J, McClelland RL, Polonsky TS, J.J. Goff DC, Greenland P, Herrington DM. ers for improvement in cardiovascular risk individuals. *JAMA*. 2012;308:788–795. doi: 10.1093/eurheartj/ehs508
86. Kavousi M, Elias-Smale S, Rutten JH, Verwoert GC, Krestin GP, Oudkerk M, de Evaluation of newer risk markers for sification: a cohort study. *Ann Intern Med*. 2010;152:1003–1010. doi: 10.1093/eurheartj/ehs508
87. Silverman MG, Blaha MJ, Krumholz HM, CT, Anaton A, Blumenthal RS, Nasir K. on coronary heart disease events in ditional risk factor burden: the Multi-Ethnic *Heart J*. 2014;35:2232–2241. doi: 10.1093/eurheartj/ehs508
88. Cainzos-Achirica M, Miedema MD, McEvoy JW, Al Rifai M, Greenland P, Dardari Z, Budoff M, Blumenthal RS, Yeboah J, Duprez DA, et al. Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA study (Multi-Ethnic Study of Atherosclerosis). *Circulation*. 2020;141:1541–1553. doi: 10.1161/CIRCULATIONAHA.119.045010
89. Ajufo E, Ayers CR, Vigen R, Joshi PH, Rohatgi A, de Lemos JA, Khera A. Value of coronary artery calcium scanning in association with the net bene-fit of aspirin in primary prevention of atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2021;6:179–187. doi: 10.1001/jamacardio.2020.4939
90. Venkataraman P, Kawakami H, Huynh Q, Mitchell G, Nicholls SJ, Stanton T, Tonkin A, Watts GF, Marwick TH; CAUGHT-CAD Investigators. Cost-effectiveness of coronary artery calcium 93. Blekkenhorst LC, Bondonno CP, Lewis Bondonno NP, Lim WH, Kun Z, Beilin and total vegetable intakes are erosclerosis in older adult women. *J* doi: 10.1161/JAHA.117.008391
94. Wand D, Jackson EA, Karvonen-MM, Derbv CA, Sternfeld B, Janssen during the midlife is prospectively atherosclerosis: the Study of Women's *Heart Assoc*. 2018;7:e010405. doi: 10.1161/JAHA.117.008391
95. Uzhova I, Mateo-Galleo R, Moreno-Leon-Latre M, Casasnovas Lenquas tive effect of adherence to multiple scoring in people with a family his- tory of coronary disease. *JACC Cardiovasc Imaging*. 2021;14:1206–1217. doi: 10.1016/j.jcmg.2020.11.008
91. Cainzos-Achirica M, Patel KV, Quispe R, Joshi PH, Khera A, Ayers C, Lima JAC, Rana JS, Greenland P, Bittencourt MS, et al. Coronary artery calcium for the allocation of GLP-1RA for primary prevention of atherosclerotic cardiovascular disease. *JACC Cardiovasc Imaging*. 2021;14:1470–1472. doi: 10.1016/j.jcmg.2020.12.024
92. Aghayan M, Asghari G, Yuzbashian E, Dehghan P, Khadem Haghighian H, Mirmiran P, Javadi M. Association of nuts and unhealthy snacks with subclinical atherosclerosis among children and adolescents with overweight and obesity. *Nutr Metab (Lond)*. 2019;16:23. doi: 10.1186/s12986-019-0350-y

- sclerosis: insights from the AWHs. *J Clin Lipidol*. 2018;12:615–625. doi: 10.1016/j.jacl.2018.03.081
96. Lee J, Song RJ, Musa Yola I, Shrout TA, Mitchell GF, Vasan RS, Xanthakis V. Association of estimated cardiorespiratory fitness in midlife with cardio-metabolic outcomes and mortality. *JAMA Netw Open*. 2021;4:e2131284. doi: 10.1001/jamanetworkopen.2021.31284
97. Javaid A, Dardari ZA, Mitchell JD, Whelton SP, Dzaye O, Lima JAC, Lloyd-Jones DM, Budoff M, Nasir K, Berman DS, et al. Distribution of coronary artery calcium by age, sex, and race among patients 30-45 years old. *J Am Coll Cardiol*. 2022;79:1873–1886. doi: 10.1016/j.jacc.2022.02.051
98. Nasir K, Cainzos-Achirica M, Valero-Elizondo J, Ali SS, Havistin R, Lakshman S, Blaha MJ, Blankstein R, Shapiro MD, Arias L, et al. Coronary atherosclerosis in an asymptomatic U.S. population: Miami Heart Study at Baptist Health South Florida. *JACC Cardiovasc Imaging*. 2022;15:1604–1618. doi: 10.1016/j.jcmg.2022.03.010
99. Bild DE, McClelland R, Kaufman JD, Blumenthal R, Burke GL, Carr JJ, Post WS, Register TC, Shea S, Szklo M. Ten-year trends in coronary calcification in individuals without clinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. *PLoS One*. 2014;9:e94916. doi: 10.1371/journal.pone.0094916
100. Budoff MJ, Kinninger A, Gransar H, Achenbach S, Al-Mallah M, Bax JJ, Berman DS, Cademartiri F, Callister TQ, Chang HJ, et al; CONFIRM Investigators. When does a calcium score equate to secondary prevention? Insights from the multinational CONFIRM Registry. *JACC Cardiovasc Imaging*. 2023;16:1181–1189. doi: 10.1016/j.jcmg.2023.03.008

21. CORONARY HEART DISEASE, ACUTE CORONARY SYNDROME, AND ANGINA PECTORIS

See Tables 21-1 through 21-3 and Charts 21-1 through 21-8

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Coronary Heart Disease

ICD-9 410 to 414, 429.2; ICD-10 I20 to I25 (includes MI ICD-10 I21 to I22).

Prevalence

(See Tables 21-1 and 21-2 and Charts 21-1 through 21-4)

- In an analysis of data on 17 266 adults with a history of CHD from NHIS 2006 to 2015, the prevalence of premature CHD (<65 years of age for females and <55 years of age for males) was higher among Asian Indian adults (aOR, 1.77 [95% CI, 1.05–2.97]) and other Asian adults (aOR, 1.68 [95% CI, 1.17–2.42]) than White adults.¹
- On the basis of data from NHANES 2017 to 2020,² an estimated 20.5 million Americans ≥20 years of age have CHD (Table 21-1). The prevalence of CHD was higher for males than females in all age groups (Chart 21-1).

prevalence of MI is 3.2% in US adults ≥20 years of age. Males have a higher prevalence of MI than females for all age groups (Chart 21-2). Overall MI prevalence is 4.5% for males and 2.1% for females. MI prevalence is 3.9% in US adults ≥20 years of age (Table 21-2).

- According to NHANES 2017 to 2020, total CHD prevalence is 7.1% in US adults ≥20 years of age. CHD prevalence is 8.7% for males and 5.8% for females. CHD prevalence by sex and ethnicity is shown in Table 21-1.
- Based on data from the NHIS 2018, the CHD prevalence estimates are 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people ≥18 years of age.³
- According to data from NHANES 2017 to 2020 (unpublished NHLBI tabulation),² the overall

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females). As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

4.5% of respondents had been told that they had had an MI. The highest age-adjusted prevalence was in West Virginia (6.1%), and the lowest was in Colorado (2.8%; Chart 21-3; unpublished NHLBI tabulation using BRFSS⁴).

- In the same survey in 2022, 4.4% of respondents had been told that they had angina or CHD. The highest age-adjusted prevalence was in Mississippi (5.8%), and the lowest was in Colorado (2.5%; Chart 21-4).⁴

Incidence

- Approximately every 40 seconds, an American will have an MI (AHA computation based on incidence data from the ARIC study of the NHLBI⁵).
- On the basis of data tabulated by the NHLBI from the 2005 to 2014 ARIC study⁵:
 - Approximately 720 000 Americans will have a new coronary event (defined as first hospital-ized MI or CHD death), and ≈335 000 will have a recurrent event.
 - The estimated annual incidence of MI is 605 000 new attacks and 200 000 recurrent attacks. Of these 805 000 first and recurrent events, it is estimated that 170 000 are silent (without significant symptoms).
 - Average age at first MI is 65.6 years for males and 72.0 years for females.
- After adjustment for social determinants of health and cardiovascular risk factors, Black males and females have similar risk for fatal CHD (ARIC, 0.67 [95% CI, 0.36–1.24]; REGARDS, 1.00 [95% CI, 0.54–1.85]) but lower risk for nonfatal CHD (ARIC, 0.70 [95% CI, 0.51–0.97]; REGARDS, 0.70 [95% CI, 0.46–1.06]) compared with White males and females.⁶

Secular Trends

- In a study of the 2010 to 2019 National Readmission Database, among 592 015 30-day readmissions and 787 008 ninety-day readmissions after index AMI hospitalization, 30-day and 90-day all-cause readmission rates after AMI decreased from 12.8% to 11.6% ($P=0.0001$) and 20.6% to 18.8% ($P=0.0001$), respectively.⁷ Downward trends were observed in both pre-HRRP (2010–2012) and post-HRRP periods (2013–2015, 2016–2019).

However, the mean length of $P=0.0001$) and adjusted total \$16 938; $P=0.0001$) for 30-sion increased over the

- In a retrospective study of 2 881 from the NIS 2008 to 2019, cular ultrasound-guided PCI (6180 versus 25 330; $P_{\text{trend}} < 0.001$). whereas opti-cal by 548.4% (246 versus 1595; $P_{\text{trend}} < 0.001$).⁸ The percentage

cal coherence tomography use in PCIs increased from 3.4% to 8.7% and 0.0% to 0.6%, respectively ($P_{\text{trend}} < 0.001$). Intravascular imaging-guided PCI was associated with lower odds of in-hospital mor-

a corresponding increase in (see Chapter 19 [Sudden Arrhythmias, and Inherited similar multisite study in tion in STEMI (IRR, 0.72 and NSTEMIs (IRR, 0.64 when the 4 weeks before and compared.¹³

- In a cohort of 1533 patients (STEMI and NSTEMI) in a Washington, DC, and tality (aOR, 0.66 [95% CI, 0.60–0.72]; $P < 0.001$), suggesting a significant increase in use and

1, 2020, and June 30, 2020, 86 had confirmed COVID-19. Furthermore, 20.0% of patients (n=17) with COVID-19 underwent coronary angiography. Those with concomitant COVID-19 and AMI had higher in-hospital mortality (27.9%) than patients without COVID-19 in the same period (3.7%; improved outcomes. $P<0.001$).¹⁴

- Among Medicare beneficiaries between 2002 and 2011, the rates of MI hospitalization declined from 1485 to 1122 per 100 000 PY.⁹
 - The rates of MI as the primary reason for hospitalization decreased over time (from 1063 to 677 per 100 000 PY between 2002 and 2011).

The percentage of MIs that were attributable to a primary reason for hospitalization decreased from 72% to 60% between 2002 and 2011.

- Among 21 738 patients with type 2 MI in the National Readmission Database, in-hospital mortality and 30-day readmission for patients with type 2 MI were 9.0% and 19.1%, respectively. AF, PAD, male sex, coagulopathy, and fluid/electrolyte imbalances were associated with higher in-hospital mortality. In addition, AF/flutter, carotid artery stenosis, diabetes, anemia, COPD, CKD, and history of MI were associated with higher odds of 30-day readmission.¹⁵
 - However, the rates of MI as a secondary reason for hospitalization increased (from 190 to 245 per 100 000 PY). The percentage of MIs that were attributable to a secondary diagnosis increased from 28% to 40%.
- In Olmsted County, Minnesota, between 2003 and 2012, the annual incidence declined for both type 1 MI (from 202 to 84 per 100 000; $P<0.001$) and type 2 MI (from 130 to 78 per 100 000; $P=0.02$).¹⁰

According to data from inpatient and ambulatory databases from 4 states (Michigan, Maryland, New York, and Florida), population trends in PCI use were examined between January 2010 and December 2017. Among a cohort of 333 819 patients (32% female; mean±SD age, 65.7±12.2 years), 1 044 698 PCIs were performed: 57.1% were elective, and 42.9% were urgent. PCI rates declined from 260.2 to 232.8 per 100 000

(−10.5%; $P_{\text{trend}}<0.001$) between 2010 and 2017. In the same period, outpatient PCI rates increased from 33.8 to 66.7 per 100 000 (+97.1%; $P_{\text{trend}}<0.001$), whereas inpatient PCI rates declined from 226.4 to 166.2 per 100 000 (−26.6%; $P_{\text{trend}}<0.001$).¹¹

Admissions and Mortality Trends

- In England, AMI hospitalizations during the COVID-19 period (February 1–May 14, 2020; n=9325) declined >50% compared with the pre-COVID-19 period (February 1–May 14, 2019; n=20 310), with

- An observational analysis of ED and inpatient data among patients with HF (n=21 262) or AMI (n=6165) from 12 hospital health systems across the St. Louis metropolitan area found that patient volume decreased for AMI during COVID-19 (6.1–6.6 events/d before COVID-19, 4.9–5.5 events/d during COVID-19; $P<0.001$).¹⁶ However, the proportion of patients with STEMI increased during COVID-19 (32.5%–37.6%) compared with before COVID-19 (29.0%–29.3%; $P=0.005$). Furthermore, in-hospital mortality increased for AMI (OR, 1.46 [95% CI, 1.21–1.76]) and STEMI (OR, 2.57 [95% CI, 2.24–2.96]) during the pandemic.
- A meta-analysis comparing AMI admissions during the COVID-19 pandemic with pre-COVID-19 levels found 35% fewer AMI hospitalizations during COVID-19 compared with the pre-COVID-19 period (OR, 0.65 [95% CI, 0.56–0.74]; $I_2=99\%$; $P<0.001$; 28 studies).¹⁷ Hospitalizations also declined for STEMI (OR, 0.71 [95% CI, 0.65–0.78]; $I_2=93\%$; $P<0.001$; 22 studies) and NSTEMI (OR, 0.66 [95% CI, 0.58–0.73]; $I_2=95\%$; $P<0.001$; 14 studies) during COVID-19 compared with before COVID-19.¹⁷ Another meta-analysis of 79 articles across 57 countries found that during the height of the COVID-19 pandemic, the IRR of STEMI hospitalizations decreased (0.80 [95% CI, 0.76–0.84]; $P<0.05$) over the reference period. However,

there was significant heterogeneity across studies ($I^2=89\%$; $P<0.0001$).¹⁸ There was an inverse association between IRRs for STEMI admissions and hospital bed availability in

Social Determinants of Health/Health Equity

- Data from the NIS October 2017 to December 2018 including 294 540 hospitalizations among adults with type 2 MI were analyzed for racial differences in individuals, individuals of other races and ethnicities (Native American, Asian or Pacific Islander, and other underrepresented racial and ethnic groups) had higher in-hospital mortality (aOR, 1.17 [95% CI, 1.03–1.33]; $P=0.016$) and longer length of stay (adjusted parameter estimate, 0.59 [95% CI, 0.22–0.97]; $P=0.002$).
- In a 2013 to 2018 cross-sectional cohort study of 289 376 patients with STEMI and 843 046 patients with NSTEMI ≥ 66 years of age from the United States, Canada, England, the Netherlands, Taiwan, and Israel, Patients with high income (those living in an area [eg, postal code] in the top 20% of the income distribution) had lower 30-day mortality (1–3 percentage points) and 1-year mortality (up to 9.1 percentage points in Israel for STEMI [95% CI, –16.7 to –1.6]) compared with patients with

found in the use of diagnostic angiograms, PCI, and CABG for Asian and Pacific Islander individuals, Black individuals, als over 15 years ($P>0.05$), except for CABG in

STEMI for Black individuals versus White individuals (difference, 2.6% to 1.4%; $P=0.03$).²³

- In an analysis of data from 72 173 census tracts (N=308 243 060) in the 2018 low income (those living in areas in the bottom 20% of the distribution).²⁰ Patients with high income also had higher rates of cardiac catheterization and PCI (1–6 percentage points), lower 30-day readmission rates (1–3 percentage points), and shorter hospital stays (0.2–0.5 days) across all 6 countries. • A longitudinal cohort study examined racial and cohort differences in the relationship between debt and MI risk in the HRS 1992 to 2018.²¹ The study compared the prewar cohort (born 1931–1941, N=8698 in 1992) and Baby Boomers (born 1948–1959, N=6792 in 2010). Higher uncured debt was associated with increased MI risk for Black adults, especially Baby Boomers (aHR, 1.11; $P<0.001$) and during recessions (aHR, 1.05; $P<0.001$). Higher mortgage debt was associated with lower risk for White Baby Boomers (aHR, 0.97; $P<0.001$) but not Black Baby Boomers (aHR, 1.13;

hood's risk for deleterious outcomes in the event of natural disasters or disease outbreaks, was associated with higher CHD prevalence ($\beta=0.0520$; SE, 0.0008; $R^2=0.57$; $P<0.0001$) when accounting for census-tract median age.²⁴

- An NIS analysis of sex differences spanning 2004 to 2015 identified 7 026 432 hospitalizations for AMI. Compared with males, females were less likely to undergo coronary angiography (aOR, 0.92 [95% CI, 0.91–0.93]) and PCI (aOR, 0.82 [95% CI, 0.81–0.83]). Females had a higher risk of mortality (aOR, 1.03 [95% CI, 1.02–1.04]) compared with males.²⁵
- An observational cohort analysis of Medicare beneficiaries hospitalized with MI (N=155 397) in a national MI registry between April 2018 and September 2019 showed that Black adults (compared with non-Black adults) had lower 30-day mortality rates in low-performing hospitals (OR: before the HRRP, 0.80 [95% CI, 0.68–0.95]; $P=0.01$) but not in high-performing hospitals.²⁶
- In 3635 patients who underwent left-sided heart catheterization for CAD at Emory University between 2004 and 2014, low neighborhood SES (a composite measure using 6 census measures capturing income, housing, education, and occupation) was associated with increased risk of cardiovascular death or MI in patients without a prior MI (HR, 2.72 [95% CI, 1.73–4.28] for the lowest versus highest quartile of neighborhood SES), but no association was observed for those with a prior MI (HR, 1.02 [95% CI, 0.58–1.81]; $P_{\text{interaction}}=0.02$).²⁷
- According to the CMS Hospital Inpatient Quality Reporting Program data on 2363 hospitals in 2018, the average 30-day mortality after AMI was 13.6% (interquartile range, 12.8%–14.3%), with higher patient factors, and hospital characteristics, including PCI capabilities.²²
- In a retrospective study of 9 million adults with NSTEMI (72%) and STEMI (28%) from 2005 through 2019, no significant improvement was
- In an observational cohort study of 135 358 patients with STEMI in California EDs from 2010 to 2019, uninsured patients had lower odds of interfacility transfer compared with insured patients (aOR, 0.93 [95% CI, 0.88–0.98]; $P=0.01$) after adjustment for time trends,

mortality observed in rural hospitals (from 13.4%–13.8% for the most urban to most rural hospitals).^{28•}
Among 3006 older adults in the SILVER-AMI study who were recruited across 94 hospitals in the
United States, low emotional support, measured with the Medical Outcomes Study Social Support
Survey, was associated with higher odds of mortality (OR, 1.43 [95% CI, 1.04–1.97]), whereas low
infor-mational support was associated with higher odds of readmission (OR, 1.22 [95% CI, 1.01–
1.47]).²⁹

- In a retrospective cohort study for-service patients (N=453 CAD, there was no significant difference to guideline-based practices that served the highest socioeconomic status. Patients at the most socioeconomically disadvantaged practices had higher rates of unstable angina (aOR, 1.04–2.05) and higher 30-day mortality rates after AMI (aOR, 1.31 [95% CI, 1.02–1.68]). After additional adjustment for patient-level Area Deprivation Index, these associations were attenuated (unstable angina: aOR, 1.20 [95% CI, 1.02–1.68]; 30-day mortality after MI: aOR, 1.31 [95% CI, 1.02–1.68]).
- An NHANES analysis spanning the 2007 to 2016 cycles examined differences in self-reported history of CAD by
- A study of 2 182 903 Medicare patients hospitalized with MI, HF, or compared outcomes in rural versus urban hospitals. Patients in rural hospitals were less likely to undergo revascularization (49.7% versus 63.6%; $P<0.001$), or to be discharged to home (45.7% versus 49.2%; $P<0.001$). Mortality at 30 days was higher for patients at rural hospitals (aHR, 1.10 [95% CI, 1.08–1.12]) compared with patients at urban hospitals. Limited English proficiency status in individuals reporting angina. Participants with limited English proficiency were 2.8 times more likely to report a history of CVD compared with those without limited English proficiency (aOR, 2.77 [95% CI, 1.02–7.44]).

[95% CI, 1.13–1.16]), and ischemic stroke (aHR, 1.20 [95% CI, 1.18–1.22]) compared with their counterparts presenting at metropolitan hospitals.³⁶ In a subset of SILVER-AMI, a community-based longitudinal study of older adults (N=1345, ≥75 years of age), there was no association between neighborhood walkability scores and hospital-free survival time or physical or mental health.³⁷

- REGARDS investigators tabulated the number of social determinants of health to determine a progressive increase in fatal CHD (0 social determinants of health, 1.30; 1 social determinant of health, 1.44; 2 social determinants of health, 2.05; ≥3

CI, 1.38–5.55]).³¹

- Disparities in cardiac rehabilitation are well recognized: Individuals who are female, of Black race, of Hispanic ethnicity, of lower educational attainment, and eligible for dual Medicare/Medicaid coverage have significantly reduced attendance compared with referents.^{32–34} Among Medicare beneficiaries, participation in cardiac rehabilitation is lower among females (18.9%) compared with males (28.6%; adjusted PR, 0.91 [95% CI, 0.90–0.93]) and among

social determinants of health, 2.86) and nonfatal

Hispanic adults (13.2%) and NH Black adults (13.6%) compared with NH White adults (25.8%; adjusted PR, 0.63 [95% CI, 0.61–0.66] and 0.70 [95% CI, 0.67–0.72], respectively).³² Likewise, in the BRFSS 2011 to 2015, participants in cardiac rehabilitation were less likely to be female (OR, 0.76 [95% CI, 0.65–0.90]), Black (OR, 0.70 [95%

MI (0 social determinants of health, 3.91; 1 social determinant of health, 4.33; ≥ 2 social determinants of health, 5.44). Compared with those with no social determinants of health, those with ≥ 3 social determinants of health had an aHR of 1.67 (95% CI, 1.18–2.37) for risk of fatal CHD.³⁸

- Among 22 152 participants free of CHD at baseline in the REGARDS cohort study, there were 463 fatal incident CHD events and 932 nonfatal MIs over a median of 10.7 years (interquartile range, 6.6–12.7 years). Compared with those without social determinants of health, those with ≥ 3 social determinants of health had a higher risk (aHR, 1.67 [95% CI, 1.18–2.37]) of fatal incident CHD, and those with ≥ 2 social determinants of health had a nonsignificant higher risk (aHR, 1.14 [95% CI, 0.93–1.41]) of nonfatal MI.³⁸

CI, 0.53–0.93], uninsured (OR, 0.53 [95% CI, 0.37–0.75]), and less educated (OR, 0.47 [95% CI, 0.37–0.61]) compared with the referents.³³ In Optum’s Clinformatics database (N=107 199), cardiac rehabilitation attendance was 31% lower for Asian adults (95% CI, 27%–36%), 43% lower for Hispanic adults (95% CI, 40%–45%), and 19% lower for Black adults (95% CI, 16%–22%) after

- In an analysis of NIS data from, January 1, 2012, through December 31, 2017, Black adults and individuals from other racial and ethnic groups with AMI compared with White individuals were less likely to undergo coronary angiography (61.9% versus 70.2% versus 73.1%) and PCI (44.6% versus 53.0% versus 58.1%; $P<0.001$).³⁹ adjustment.³⁴
 - A systematic review of 181 studies conducted prior to 2010 found that Black patients were less likely to receive guideline-recommended medical therapy for CHD (aOR, 0.73–0.98) and HF (aOR, 0.59 [95% CI, 0.51–0.70]) than those with commercial insurance.³⁵
- An administrative claims analysis of Medicaid, commercial insurance, and Medicare claims from 2015 to 2018 identified that patients with Medicaid were less likely to receive guideline-concordant testing for MI (aOR, 0.84 [95% CI,

marily in high-income countries found that lower socioeconomic position (education, income, insurance, occupation, or composite) was associated with higher incidence of ACS (IRR, 1.1–4.7), higher prevalence of ACS (OR, 1.8–3.9), higher odds of receiving suboptimal medical care (OR, 1.1–10.0), and higher mortality after ACS (HR, 1.1–4.13).⁴⁰

Risk Prediction

- In a prospective study of 128 322 males and 135 103 females from the UK Biobank study, higher serum levels of sex hormone-binding globulin were associated with a decreased risk of CHD in both males (aHR per 1-log nmol/L increase, 0.88 [95% CI, 0.83–0.94]) and females (aHR, 0.89 [95% CI, 0.83–0.96]).⁴¹ A meta-analysis of 216 417 males and 138 282 females from 11 associated with decreased CHD risk in males (aRR, 0.81 [95% CI, 0.74–0.89]) and females (aRR, 0.86 [95% CI, 0.78–0.94]) when the highest quartile was compared with the lowest quartile.⁴¹
- Two large cohort studies (MESA, N=1991; Rotterdam Study, N=1217) examining adults 45

CAC >10 had higher risk of CHD death (aHR, 2.83 [95% CI, 2.07–3.86]) than those with CAC=0.⁴⁶ This risk was not significantly higher among adults <40 years of age but was significantly higher among adults >40 to 50 years of age (aHR, 2.97 [95% CI, 1.32–6.69]), 50 to 60 years of age (aHR, 5.08 [95% CI, 2.68–9.63]), 60 to 70 years of age (aHR, to 79 years of age (median: MESA, 61 years of age; Rotterdam Study, 67 years of age) demonstrated that incorporating a CAC score significantly improved risk discrimination compared with a traditional risk factor model alone (MESA: change in C statistic, 0.09; Rotterdam Study: change in C sta-

- Among 66 636 asymptomatic adults in the CAC Consortium, those with extremely high CAC scores (≥ 1000) had higher adjusted risk of CVD (HR, 5.04 [95% CI, 3.92–6.48]), CHD (HR, 6.79 [95% CI, 4.74–9.73]), all-cause mortality (HR, 2.89 [95% CI, 2.53–3.31]), and cancer (HR, 1.55 [95% CI, 1.23–1.95]) than those with CAC=0.⁴⁷ Moreover, those with CAC ≥ 1000 had higher adjusted risk of CVD (HR, 1.71 [95% CI, 1.41–2.08]), CHD (HR, 1.84 [95% CI, 1.43–2.36]), all-cause mortality (HR, 1.51 [95% CI, 1.33–1.70]), and cancer (HR, 1.36 [95% CI, 1.07–1.73]) than those with CAC scores of 400 to 999. Notably, the addition of a PRS did not yield a similar improvement.⁴²
- In 9066 participants 45 to 79 years of age from the REGARDS study, the observed and predicted ASCVD risks using the Pooled Cohort Risk Equations were similar in people with high social deprivation, although ASCVD risk was overestimated in those with low social deprivation (observed incident rate, 6.23 [95% CI, 5.31–7.31] versus predicted incident rate, 8.02; Hosmer-Lemeshow $\chi^2=12.43$; $P=0.01$).⁴³
- In the WHI, although the risk of ASCVD was overestimated with the Pooled Cohort Risk Equations, adding ASCVD events identified through linkage with CMS claims that were not self-reported resulted in alignment of the observed and predicted risks (observed [predicted] risks for baseline 10-year risk categories of <5%, 5%–7.5%, 7.5%–10%, and $\geq 10\%$ were 3.8 [4.3], 7.1 [6.4], 8.3 [8.7], and 18.9 [18.7], respectively).⁴⁴
- In 14 169 patients with ASCVD risk <5% and self-reported family history of CHD from the multicenter CAC Consortium followed up for ≈ 12 years, those

- Among 16 289 adults (6526 males, 9763 females) in the HCHS/SOL, WC cut points of >102 cm in males (current joint interim statement criterion) and >97 cm (9 points above the joint interim statement criterion) in females provide optimal discrimination for CHD (evidence of prior MI from ECG or self-report of MI, angina, or coronary procedures).⁴⁸• A precatheterization model and bedside risk score were developed and validated with data from 706 263 PCIs at 1608 sites between July 2018 and June 2019 to predict in-hospital mortality. Variables that predicted in-hospital mortality included cardiovascular instability, level of consciousness after cardiac arrest, and procedural urgency. The C indexes of the precatheterization model and bedside risk score were 0.940 and 0.923, respectively. The simplified bedside score includes age, CKD, cardiovascular instability, and the presence or absence of cardiac arrest before PCI. The total score ranges from 2 to 31 points, with an overall score ≤ 5 corresponding to a predicted mortality rate of <0.1% and a score of ≥ 27 associated with mortality rate of >85%.⁴⁹ with CAC scores >100 had a >10-fold higher risk of CHD mortality than patients with CAC=0 (HR, 10.4 [95% CI, 3.2–33.7]).⁴⁵ Furthermore, addition of CAC to a model with traditional risk factors (age, sex, race, hypertension, hyperlipidemia, diabetes, and smoking status) improved the prediction for CHD mortality (AUC, 0.72 for the model with traditional risk factors and 0.82 for the model adding

- A coronary age calculator was derived with traditional risk factors and CAC score in a MESA cohort of 6727 adults and compared with chronological age, the MESA CHD Risk Score, and CAC alone. The derived coronary age with CAC was identical to the MESA CHD Risk Score in predicting 10-year risk of CHD and had the highest discrimination (AUC, 0.76) compared with chronological age (AUC, 0.63) and coronary age without CAC (AUC, 0.70).⁵⁰
- In a large competing-risk analysis among 66 363 adults from the CAC Consortium, participants with

- In a cohort of 272 307 White Biobank study, the integrated enhanced PCE were CAD cases.⁵¹ The C statistics PCE, and PRS-enhanced CI, 0.634–0.646), 0.718 (95% and 0.753 (95% CI, 0.748– addition of the integrated PRS risk threshold yielded an NRI 0.102–0.129) for cases and – 0.025 to – 0.022) for controls (overall, 0.093 [95% CI, 0.08–0.104]). Among the incident CAD cases, 14.2% were correctly reclassified to the higher-risk category, and 2.6% were incorrectly reclassified to the lower-risk category.
 - The T2-risk score, a risk stratification tool for predicting the primary outcome of death or future MI among patients with type 2 MI, was derived from the High-STEACS trial (2013–2016), the APACE study (2006–2018), and single-center consecutive patients at a hospital in Stockholm (2011–2014).⁵² The T2-risk score, which includes age, IHD, diabetes, HF, myocardial ischemia on ECG, anemia, heart rate, eGFR, and maximal cardiac troponin concentration, had good discrimination (AUC, 0.76 [95% CI, 0.73–0.79]) for the primary outcome and was well calibrated. The T2-risk score improved discrimination over the Global Registry of Acute Coronary Events 2.0 risk score in all cohorts.
- Genetics and Family History**
Family History as a Risk Factor
- Among adults ≥20 years of age, 13.8% (SE, 0.6%) reported having a parent or sibling with a heart attack or angina before 50 years of age. The racial and ethnic breakdown from NHANES 2017 to 2020 is as follows (unpublished NHLBI tabulation)²:
 - 60 to 79 years of age, males and 21.2% (SE, 2.6%) for
 - ≥80 years of age, 11.1% and 13.3% (SE, 2.1%) for
 - Data from a longitudinal (N=49 255) demonstrated an family history of premature or bypass surgery and ≈50% for both HD (from 8.9% mortality (from 14.1% to
 - For NH White people, 14.0% (SE, 1.5%) for males and 15.7% (SE, 0.9%) for females.
 - For NH Black people, 9.7% (SE, 1.5%) for males and 14.4% (SE, 1.2%) for females.
 - For Hispanic people, 8.1% (SE, 1.1%) for males and 12.9% (SE, 1.4%) for females.
 - For NH Asian people, 6.3% (SE, 1.3%) for males and 8.4% (SE, 1.5%) for females.
 - Because the incidence of HD increases with age, the prevalence of family history will vary depending on the age at which family history is assessed. The distribution of reported family history of heart attack by age of survey respondent in the US population as measured by NHANES 2017 to 2020 is as follows (unpublished NHLBI tabulation)²:
 - 20 to 39 years of age, 7.8% (SE, 1.3%) for males and 10.1% (SE, 0.8%) for females.
 - 40 to 59 years of age, 16.1% (SE, 1.7%) for males and 16.9% (SE, 1.4%) for females.

Genetic Predictors of CHD

- CHD is heritable. From 36 years of follow-up data in 20 966 Swedish twins, the heritability of CHD mor- tality was 57% for males and 38% for females.⁵⁴ Of note, estimated heritability was operative through- out the life span but more prominently at younger ages of death, particularly for males.
- The application of GWASs to large cohorts of sub- jects with CHD has identified consistent genetic variants associated with CHD. Although several CHD loci indicate roles for atherosclerosis and traditional CVD risk factors, other loci highlight the importance of biological processes (ie, cellular adhesion, leukocyte migration and atherosclerosis, coagulation and inflammation, and vascular smooth muscle cell differentiation) in the arterial wall.⁵⁵• The first GWAS identified a locus on chromosome 9p21.3, which is the most consistently replicated genetic marker for CHD and MI in populations of European ancestry.⁵⁶ The primary SNP at 9p21.3 is common; 50% of the population of European ancestry is estimated to harbor 1 risk allele, and 23% harbor 2 risk alleles.⁵⁷
 - A meta-analysis of 22 studies (N=35 872 cases; N=95 837 controls) identified the 10-year HD risk for a male 65 years of age with two 9p21.3 risk alleles and no other traditional risk fac- tors as ≈13.2%, whereas a similar male with 0 alleles would have a 10-year risk of ≈9.2%. The 10-year HD risk for a female 40 years of age with 2 alleles and no other traditional risk factors is ≈2.4%, whereas a similar female with 0 alleles would have a 10-year risk of ≈1.7%.⁵⁷
- GWASs have identified multiple loci associated with CAD implicating pathways in blood vessel morphogenesis, lipid metabolism, nitric oxide sig- naling, inflammation, and basic cellular processes governing the cell cycle,⁵⁸ division/replication, and growth. One large, ancestrally diverse GWAS included n=243 392 CAD case and n=849 686 control MVP participants.⁵⁹ After meta-analysis with predominantly European ancestry GWASs from CARDIoGRAMplusC4D and the UK Biobank, this GWAS identified 33 novel loci. Further meta- analysis with Biobank Japan and inclusion of MVP

Black participants and Hispanic participants identified 66 novel loci. These loci did not demonstrate heterogeneity across ancestral populations. Most of these novel loci (58%) were associated with CAD risk factors (eg, blood lipids, BP, diabetes, obesity, or smoking).

Large-scale collaborative genetic studies of CAD (n=72 868 cases and n=120 770 controls) focused on the coding regions of the genome (exons) have identified additional loci, 4), which is an inhibitor of lipoprotein lipase.⁶⁰

These variants are associated with low plasma triglycerides and high HDL-C.

- A study of X chromosome genetic variation in >500 000 multiancestry individuals from the TOPMed Consortium found common alleles on

- In the FOURIER study (N=14 298), patients without multiple clinical risk factors or high genetic risk as defined by a 27-CHD-variant PRS did not derive benefit from evolocumab, whereas patients with high genetic risk, regardless of clinical risk, had reduced risk of major coronary events (HR, 0.69 [95% CI, 0.55–0.86]; $P=0.0012$).⁶⁷

chromosome Xq23 to be strongly associated with lower TC, LDL-C, and triglycerides in both females and males and associated with reduced odds for CHD and type 2 diabetes.⁶¹ Every additional rs5942634-T allele, the lead cholesterol-lowering variant in chromosome Xq23, was associated with

change in C statistic for incident CAD prediction between a PCE and GRS model was 0.02 (95% CI, 0.01–0.03) with an overall NRI of 4.0% (95% CI, 3.1%–4.9%).⁶⁸ In the ARIC and MESA studies, adding a GRS to the PCE did not significantly increase the C statistic in either cohort for prediction of incident CHD events (change in C statistic: ARIC, –0.001 [95% CI, –0.009 to 0.006]; MESA, 0.021 [95% CI, –0.0004 to 0.043]).⁶⁹ In an East Asian cohort (N=41 271), addition of a PRS including 540 genetic variants to clinical risk factors had an NRI for CAD of 3.2% (95% CI,

estimated ORs of 0.98 (95% CI, 0.96–0.99) for CHD and 0.97 (95% CI, 0.96–0.99) for type 2 diabetes.

- Hematopoietic somatic variants (clonal hematopoiesis of indeterminate potential) that accumulate with age are also independent

0.9%–5.8%).⁷⁰

- GRSs derived from 1 ancestry may have limited generalizability to individuals of different ancestries, predictors of CHD events. Carriers of clonal hematopoiesis of indeterminate potential had a risk of CHD 1.9 times greater

necessitating the development of GRSs that are ancestry specific.⁷¹ An example is a GRS for CAD derived and validated in South Asian individuals (OR per 1 SD, 1.58 [95% CI, 1.42–1.76]) that outperformed previous scores based on European ancestral populations.⁷²

than that of noncarriers (95% CI, 1.4–2.7) and a risk of MI 4.0 times greater than that of noncarriers (95% CI, 2.4–6.7).⁶² Clonal hematopoiesis of indeterminate potential itself has germline genetic determinants.⁶³

Clinical Utility of Genetic Markers

- Studies have shown that patients with early-onset MI have a higher proportion of high PRS than those with FH variants; for example, ≈2% carry a rare FH genetic variant, whereas ≈17% have a high PRS.⁶⁴
- Even in individuals with high genetic risk, prevention strategies may have benefit. For example, in 4 studies across 55 685 individuals, genetic and lifestyle factors were independently associated with CHD, but even in individuals at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower RR of CHD than an unfavorable lifestyle (HR, 0.54 [95% CI, 0.47–0.63]).⁶⁵
- A summary of the 5 most highly cited studies of PRS concluded that the change in C statistic with the addition of PRS to the standard risk model improves the C statistic by –0.001 to 0.021 and that PRS has a limited contribution to primary prevention of CAD.⁶⁶

• Data from the NHIS 2017 indicate that being unaware of all 5 MI symptoms was more common in males (OR, 1.23 [95% CI, 1.05–1.44]), Hispanic individuals (OR, 1.89 [95% CI, 1.47–2.43]), those not born in the United States (OR, 1.85 [95% CI, 1.47–2.33]), and those with a high school or lower education (OR, 1.31 [95% CI, 1.09–1.58]).⁷³

Compared with adults born in the United States, adults born in Europe, Russia, Africa, the Middle East, the Indian subcontinent, Asia, and Southeast Asia were likely to be aware of all 5 MI symptoms in the NHIS 2017 cycle.⁷⁴

• Data from an online survey of US females (≥25 years of age) showed that awareness related to CHD as a leading cause of death among females declined from 65% in 2009 to 44% in 2019. The decline in awareness was observed in all racial and ethnic groups and ages except females ≥65 years of age.

Moreover, NH Black females (OR, 0.31 [95% CI, 0.19–0.49]) and Hispanic females (OR, 0.14 [95% CI, 0.07–0.28]) and 25- to 34-year-old females (OR, 0.19 [95% CI, 0.10–0.34]) experienced the

greatest 10-year decline in awareness from 2019 to 2009.⁷⁵

Time of Symptom Onset and Arrival at Hospital

- The weekend effect, that is, presentation with ACS on a weekend rather than weekday, has been examined with regard to timing and use of invasive management strategies. An analysis of NIS data spanning 2000 to 2016 identified statistically different rates of coronary angiography (59.9% versus 58.8%; $P<0.001$) and PCI (38.4% versus 37.6%; $P<0.001$) between weekend and weekday ACS presentations, more pronounced when early coronary angiography was examined (26% versus 21%; $P<0.001$).⁷⁶ Weekend presentation was not associated with increased risk of mortality compared with weekday presentation with ACS (OR, 1.01 [95% CI, 1.00–1.01]). A meta-analysis of 56 studies (N=384 452) concluded that individuals with STEMI presenting during off-hours had similar short-term (RR, 1.07 [95% CI, 1.00–1.14]), midterm (RR, 1.00 [95% CI, 0.95–1.05]), and long-term (RR, 0.95 [95% CI, 0.86–1.04]) mortality compared with those presenting during regular working hours.⁷⁷
- A European registry of 6609 patients treated at 77 high-volume PCI centers determined that the COVID-19 pandemic was associated with a significant increase in door-to-balloon and total ischemia times.⁷⁸ Door-to-balloon time >30 minutes was 57.0% in the period of March to April 2020 compared with 52.9% in March to April 2019 ($P=0.003$), and total ischemia time >12 hours was 11.7% in the 2020 period compared with 9.1% in 2019 ($P=0.001$).
- In a meta-analysis including 57 136 patients from 10 studies, door-to-balloon time of >90 minutes versus ≤90 minutes was associated with higher in-hospital or 30-day mortality (OR, 1.52 [95% CI, 1.40–1.65]). An increased risk of 6-month to 12-month mortality was also observed for >90-minute door-to-balloon delay in 14 261 patients from 8 studies (OR, 1.53 [95% CI, 1.13–2.06]).⁷⁹
 - Rural EMS response has been longer than activation from suburban or metropolitan locations. National data from 2015 indicated that the mean response time for EMS was 14.5 minutes (9.5 minutes) in rural zip codes, 7.0 minutes (4.4 minutes) in urban zip codes, and 7.7 minutes (5.4 minutes) in suburban zip codes.⁸⁰
- Analysis of a multinational registry of PCI for STEMI that included 109 high-volume centers determined that in 2020 the incidence of PCI was significantly less than in 2019 (IRR, 0.84 [95% CI, 0.83–0.86]), accompanied by increased likelihood of door-to-balloon time >30 minutes (OR, 1.1 [95% CI, 1.03–1.17]).⁸¹

Operations and

- In 2021, an CABGs, 110 245 carotid endarterectomy and stenting

Comparison of Percutaneous

- An analysis of pared with combined short-term (ie, tality (OR, postoperative $I_2=90\%$)
- In an analysis SYNTAX trials MI and left PCI) was 0.29 [95% CI, up of 59.8 months).⁸⁴
- At 10 years of 1800 trial death was and among CAD; greater risk of with PCI (HR,
- The with stable on stress treatment. difference in cardiovascular angina, randomized to [95% CI, 100 patients arms).⁸⁶
- In patients intermediate difference in or death was CABG ischemia-CI, 1.39–CI, 1.03–
- In the NCDR cedures were lesions. A stroke, quent in CI, 1.39–1.53])

• In 4041 patients with STEMI with multivessel CAD randomized to complete revascularization versus culprit lesion-only PCI, those with complete revascularization experienced lower rates of a composite end point of cardiovascular death or MI (HR, 0.74 [95% CI, 0.60–0.91]; $P=0.004$) and a composite end point of cardiovascular death, MI, or ischemia-driven revascularization (HR, 0.51 [95% CI, 0.43–0.61]; $P<0.001$) at a median follow-up of 1.5 years.⁹⁰

• In 744 hospitals in the ACTION registry, preactivation of the catheterization laboratory >10 minutes before hospital arrival compared with no preactivation was associated with shorter times to the catheterization laboratory (median, 17 minutes [interquartile range, 7–25 minutes] versus 28 minutes [interquartile range, 18–39 minutes]), shorter door-to-device time (median, 40 minutes [interquartile range, 30–51 minutes] versus 52 minutes [interquartile range, 41–65 minutes]), and lower in-hospital mortality (2.8% versus 3.4%; $P=0.01$).⁹⁰

• In the ISCHEMIA randomized trial including 5179

(aOR, 0.57 [95% CI, 0.54–0.60]) and 30-day MI readmission (aOR, 0.46 [95% CI, 0.35–0.59]) were lower among those with type 2 MI than those with type 1 MI.⁹³

• In a Swedish population-based registry (N=4085), PCI for unprotected left main CAD increased from 121 procedures in 2005 to 589 in 2017.⁹⁴ The risk of major adverse cardiac events in patients with stable coronary disease and moderate or severe ischemia, an initial invasive strategy did not reduce ischemic cardiovascular events or death compared with an initial conservative strategy (risk difference, –1.8% [95% CI, –4.7% to 1%] at 5 years).⁹¹

Secular Trends in Procedures

• In an analysis of the NIS, among patients ≥ 70 years of age with non-ST-segment-elevation ACS or STEMI, the proportion of patients undergoing PCI increased from 7.3% in 1998 to 24.9% in 2013 in those with non-ST-segment-elevation ACS and from 11% in 1998 to 35.7% in 2013 in those with

Cardiac Rehabilitation

- In the BRFSS from 2005 to 2015, <40% of patients self-reported participation in cardiac rehabilitation after AMI. Between 2011 and 2015, patients who declared participation in cardiac rehabilitation were less likely to be female (OR, 0.76 [95% CI, 0.65–0.90]; $P=0.002$) or Black (OR, 0.70 [95% CI, 0.53–0.93]; $P=0.014$), were less well educated (high school versus college graduate: OR, 0.69 [95% CI, 0.59–0.81]; $P<0.001$; less than high school versus college graduate: OR, 0.47 [95% CI, 0.37–0.61]; $P<0.001$), and were more likely to be retired or self-employed (OR, 1.39 [95% CI, 1.24–1.73]; $P=0.003$) than patients who did not participate in cardiac rehabilitation.³³
- Among 366 103 Medicare fee-for-service beneficiaries eligible for cardiac rehabilitation in 2016, only 24.4% participated in cardiac rehabilitation; among those who participated, the mean time to initiation was 47.0 days (SD, 38.6 days), and 26.9% completed cardiac rehabilitation with ≥ 36 sessions. Participation decreased with increasing age and was lower in females, Hispanic people, Asian people, those eligible for dual Medicare/Medicaid coverage, and those with ≥ 5 comorbidities.³²
- An analysis of HCUP Inpatient and State Ambulatory and Surgery and Services Databases quantified the number of patients who underwent PCI from 2010 to 2017 in Florida, Maryland, Michigan, and New

• A systematic review of 9 studies concluded that

home-based cardiac rehabilitation is cost-effective, albeit recognizing heterogeneity across studies, limited duration of follow-up, and absence of consideration of diversity of cardiac rehabilitation

York.¹¹ In these 4 states, PCI rates declined from 260.2 per 100 000 individuals in 2010 to 232.8 per 100 000 individuals in 2017 (−10.5%; $P_{\text{trend}} < 0.001$). This decline was attributed to a decrease in elective PCI across these years of

participants.⁹⁵

−34.4%. Rates of urgent PCI increased from 95.0 per 100 000 individuals in 2010 to 109.2 in 2017 (+15.0%; $P_{\text{trend}} < 0.001$).

- Among 216 657 adults with type 1 MI, 37 675 adults with type 2 MI, and 1521 with both type 1 and type

- In an administrative analysis of individuals eligible for cardiac rehabilitation (N=107 199), 28 433 (26.5%) attended cardiac rehabilitation.³⁴ After adjustment, compared with White individuals, the probability of attending cardiac rehabilitation was 31% lower for Asian individuals (95% CI, 27%–36%), 19% lower for Black individuals (95% CI, 16%–22%), and 43% lower for Hispanic individuals (95% CI, 40%–45%).
- 2 MI in the Nationwide Readmissions Database, use of coronary angiography (10.9% versus 57.3%; $P<0.001$), PCI (1.7% versus 38.5%; $P<0.001$), and CABG (0.4% versus 7.8%; $P<0.001$) was lower among patients with type 2 MI than those with type 1 MI. Furthermore, the risks of in-hospital mortality

- In a randomized trial in patients undergoing cardiac rehabilitation after ACS with PCI, patients receiving digital health lifestyle interventions had more weight loss at 90 days than the control group (-5.1 ± 6.5 kg versus -0.8 ± 3.8 kg [mean $\pm$ SD]; $P=0.02$) and

a nonsignificant decrease in rehospitalizations and ED versus 26.6%; RR, 0.30 [95% $P=0.054$].⁹⁶

- In an observational study with IHD, the 1-year mortality between those who accepted rehabilitation ($n=490$) did not (HR, 0.67 [95% CI, 0.45–1.00] vs 0.90).

who participated in home-based cardiac rehabilitation had an HR of 0.64 (95% CI, 0.45–

– CHD mortality was 371 506 CHD any-mention mortality was – MI mortality was 103 905 mention mortality was 151

- From 2012 to 2022, the annual rate of deaths attributable to CHD declined 16.9%, number of deaths stayed relatively stable (published NHLBI tabulation using age-adjusted death rates by sex, race, and ethnicity can be found in Table 0.90) compared with those who declined.

- In 2022, 79% of CHD deaths occurred out of hospital. According to US mortality data, 294 458 CHD deaths occurred out of hospital or in hospital EDs in 2022 (unpublished NHLBI tabulation using CDC

Mortality

(See Table 21-1)

- In an observational study using the NIS and National Readmission Database between 2017 and 2019, which compared Takotsubo syndrome (n=43 335), type 1 MI (n=2 035 055), and type 2 MI (n=639 075), mortality

WONDER¹⁰³).

risk was lower in Takotsubo syndrome compared with type 1 MI (aOR, 0.3; $P<0.001$) and type 2 MI (aOR, 0.3; $P<0.001$). Type 1 MI had higher mortality (aOR, 1.2; $P<0.001$) than

- The estimated average number of YLL because of an MI death was 14.6 in 2022 (unpublished NHLBI tabulation using CDC WONDER¹⁰³).
- Approximately 35% of the people who experience a coronary event in a given year will die as a result of it, and ≈14% who experience an MI will die of it (unpublished NHLBI tabulation using ARIC Community Surveillance [2005–2014]).⁵
- An analysis of the multicenter NCDR Chest Pain–MI type 2 MI.⁹⁸
 - In a meta-analysis of 81 studies involving 157 439 patients with COVID-19, those with preexisting CHD had a higher risk of mortality (OR, 2.45 [95% CI, 2.04–2.94]; $P<0.001$), severe/critical COVID-19 (OR, 2.57 [95% CI, 1.98–3.33]; $P<0.001$), ICU/coronary care unit admission (OR, 2.75 [95%

Registry (N=155 397 patients and 763 hospitals) CI, 1.61–4.72]; $P=0.002$), and lower odds of dis-charge/recovery (OR, 0.43 [95% CI, 0.28–0.66]; $P<0.001$) compared with those without preexisting

reported that 30-day mortality among hospitalized patients with MI decreased from 6.6% to 5.0% in Black individuals and from 5.2% to 4.0% in non-Black individuals in the period of 2008 to 2016. Furthermore, racial differences in readmission were not significant after covariate adjustment.²⁶

• According to data on >4 million Medicare fee-for-service beneficiaries with AMI, 30-day mortality declined from 1995 through 2014 (20.0% to

CHD.⁹⁹

- In a propensity score–matched analysis of 159 890 STEMI hospitalizations from the 2020 NIS database, 1.38% had concurrent COVID-19.¹⁰⁰ These patients had higher in-hospital mortality (17.8% versus 9.1%) and lower rates of same-day PCI (63.6% versus 70.6%) and CABG (3.0% versus 6.8%) compared with those without COVID-19. However, COVID-19–positive patients with STEMI receiving same-day PCI had lower odds of in-hospital mortality (aOR, 0.42 [95% CI, 0.20–0.85]).

12.4%). Mortality was higher in females, but over

- In a meta-analysis of 4 retrospective, nonrandomized, observational cohort studies among 184 951 patients ≥18 years of age diagnosed with NSTEMI, early treatment (administered within 24 hours) with β-blockers was associated with a significant reduction in in-hospital mortality compared with no β-blocker treatment (OR, 0.43 [95% CI, 0.36–0.51];

- time, the difference in 30-day mortality between males and females reduced.¹⁰⁴
- Other data indicate that the rapid increase in the population ≥65 years of age has contributed to the reduction of HD mortality. From CDC WONDER data from 2011 through 2017, a deceleration in the decline in HD mortality was observed with a <1% annualized decrease. Taking into account the increase in the growth of the population ≥65 years of age combined with the slowing of the decrease in HD mortality resulted in an increase in the absolute number of HD deaths since 2011 (50 880 deaths; 8.5% total increase). However, the age-adjusted mortality for CHD continued to decline (2.7% annualized decrease) and the absolute number of CHD deaths declined (2.5% total decrease over the time period) between 2011 and 2017.¹⁰⁵
 - An analysis of those enrolled in Medicare Advantage or traditional Medicare from 2009 to 2018 presenting with STEMI (n=557 309) and NSTEMI (n=1 670 193) identified significant 30-day $P=0.0022$).¹⁰¹
 - On the basis of 2022 mortality data (unpublished NHLBI tabulation using NVSS¹⁰²):

mortality rate differences in 2009 that were no longer present in 2018.¹⁰⁶ In 2018, the 30-day mortality for STEMI was 17.7% in those with Medicare Advantage and 17.8% in those with traditional Medicare (difference, 0.0 percentage points [95% CI, -0.7 to 0.6]); for NSTEMI, the 30-day mortality rate was 10.9% in those with Medicare Advantage and 11.1% in those with traditional Medicare (difference, -0.2 percentage points [95% CI, -0.4 to 0.1]).

- An analysis of the ISCHEMIA trial (N=5179) compared 4-year mortality in trial participants classified as having mild/no ischemia, moderate ischemia, or severe ischemia. Compared with those with mild/no ischemia, 4-year mortality

in 2011 and 2018 found that Black individuals had higher overall mortality than White individuals (OR, 1.11 [95% CI, 1.05–1.18]).¹¹⁵ Likewise, odds of death were higher in females compared with males (OR, 1.26 [95% CI, 1.21–1.30]).

- A pooled analysis of 21 randomized PCI trials including 32 877 patients (27.8% females) found that in rates were similar in those with moderate (HR, 0.89 [95% CI, 0.61–1.30]) and severe (HR, 0.83 [95% CI, 0.57–1.21]) ischemia.¹⁰⁷ In extended follow-up (median, 5.7 years), ISCHEMIA participants randomized to an initial

- get lesion vascularization (HR, 1.23 [95% CI, 1.05–1.44]) but not all-cause or cardiovascular mortality (HR, 0.91 [95% CI, 0.75–1.09] and 0.97 [95% CI, 0.73–1.29], respectively).¹¹⁶
- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the (unpublished NHLBI tabulation):
 - At ≥ 45 years of age, 18% of males and 23% of invasive strategy did not have increased mortality (HR, 1.00 [95% CI, 0.85–1.18]) compared with those randomized to an initial invasive strategy.¹⁰⁸
 - A meta-analysis of 56 studies determined that females with STEMI have higher mortality risk (OR, 1.91 [95% CI, 1.84–1.99]) than males.¹⁰⁹
 - An NIS analysis spanning 2004 to 2018 determined that females had a higher incidence of mortality after PCI than males (1.12% mortality compared

- At 45 to 64 years of age, 3% of White males, 5% of White females, 9% of Black males, and 10% of Black females will die.
 - At 65 to 74 years of age, 14% of White males, 18% of White females, 22% of Black males, and 21% of Black females will die.
 - At ≥ 75 years of age, 27% of White males, 29% of White females, 19% of Black males, and 31% of Black females will die.
with 0.78%).¹¹⁰
- A prospective analysis of data on 5064 Black adults in the JHS between 2019 and 2021 found that

- In part because females have MIs at older ages than males, they are more likely to die of MI within a few weeks. participants with CHD (HR, 1.59 [95% CI, 1.22–2.08]), diabetes (HR, 1.50 [95% CI, 1.22–1.85]), or stroke (HR, 1.74 [95% CI, 1.24–2.42]) had higher risk for all-cause mortality compared with those with no cardiometabolic morbidities.¹¹¹ Those with ≥ 2 cardiometabolic morbidities had higher risk of all-

- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012), within 5 years after a first MI (unpublished NHLBI tabulation):
 - At ≥45 years of age, 36% of males and 47% of females will die.
 - At 45 to 64 years of age, 11% of White males, 17% of White females, 16% of Black males, and

Social Determinants and Health Equity of Mortality

- In-hospital mortality is higher in females than in males with STEMI (7.4% versus 4.6%) and NSTEMI (4.8% versus 3.9%). An analysis of NCDR data from 2010 to 2015 reported that females admitted with STEMI had decreased survival to discharge compared with males (OR, 0.63 [95% CI, 0.52–0.76]).^{112,113} Females experience longer door-to-balloon times and lower rates of GDMT than males; however, a 4-step systems-based approach to minimize STEMI care variability at the Cleveland Clinic decreased the difference in 30-day mortality between males and females.¹¹⁴
- An analysis of the STS database including 1 042 056 patients who underwent isolated CABG between

28% of Black females will die.

- At 65 to 74 years of age, 25% of White males, 30% of White females, 33% of Black males, and 44% of Black females will die.
- At ≥75 years of age, 55% of White males, 60% of White females, 61% of Black males, and 64% of Black females will die.
- An analysis conducted in the CARDIA study (N=5112) with a median follow-up >33 years identified that premature CVD risk in Black participants was attenuated after adjustment for lifestyle, neighborhood, and socioeconomic factors.¹¹⁷ For example, the 2.4-fold increased CVD risk in Black females (95% CI, 1.71–3.49) relative to White females was no longer significant after adjustment for clinical, lifestyle, socioeconomic, and neighborhood factors.

The largest decreases in the for CVD risk occurred with (87%), neighborhood (32%), (23%) factors.

- In MESA, an analysis (N=6814) that compared with White participants had increased risk of [95% CI, 1.19–1.51]), which ment for socioeconomic 1.01–1.34]).¹¹⁸
- A large regional health care system in Northern California conducted an analysis of 1-year mean residential-level estimates of PM_{2.5} in individuals with ASCVD. A 10-μg/m₃ increase in PM_{2.5} exposure was associated with an HR of 1.20 (95%, 1.11–1.30) increased risk of
- SES, those residing in the rienced higher rates of in- [95% CI, 1.02–1.18]) and [95% CI, 1.05–1.15]).¹²⁴
- In an analysis of the NIS, sentina with spontaneous tion had higher odds of in- than females without dissection (3.8%; OR, 1.87 $P<0.001$) in a propensity-matched cardiovascular mortal- ity but not stroke or MI.¹¹⁹
- A meta-analysis of 30 cardiac surgery studies identified that females have an increased risk of short-

- In the NCDR ACTION Registry–GWTG, patients with STEMI or NSTEMI with nonobstructive coronary arteries (<50% stenosis) had lower in-hospital mortality than patients with obstructive CAD (1.1% versus 2.9%; $P<0.001$). Nonobstructive coronary arteries were more common in females than males (10.5% versus 3.4%; $P<0.001$), but no difference in in-hospital mortality was observed between females and males with nonobstructive coronary arteries term mortality after CABG (aOR, 1.40 [95% CI, 1.32–1.49]; $I^2=79\%$) compared with males.^{.83}
- Sex differences in outcomes after MI are well established. In Olmsted County, Minnesota, mortality risk after premature MI (defined as 18–55 years of age in males and 18–65 years of age in females) declined by 66% in females (HR, 0.34 [95% CI, 0.17–0.68]) from 1987 through 2012. In contrast, no significant decline in mortality was observed in males.^{.120} A multicenter study in London, UK (N=26 799), determined that multivariable-adjusted sex differences in survival after STEMI over a median of 4.1 years (interquartile range, 2.2–5.8 years) of follow-up were significant in those >55 years of age (HR, 1.20 [95% CI, 1.09–1.41] for females compared with males).^{.121}

Complications

- A comparison of 2 NIS cohorts of young adults (18–44 years of age) hospitalized with AMI in 2007 and 2017 revealed an overall increased admission rate, with a decline in

($P=0.84$).^{.126}

males (77.1% to 66.1%) and a rise in females (28.9% to 33.9%).^{.122} Post-AMI complications, including cardiogenic shock (aOR, 1.16 [95% CI, 1.06–1.27]) and SVT (aOR, 3.76 [95% CI, 3.18–4.44]), increased, whereas all-cause mortality was comparable in these 2 time periods. (aOR, 1.01 [95% CI, 0.93–1.10]; $P=0.749$).

- STEMI confers greater in-hospital risks than NSTEMI, including death (6.4% for STEMI, 3.4% for NSTEMI), cardiogenic shock (4.4% versus 1.6%, respectively), and bleeding (8.5% versus 5.5%, respectively).^{.123} In the NCDR ACTION Registry–GWTG, a measure of neighborhood SES based on census data was associated with in-hospital deaths and major bleeding in patients with AMI. Compared

- In a propensity score–matched analysis from the NIS HCUP that included discharges with MI as the principal diagnosis from 2012 to 2014, patients with concomitant delirium had higher rates of in-hospital mortality than those without delirium (10.5% versus 7.6%; RR, 1.39 [95% CI, 1.2–1.6]; $P<0.001$).¹²⁷
- In a trial of patients presenting with STEMI (N=402), those with HF symptoms (New York Heart Association functional class ≥ 2 ; n=76) within 30 days after PCI for STEMI experienced increased risk of death or hospitalization for HF within 1 year compared with those without HF symptoms (HR, 3.78 [95% CI, 1.16–12.22]; $P=0.03$).¹²⁸
- The burden of rehospitalizations for AMI is substantial. Among Medicare fee-for-service patients ≥ 65 years of age who were discharged alive after AMI in 2009 to 2014, the rate of 1-year recurrent AMI was 5.3% (95% CI, 5.27%–5.41%) with a median of 115 days (interquartile range, 34–230 days) of time from discharge to recurrent AMI.¹²⁹
- Sudden death after MI is common. A secondary analysis of IMPROVE-IT (N=18 144) determined the cumulative incidence rate of sudden death after MI as 2.47% (95% CI, 2.23%–2.73%) at the 7-year follow-up.¹³⁰

Age, Sex, Race, and Complications

- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012; unpublished NHLBI tabulation), of those who have a first MI, the percentage with a recurrent MI or fatal CHD within 5 years is as follows:
 - At ≥ 45 years of age, 17% of males and 21% of females with those in the highest quintile of neighborhood females.

-
- At 45 to 64 years of age, 11% of White males, 15% of White females, 22% of Black males, and 32% of Black females.
 - At 65 to 74 years of age, 12% of White males, 17% of White females, 30% of Black males, and 30% of Black females.
 - At ≥75 years of age, 21% of White males, 21% of White females, 45% of Black males, and 20% of Black females.
 - The percentage of people with a first MI who will have HF in 5 years is as follows:
 - At ≥45 years of age, 16% of males and 22% of females versus 5.8% in males; HR, 1.13 [95% CI, 1.05–1.21]).¹³²
 - An Australian registry of individuals who had undergone PCI (N=13 996) from 2008 to 2020 determined that female sex was associated with increased 2-year
- Hospital Discharges and Ambulatory Care (See Chart 21-5)*

- From 2011 to 2021, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1 193 438 to 886 904.
- At 45 to 64 years of age, 6% of White males, 10% of White females, 13% of Black males, and 25% of Black females.

charges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1 193 438 to 886 904.

- From 1997 through 2021, the number of hospital discharges for CHD generally declined (Chart 21-5).
 - At 65 to 74 years of age, 12% of White males, 16% of White females, 20% of Black males, and 32% of Black females.
 - At ≥75 years of age, 25% of White males, 27% of White females, 23% of Black males, and 19% of NH Black females.

tal discharges for CHD generally declined (Chart 21-5).

- The percentage of people with a first MI who will have an incident stroke within 5 years is as follows:
 - At ≥45 years of age, 4% of males and 7% of females.
 - At ≥45 years of age, 5% of White males, 6% of

- In 2019, there were 14 167 000 physician office visits for CHD (unpublished NHLBI tabulation using NAMCS¹³⁴). In 2021, there were 909 467 ED vis-its with a primary diagnosis of CHD (unpublished NHLBI tabulation using HCUP⁸²).
- In the NIS, the mean length of hospital stay for patients with STEMI with primary PCI declined from 3.3 days in 2005 to 2.7 days in 2014; the proportion of hospitalizations with length of stay >3 days declined from 31.9% in 2005 to 16.9%
 White females, 4% of Black males, and 10% of Black females.
- The median survival time (in years) after a first MI is as follows:
 - At ≥45 years of age, 8.2 for males and 5.5 for females.
 - At ≥45 years of age, 8.4 for White males, 5.6 for White females, 7.0 for Black males, and 5.5 for Black females.
- In 2014.¹³⁵
- In the CathPCI registry, a composite of use of evi-
- A systematic review and pooled analysis of 4 CABG trials compared sex differences in outcomes between females (n=2714) and males (n=10 479).
 Over the 5-year follow-up, females had a sig-nificantly increased risk of major adverse cardiac and cerebrovascular events (aHR, 1.12 [95% CI, 1.04–1.21]), MI (aHR, 1.30 [95% CI, 1.11–1.52]), and repeat revascularization (aHR, 1.22 [95% CI, 1.04–1.43]) but not stroke (aHR, 1.17 [95% CI,

dence-based medical therapies, including aspirin, P2Y12 inhibitors, and statins, was high (89.1% in 2011 and 93.5% in 2014). However, in the ACTION-GWTG registry, metrics shown to need improvement were defect-free care (median hospital performance rate, 78.4% in 2014), P2Y12 inhibitor use in eligible medically treated patients with AMI (56.7%), and use of aldosterone antagonists in patients with LV systolic dysfunction and either diabetes or HF (12.8%).¹²³

- Among 147 600 individuals with premature ASCVD (≤ 55 years of age) receiving care in the Veterans Affairs health care system from October 1, 2014, through September 30, 2015, there were 10 413 females and 137 187 males. In adjusted analyses, females were less likely to receive antiplatelet therapy (OR, 0.47 [95% CI, 0.45–0.50]),¹³¹

- A meta-analysis of 56 studies of STEMI identified that compared with males, females hospitalized with

any statin (OR, 0.62 [95% CI, 0.59–0.66]), or high-intensity statin (OR, 0.63 [95% CI, 0.59–0.66])
 STEMI are more likely to experience repeat MI (OR, 1.25 [95% CI, 1.00–1.56]), stroke (OR, 1.67 [95% CI, 1.27–2.20]), and major bleeding (OR, 1.82 [95% CI, 1.56–2.12]).¹⁰⁹ than males.¹³⁶ Database determined that after hospitalization for AMI, females had 13% increased risk of 6-month HF hospitalization compared with males (6.4% in

- An analysis of the US Nationwide Readmissions

- Among individuals presenting with an MI or under-going coronary revascularization in the Veterans Affairs health care system from July 24, 2015, through December 9, 2019 (N=81 372), the proportions receiving lipid-lowering intensification were 33.3% at 14 days, 41.9% at 3 months, and 47.3% at 12 months after hospitalization.¹³⁷ Lipid-lowering

intensification was defined as using therapies to achieve LDL 100 mg/dL.

- An analysis of the ISCHEMIA compared days alive out of the hospital among patients receiving mild/no ischemia, ischemia and randomized to conservative management was no significant difference (1415.0 days with mild/no ischemia, 1412.2 days with invasive

Cost

- The estimated direct cost of CHD (average annual) was \$52.8 million (unpublished NHLBI)
- The estimated direct and indirect cost of CHD from 2020 to 2021 (average annual) (MEPS¹³⁹ unpublished NHLBI)
- MI (\$14.3 billion) and CHD (\$8.7 billion) of the 10 most expensive diseases in 2017.¹⁴⁰
 - In 642 105 Medicare beneficiaries with AMI between 2011 and 2014, median costs were \$22 128 but hospitals. Median costs were \$24 174 in the first quartile versus \$24 174 in the third quartile of hospitals.¹⁴¹
 - In Medicare beneficiaries with 180-day expenditures of \$32 182 per person in 1999 to 2008 and remained relatively

expenditures of \$36 668 in 2013 to 2014.¹⁴²

- In 11 969 patients with AMI from 233 US hospitals who underwent PCI from 2010 to 2013, average hospital costs were higher for patients with STEMI (\$19 327) compared with patients with NSTEMI (\$18 465; $P=0.002$) and higher among elderly patients (\$19 575 for those ≥ 65 years of age versus \$18 652 for those < 65 years of age; $P=0.004$).

Forty-five percent of costs were related to the catheterization laboratory, 22% to room and board, 14% to supplies, and 9% to pharmacy costs. At 1 year after discharge, hospital and ED costs averaged \$8037, with three-quarters attributable to hospitalizations (\$6116

hospital stays (7 days versus 6 days for those with minimally invasive

- An observational analysis of (18–45 years of age) who were hospitalized from 2004 to 2018 NIS found that care cost significantly more in 2004 to \$24 173 in 2018

Global Burden

(See Table 21-3 and Charts 21-6

- Based on 204 countries and territories
 - An estimated 8.99 (95% UI, 8.49–9.49) million total deaths attributable to CHD (Table 21-3). Among countries, rates were highest for Central and North Africa and the lowest for high-income countries (Table 21-6).
 - Globally, it was estimated that 221.45–295.49 million people had IHD, and it was more prevalent in males (145.31 [95% UI, 138.97–151.65] million) than females (108.97 [95% UI, 95.25–122.69] million). North Africa had the highest prevalence of IHD, followed by Central Asia (Chart 21-6).
- Among 31 443 respondents in the WHO SAGE Wave 1, 16.6% (95% UI, 15.2–18.0%) reported a history of CHD and was higher in females than males (17.6% versus 15.6%, respectively). Among those with a history of CHD, 13.3% (95% UI, 12.1–14.5%) reported a history of IHD, 10.1% (95% UI, 9.1–11.1%) reported a history of AMI, and 1.1% (95% UI, 0.6–1.6%) reported a history of stroke. Among those with a history of CHD, 13.3% (95% UI, 12.1–14.5%) reported a history of IHD, 10.1% (95% UI, 9.1–11.1%) reported a history of AMI, and 1.1% (95% UI, 0.6–1.6%) reported a history of stroke. Among those with a history of CHD, 13.3% (95% UI, 12.1–14.5%) reported a history of IHD, 10.1% (95% UI, 9.1–11.1%) reported a history of AMI, and 1.1% (95% UI, 0.6–1.6%) reported a history of stroke. Among those with a history of CHD, 13.3% (95% UI, 12.1–14.5%) reported a history of IHD, 10.1% (95% UI, 9.1–11.1%) reported a history of AMI, and 1.1% (95% UI, 0.6–1.6%) reported a history of stroke.

for hospitalizations, \$1334 for outpatient hospital stays, and \$587 for ED visits).¹⁴³ Among 26 255 patients with isolated CABG in a regional STS database between 2012 and 2019, the median hospital cost was higher among those with open CABG (\$35 011) than those with minimally invasive CABG surgery (\$27 906; $P<0.001$) after propensity score matching. There were no significant differences in mortality or morbidity, although patients with open CABG had longer

Acute Coronary Syndrome

ICD-9 410, 411; ICD-10 I20.0, I21, I22.

- In a study of 9450 patients with ACS, a modified GRACE risk score incorporating continuous high-sensitivity cardiac troponin at presentation showed improved discrimination and reclassification for in-hospital (AUC, 0.878 versus 0.780; NRI, 0.097), 30-day (AUC, 0.858 versus 0.771; NRI, 0.08), and 1-year (AUC, 0.813 versus 0.797; NRI, 0.056) all-cause mortality compared with the original GRACE score.¹⁴⁷
- In a 2019 to 2020 NIS study (N=32 355 827), patients with STEMI with COVID-19 had higher mortality (aOR, 3.10 [95% CI, 2.40–4.02]; $P<0.01$) and longer length of stay (aOR, 1.66 [95% CI, 1.07–2.25]; $P<0.01$), and unstable patients with NSTEMI had longer admission-to-PCI times (0.45 days [95% CI, 0.16–0.76 days]; $P<0.01$).¹⁴⁸
- In 2021, there were 591 129 ACS principal diagnosis discharges. This estimate was derived by adding the principal diagnoses for MI (584 499) to those

for unstable angina (6630; unpublished NHLBI tabulation using HCUP₈₂).

- When all listed discharge diagnoses in 2021 were included, the corresponding number of inpatient hospital discharges was 1 391 719 unique hospitalizations for ACS. Of the total, 1 375 674 were for MI alone, and 16 045 were for unstable angina alone (unpublished NHLBI tabulation₈₂).
- In a population-level study in Italy, the the COVID-19 outbreak) to 120 (after the COVID-19 outbreak) cases per 100 000 residents per year (IRR, 0.68 [95% CI, 0.65–0.70]).¹⁴⁹ Females (IRR, 0.60 [95% CI, 0.57–0.65]) had fewer PCIs for ACS than males (IRR, 0.70 [95% CI: 0.68–0.73]; $P_{\text{interaction}} < 0.011$).
- Among 17 562 patients with ACS between 2005 and 2017 who lived beyond 30 days in a large PCI registry in Australia, 83.3% were on a β -

to present with non-ST-segment-elevation ACS (60.3% versus 46.7%; $P < 0.001$). This sex difference was driven mainly by a higher prevalence of ACS with nonobstructive coronary arteries (20.9% versus 6.6%) in young females because ACS without coronary lesions was mostly non-ST-segment-elevation ACS (77.7% versus 22.3%). There was no

blocker. Risk of overall mortality was lower among those who were on a β -blocker (aHR, 0.87 [95% CI, 0.78–0.97]; $P = 0.014$) compared with those who were not. This mortality benefit was observed among patients with LVEF $< 35\%$ (aHR, 0.63 [95% CI, 0.44–0.91]; $P = 0.013$) and 35% to 50% (aHR, 0.80 [95% CI, 0.68–0.95]; $P = 0.01$) but not among those with LVEF $> 50\%$.¹⁵⁰

- In a retrospective analysis of 43 446 patients who were referred for cardiac catheterization at a medical center in Massachusetts between January 2006

ABC-ACS ischemia model for predicting 1-year risk of CVD and MI that included growth differentiation factor 15 and NT-proBNP had greater prognostic value than all candidate variables (C indices, 0.71 and 0.72 in the development and validation cohorts, respectively).¹⁵⁴

- A retrospective cohort study of 257 948 adults in the NIH Research Health Informatics Collaborative with suspected ACS in the United Kingdom between 2010 and 2017 found a positive and graded association between high-sensitivity CRP level and mortality at baseline.¹⁵⁵ This association persisted after 3 years for those with high-sensitivity CRP of 2.0 to 4.9 mg/L (aHR, 1.32 [95% CI, 1.18–1.48]), 5 to 9.9 mg/L (aHR, 1.40 [95% CI, 1.26–1.57]), and 10 to 15 mg/L (aHR, 2.00 [95% CI, 1.75–2.28]).

Stable AP

ICD-9 413; ICD-10 I20.1 to I20.9.

and June 2017, 26 545 patients had ACS. Younger patients with ACS (<35 years of age) were more likely to be White, obese, and a smoker and to report a family history of CAD, but they were less likely to have diabetes, hypertension, and hyperlipidemia than older patients. Younger patients with ACS also had a higher prevalence of elevated troponin, late-presentation STEMI, and cardiogenic shock than older patients. Compared with patients with ACS who were 36 to 54 years of age, those who were ≤35 years of age had higher odds of 30-day mortality (aOR, 5.65 [95% CI, 2.49–12.82];

Prevalence

$P<0.001$).¹⁵¹ • A retrospective analysis of 801 195 patients with ACS in the NIS identified disparities in outcomes of patients admitted based on insurance (Medicaid, Medicare, private, and no insurance). Patients who had no insurance (aOR, 1.46 [95% CI, 1.26–1.69]; $P\leq 0.01$) or were on Medicaid (aOR, 1.16 [95% CI, 1.03–1.30]; $P=0.01$) had higher mortality than those who had private insurance.¹⁵²

- A retrospective analysis of data on 10 019 patients from the Epi-Cardio Registry in Argentina was conducted to examine sex differences in the presentation of ACS.¹⁵³ Females were more likely than males

(See Table 21-2 and Chart 21-8)

- According to data from NHANES 2017 to 2020, the prevalence of AP among adults (≥20 years of age) was 3.9% (10.8 million adults; Table 21-2).
- On the basis of NHANES 2017 to 2020, the prevalence of AP increased with age from <1% among males and females 20 to 39 years of age to >9% among males and females ≥80 years of age (Chart 21-8).
- On the basis of data from NHANES in 2009 to 2012, an average of 3.4 million people ≥40 years of age in the United States had angina each year compared with 4 million in 1988 to 1994. Declines in angina symptoms have occurred for NH White people but not for NH Black people.¹⁵⁶
- Among 1612 of 4139 eligible patients diagnosed with CAD in a network consisting of 15 primary care clinics in Massachusetts, the prevalence of angina was measured with the Seattle Angina Questionnaire-7; 21.2% reported angina symptoms at least once monthly, and among those, 12.5% reported daily or weekly angina symptoms, and 8.7% reported monthly angina symptoms.¹⁵⁷

Table 21-1. CHD in the United States

Population group	Prevalence, CHD, 2017–2020, ≥20 y of age	Prevalence, MI, 2017–2020, ≥20 y of age	Mortality,* CHD, 2022, all ages	Age-adjusted mortality rates per 100 000 (95% CI),* CHD, 2022
Both sexes	20 500 000 (7.1%) [95% CI, 6.1%–	9 300 000 (3.2%) [95% CI, 2.5%–	371 506	87.6 (87.3–87.9)
Males	11 700 000 (8.7%)	6 100 000 (4.5%)	223 952 (60.3%)†	121.9 (121.4–122.4)
Females	8 800 000 (5.8%)	3 200 000 (2.1%)	147 554 (39.7%)†	60.3 (60.0–60.6)
NH White males	9.4%	4.8%	172 181	126.8 (126.2–127.4)
NH White females	5.9%	2.2%	112 164	61.9 (61.5–62.3)
NH Black males	6.2%	4.0%	24 839	144.1 (142.2–146.0)
NH Black females	6.8%	2.3%	18 264	75.8 (74.7–76.9)

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹⁵⁸ CHD includes people who responded “yes” to at least 1 of the questions in “Has a doctor or other health professional ever told you that you had CHD, angina or AP, heart attack, or MI?” Those who answered “no” but were diagnosed with Rose angina are also included (the Rose questionnaire is administered only to survey participants >40 years of age). CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading.

AP indicates angina pectoris; CHD, coronary heart disease; COVID-19, coronavirus disease 2019; ellipses (...), data not available; MI, myocardial infarction; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Mortality for Hispanic people, NH American Indian or Alaska Native people, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown under-reporting on death certificates of American Indian or Alaska Native decedents, Asian and Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total CHD and MI mortality that is for males vs females.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey.² Percent-ages for racial and ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities study (2005–2014),⁵ unpublished tabulation by NHLBI, extrapolated to the 2014 US population. Mortality (for underlying cause of CHD): unpublished NHLBI tabulation using National Vital Statistics System¹⁰² and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.¹⁰³

Table 21-2. AP* in the United States

Population group	Prevalence, 2017–2020, ≥20 y of age
Both sexes	10 800 000 (3.9%) [95% CI, 3.3%–4.5%]
Males	5 600 000 (4.3%)
Females	5 200 000 (3.6%)
NH White males	4.7%
NH White females	3.5%
NH Black males	2.7%
NH Black females	4.1%
Hispanic males	3.6%
Hispanic females	4.3%
NH Asian or Pacific Islander males	2.7%
NH Asian or Pacific Islander females	2.7%

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹⁵⁸ AP includes people who either answered “yes” to the question of ever having angina or AP or being diagnosed with Rose angina (the Rose questionnaire is administered only to survey participants >40 years of age).

AP indicates angina pectoris; COVID-19, coronavirus disease 2019; ellipses (...), data not available; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*AP is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable AP is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for AP without myocardial infarction.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.² Percentages for racial and ethnic groups are age adjusted for US adults ≥ 20 years of age. Estimates from NHANES 2017 to 2020 were applied to 2020 population estimates (≥ 20 years of age).

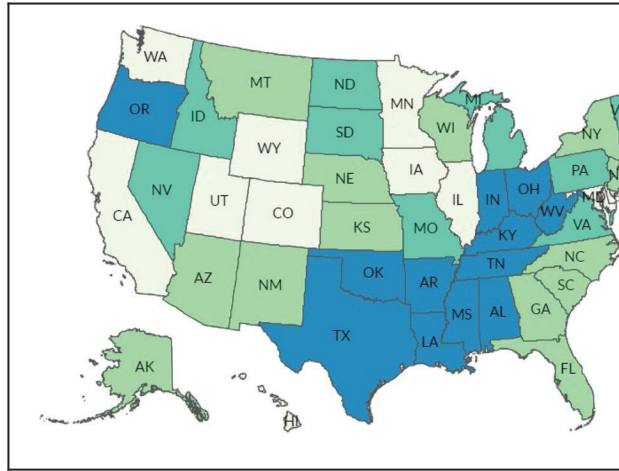


Chart 21-3. “Ever told you had a heart attack (MI)?” Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2022).

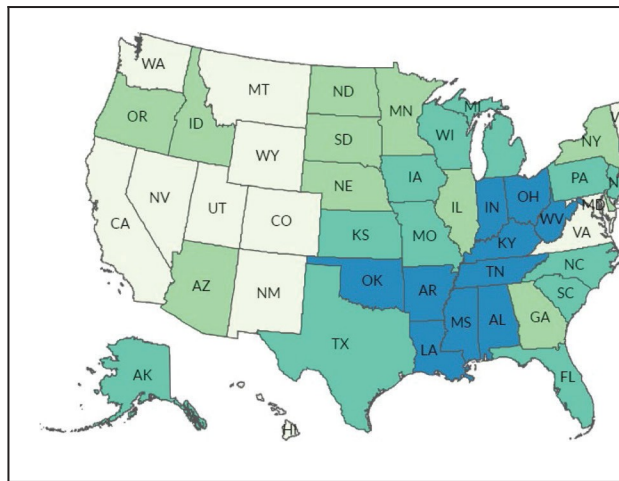


Chart 21-4. “Ever told you had angina or CHD?” Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2022).

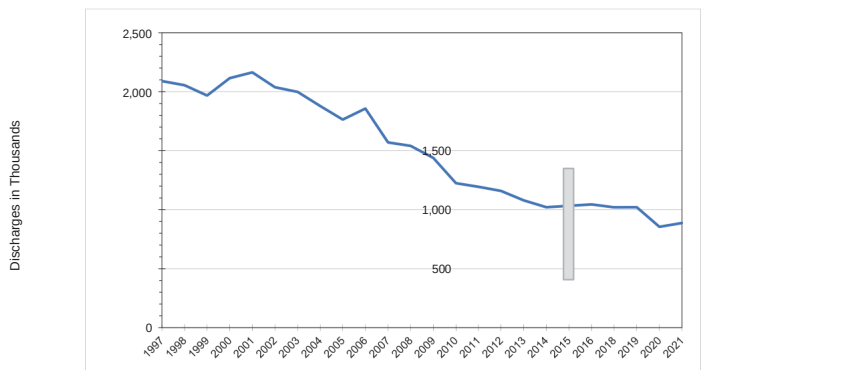


Chart 21-5. Hospital discharges for CHD, United States (HCUP, 1997–2021).

Hospital discharges include people discharged alive, dead, and status unknown.

CHD indicates coronary heart disease; and HCUP, Healthcare Cost and Utilization Project.

*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th

revision to the 10th revision of the *International Classification of Diseases*.

This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute

tabulation using HCUP.⁸²

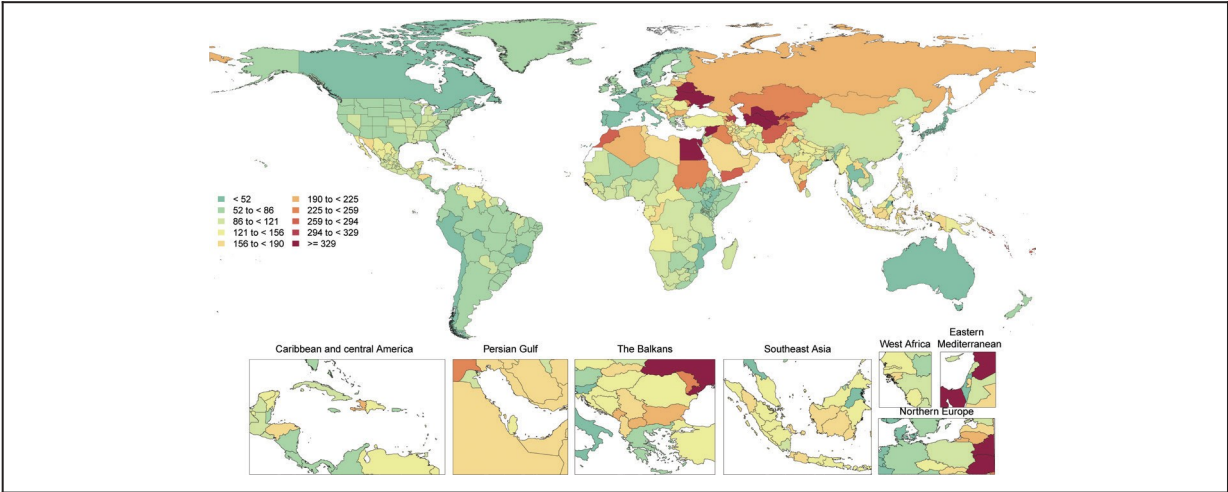


Chart 21-6. Age-standardized global mortality rates of IHD per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and IHD, ischemic heart disease. Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁴⁵

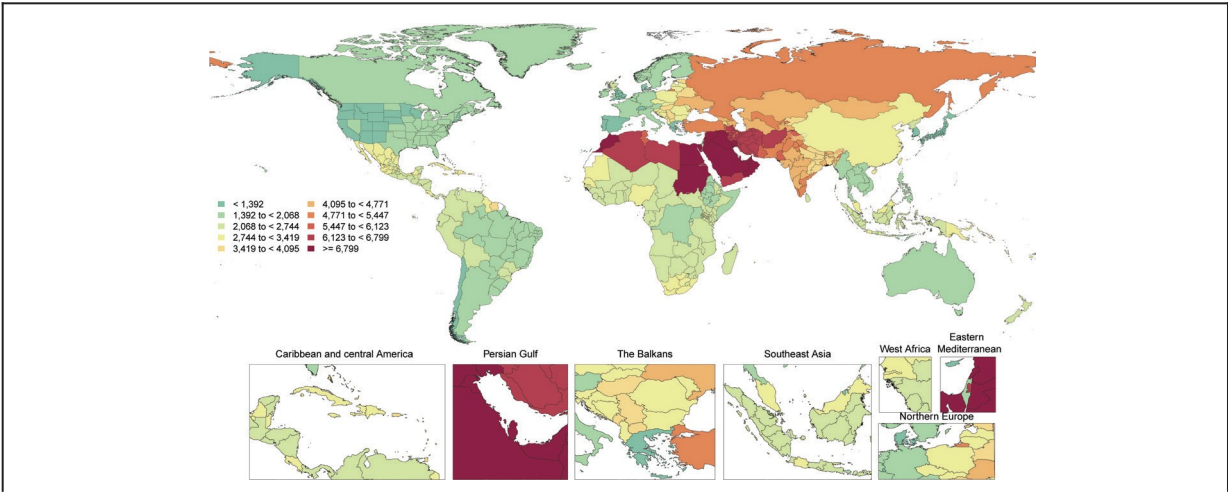


Chart 21-7. Age-standardized global prevalence rates of IHD per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and IHD, ischemic heart disease. Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁴⁵

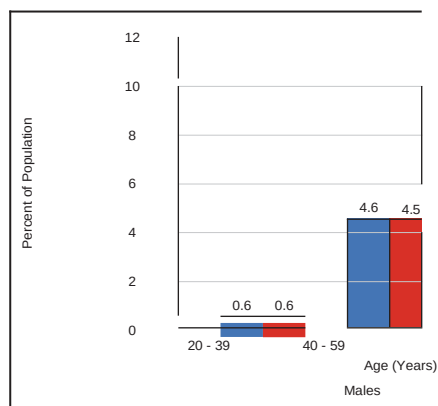


Chart 21-8. Prevalence of AP by age and sex, United States (NHANES, 2017–2020).

In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹⁵⁸ AP includes people who either answered “yes” to the question of ever having angina or AP or being diagnosed with Rose angina. AP indicates anginal pectoris; COVID-19, coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.²

REFERENCES

1. Kianoush S, Rifai MA, Jain V, Samad Z, Rana J, Dodani S, Jia X, Lee M, Khan SU, Gupta K, et al. Prevalence and predictors of premature coronary heart disease among Asians in the United States: a National Health Interview Survey study. *Curr Probl Cardiol.* 2023;48:101152. doi: 10.1016/j.cpcardiol.2022.101152
2. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 1, 2024.
3. Centers for Disease Control and Prevention and National Center for

of type 2 myocardial infarction in a 2020:141:454–463. doi:

11. Almarzoon ZI, Wadhwa RK, Xu J, Yeh of percutaneous coronary 2021:6:1219–1220. doi:
12. Rashid Hons M, Gale Hons CP, Curzen De Belder Hons M, Timmis Hons A, Hains Hons J, Wu J, et al. Impact of on the incidence and management of tients presenting with acute Assoc. 2020:9:e018379. doi:
13. Mesnier J, Cottin Y, Coste P, Ferrari E, Anoultant D, Cavla G, Boulet C, et cardial infarction before and after of COVID-19 and patient profile in *Health.* 2020:5:e536–e542. doi:
14. Case RC, Yerasi C, Forrestal RJ, Shea Health Statistics. National Health Interview Survey: public-use data files and documentation. Accessed March 27, 2024.
4. Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System (BRFSS): BRFSS Prevalence & Trends Data. Accessed March 7, 2024.
5. ARIC. Atherosclerosis Risk in Communities (ARIC) Study: Community Surveillance Component, 2005–2014. Accessed April 1, 2024.
6. Colantonio LD, Gamboa CM, Richman JS, Levitan EB, Soliman EZ, Howard G, Safford MM. Black-White differences in incident fatal, nonfatal, and total coronary heart disease. *Circulation.* 2017;136:152–166. doi: 10.1161/CIRCULATIONAHA.116.025848
7. Sana MK, Kumi D, Park DY, Asemota IR, DeAngelo S, Yilmaz M, Hammo H, Shaka H, Vij A. Impact of hospital readmissions reduction program policy on 30-day and 90-day readmissions in patients with acute myocardial infarction: a 10-year trend from the National Readmissions Database. *Curr Probl Cardiol.* 2023;48:101696. doi: 10.1016/j.cpcardiol.2023.101696
8. Park DY, Vemmou E, An S, Nikolakopoulos I, Regan CJ, Cambi BC, Frampton J, Vij A, Brilakis E, Nanna MG. Trends and impact of intravascular ultrasound and optical coherence tomography on percutaneous coronary intervention for myocardial infarction. *IJC Heart Vasc.* 2023;45:101186. doi: 10.1016/j.ijcha.2023.101186
9. Sacks NC, Ash AS, Ghosh K, Rosen AK, Wong JB, Rosen AB. Trends in acute myocardial infarction hospitalizations: are we seeing the whole picture? *Am Heart J.* 2015;170:1211–1219. doi: 10.1016/j.ahj.2015.09.009
10. Raphael CE, Roger VL, Sandoval Y, Singh M, Bell M, Lerman A, Rihal CS, Gersh BJ, Lewis B, Lennon RJ, et al. Incidence, trends, and outcomes

Zhang C, Satler LF, Ben-Dor I, Hashim H, et al. Comparison of characteristics and outcomes of patients with acute myocardial infarction with versus without coronavirus-19. *Am J Cardiol.* 2021;144:8–12. doi: 10.1016/j.amjcard.2020.12.059

15. Tripathi B, Tan BE, Sharma P, Gaddam M, Singh A, Solanki D, Kumar V, Sharma A, Akhtar T, Michos ED, et al. Characteristics and Outcomes of Patients Admitted With Type 2 Myocardial Infarction. *Am J Cardiol.* 2021;157:33–41. doi: 10.1016/j.amjcard.2021.07.013

16. Fox DK, Waken RJ, Johnson DY, Hammond G, Yu J, Fanous E, Maddox TM, Joynt Maddox KE. Impact of the COVID-19 pandemic on patients without COVID-19 with acute myocardial infarction and heart failure. *J Am Heart Assoc.* 2022;11:e022625. doi: 10.1161/JAHA.121.022625

17. Pourasghari H, Tavolinejad H, Soleimanpour S, Abdi Z, Arabloo J, Bragazzi NL, Behzadifar M, Rashedi S, Omid N, Ayoubian A, et al. Hospitalization, major complications and mortality in acute myocardial infarction patients during the COVID-19 era: a systematic review and meta-analysis. *IJC Heart Vasc.* 2022;41:101058. doi: 10.1016/j.ijcha.2022.101058

18. Sofi F, Dinu M, Reboldi G, Stracci F, Pedretti RFE, Valente S, Gensini G, Gibson CM, Ambrosio G. Worldwide differences of hospitalization for ST-segment elevation myocardial infarction during COVID-19: a systematic review and meta-analysis. *Int J Cardiol.* 2022;347:89–96. doi: 10.1016/j.ijcard.2021.10.156

19. Mhanna M, Minhas AMK, Ariss RW, Nazir S, Khan SU, Vaduganathan M, Blankstein R, Alam M, Nasir K, Virani SS. Racial disparities in clinical outcomes and resource utilization of type 2 myocardial infarction in the United States: insights from the National Inpatient Sample Database. *Curr Probl Cardiol.* 2023;48:101202. doi: 10.1016/j.cpcardiol.2022.101202

20. Landon BE, Hatfield LA, Bakx P, Banerjee A, Chen YC, Fu C, Gordon M, Heine R, Huang N, Ko DT, et al. Differences in treatment patterns and outcomes of acute myocardial infarction for low- and high-income patients in 6 countries. *JAMA.* 2023;329:1088–1097. doi: 10.1001/jama.2023.1699

21. Hamil-Luker J, O'Rand AM. Black/White differences in the relationship between debt and risk of heart attack across cohorts. *SSM Popul Health.* 2023;22:101373. doi: 10.1016/j.ssmph.2023.101373

22. Ward MJ, Nikpay S, Shermeyer A, Nallamotheu BK, Rokos I, Self WH, Hsia RY. Interfacility transfer of uninsured vs insured patients with ST-segment elevation myocardial infarction in California. *JAMA Netw Open.* 2023;6:e2317831. doi: 10.1001/jamanetworkopen.2023.17831

23. Ashraf M, Zlochiver V, Sajed SM, Sajed S, Bajwa T, Allaqaband SQ, Jan MF. Racial disparities in diagnostic evaluation and revascularization in patients with acute myocardial infarction-a 15-year longitudinal study. *Curr Probl Cardiol.* 2023;48:101733. doi: 10.1016/j.cpcardiol.2023.101733

24. Bevan G, Pandey A, Griggs S, Dalton JE, Zidar D, Patel S, Khan SU, Nasir K, Rajagopalan S, Al-Kindi S. Neighborhood-level social vulnerability and prevalence of cardiovascular risk factors and coronary heart disease. *Curr Probl Cardiol.* 2023;48:101182. doi: 10.1016/j.cpcardiol.2022.101182

25. Matetic A, Shamkhani W, Rashid M, Volgman AS, Van Spall HGC, Coutinho T, Mehta LS, Sharma G, Parwani P, Mohamed MO, et al. Trends of sex differences in clinical outcomes after myocardial infarction in the United States. *CJC Open.* 2021;3:S19–S27. doi: 10.1016/j.cjco.2021.06.012

26. Pandey A, Keshvani N, Khera R, Lu D, Vaduganathan M, Joynt Maddox KE, Das SR, Kumbhani DJ, Goyal A, Girotra S, et al. Temporal trends in racial differences in 30-day readmission and mortality rates after acute myocardial infarction among Medicare beneficiaries. *JAMA Cardiol.* 2020;5:136–145. doi: 10.1001/jamacardio.2019.4845

27. Topel ML, Kim JH, Mujahid MS, Sullivan SM, Ko Y-A, Vaccarino V, Quyyumi AA, Lewis TT. Neighborhood socioeconomic status and adverse outcomes

-
- in patients with cardiovascular disease. *Am J Cardiol.* 2019;123:284–290. doi: 10.1016/j.amjcard.2018.10.011
28. Alghanem F, Clements JM. Narrowing performance gap between rural and urban hospitals for acute myocardial infarction care. *Am J Emerg Med.* 2020;38:89–94. doi: 10.1016/j.ajem.2019.04.030
29. Green YS, Hajduk AM, Song X, Krumholz HM, Sinha SK, Chaudhry SI. Usefulness of social support in older adults after hospitalization for acute myocardial infarction (from the SILVER-AMI Study). *Am J Cardiol.* 2020;125:313–319. doi: 10.1016/j.amjcard.2019.10.038
- based payment. *Circ Cardiovasc Qual Outcomes.* 2020;13:e005977. doi: 10.1161/CIRCOUTCOMES.119.005977
31. Herbert BM, Johnson AE, Paasche-Orlow MK, Brooks MM, Magnani from the Women's Health Initiative. *JAMA Intern Med.* 2018;178:1231–1240. doi: 10.1001/jamainternmed.2018.2875
45. Dudum R, Dzaye O, Mirbolouk M, Dardari ZA, Orimoloye OA, Budoff MJ, Berman DS, Rozanski A, Miedema MD, Nasir K, et al. Coronary artery calcium scoring in low risk patients with family history of coronary heart disease: validation of the SCCT guideline approach in the coronary artery calcium consortium. *J Cardiovasc Comput Tomogr.* 2019;13:21–25. doi: 10.1016/j.jcct.2019.03.012
46. Blaha MJ, Cainzos-Achirica M, Dardari Z, Blankstein R, Shaw LJ, Rozanski A, Rumberger JA, Dzaye O, Michos ED, Berman DS, et al. All-cause and cause-specific mortality in individuals with zero and minimal coronary artery calcium: a long-term. JW. Disparities in reporting a history of cardiovascular disease among adults with limited English proficiency and angina. *JAMA Netw Open.*

10.1016/j.atherosclerosis.2019.11.008

47. Peng AW, Mirbolouk M, Orimoloye OA, Osei AD, Dardari Z, Dzaye O, Budoff MJ, Shaw L, Miedema MD, Rumberger J, et al. Long-term all-cause and cause-specific mortality in asymptomatic patients with $\text{cac} \geq 1,000$: results from the CAC Consortium. *JACC Cardiovasc Imaging*. 2020;13:83–93. doi: 10.1016/j.jcmg.2019.02.005
- 2021;4:e2138780. doi: 10.1001/jamanetworkopen.2021.38780
32. Ritchey MD, Maresh S, McNeely J, Shaffer T, Jackson SL, Keteyian SJ, Brawner CA, Whooley MA, Chang T, Stolp H, et al. Tracking cardiac re-habilitation participation and completion among Medicare beneficiaries to inform the efforts of a national initiative. *Circ Cardiovasc Qual Outcomes*. 2020;13:e005902. doi: 10.1161/CIRCOUTCOMES.119.005902
33. Peters AE, Keeley EC. Trends and predictors of participation in cardiac re-habilitation following acute myocardial infarction: data from the Behavioral Risk Factor Surveillance System. *J Am Heart Assoc*. 2018;7:e007664. doi: 10.1161/jaha.117.007664

48. Chirinos DA, Llabre MM, Goldberg R, Gellman M, Mendez A, Cai J, Sotres-Alvarez D, Daviglius M, Gallo LC, Schneiderman N. Defining abdominal obesity as a risk factor for coronary heart disease in the U.S.: results from the Hispanic Community Health Study/Study of Latinos (HCHS/ SOL). *Diabetes Care*. 2020;43:1774–1780. doi: 10.2337/dc19-1855
49. Castro-Dominguez YS, Wang Y, Mingos KE, McNamara RL, Spertus JA, Dehmer GJ, Messenger JC, Lavin K, Anderson C, Blankinship K, et al. Predicting in-hospital mortality in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol*. 2021;78:216–229. doi: 10.1016/j.jacc.2021.04.067
34. Garfein J, Guhl EN, Swabe G, Sekikawa A, Barinas-Mitchell E, Forman DE, Magnani JW. Racial and ethnic differences in cardiac rehabilitation participation: effect modification by household income. *J Am Heart Assoc*. 2022;11:e025591. doi: 10.1161/JAHA.122.025591
35. Kini V, Mosley B, Raghavan S, Khazanie P, Bradley SM, Magid DJ, Ho PM, Masoudi FA. Differences in high- and low-value cardiovascular testing by health insurance provider. *J Am Heart Assoc*. 2021;10:e018877. doi: 10.1161/JAHA.120.018877
36. Loccoch EC, Joynt Maddox KE, Wang Y, Kazi DS, Yeh RW, Wadhera RK. Rural-urban disparities in outcomes of myocardial infarction, heart failure, and stroke in the United States. *J Am Coll Cardiol*. 2022;79:267–279. doi: 10.1016/j.jacc.2021.10.045
37. Roy B, Hajduk AM, Tsang S, Geda M, Riley C, Krumholz HM, Chaudhry SI. The association of neighborhood walkability with health outcomes in older adults after acute myocardial infarction: the SILVER-AMI study. *Prev Med* Rep. 2021;23:101391. doi: 10.1016/j.pmedr.2021.101391
38. Safford MM, Reshetnyak E, Sterling MR, Richman JS, Muntner PM, Durant RW, Booth J, Pinheiro LC. Number of social determinants of health and fatal and nonfatal incident coronary heart disease in the REGARDS study. *Circulation*. 2021;143:244–253. doi: 10.1161/CIRCULATIONAHA.120.048026
39. Subramaniam AV, Patlolla SH, Cheungpasitporn W, Sundaragiri PR, Miller PE, Barsness GW, Bell MR, Holmes DR Jr, Vallabhajosyula S. Racial and ethnic disparities in management and outcomes of cardiac arrest complicating acute myocardial infarction. *J Am Heart Assoc*. 2021;10:e019907. doi: 10.1161/JAHA.120.019907
40. Simoni AH, Frydenlund J, Kragholm KH, Bøggild H, Jensen SE, Johnsen SP. Socioeconomic inequity in incidence, outcomes and care for acute coronary syndrome: a systematic review. *Int J Cardiol*. 2022;356:19–29. doi: 10.1016/j.ijcard.2022.03.053
41. Li J, Zheng L, Chan KHK, Zou X, Zhang J, Liu J, Zhong Q, Madsen TE,

50. Blaha MJ, Naazie IN, Cainzos-Achirica M, Dardari ZA, DeFilippis AP, McClelland RL, Mirbolouk M, Orimoloye OA, Dzaye O, Nasir K, et al. Derivation of a coronary age calculator using traditional risk factors and coronary artery calcium: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc.* 2021;10:e019351. doi: 10.1161/JAHA.120.019351
51. King A, Wu L, Deng HW, Shen H, Wu C. Polygenic risk score improves the accuracy of a clinical risk score for coronary artery disease. *BMC Med.* 2022;20:385. doi: 10.1186/s12916-022-02583-y
52. Taggart C, Monterrubio-Gómez K, Roos A, Boeddinghaus J, Kimenai DM, Kadesjo E, Bularga A, Wereski R, Ferry A, Lowry M, et al. Improving risk stratification for patients with type 2 myocardial infarction. *J Am Coll Cardiol.* 2023;81:156–168. doi: 10.1016/j.jacc.2022.10.025
53. Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study. *Circulation.* 2012;125:3092–3098. doi: 10.1161/CIRCULATIONAHA.111.065490
54. Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, De Faire U. Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. *J Intern Med.* 2002;252:247–254. doi: 10.1046/j.1365-2796.2002.01029.x
55. Howson JMM, Zhao W, Barnes DR, Ho WK, Young R, Paul DS, Waite LL, Freitag DF, Fauman EB, Salfati EL, et al. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. *Nat Genet.* 2017;49:1113–1119. doi: 10.1038/ng.3874
56. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science.* 2007;316:1491–1493. doi: 10.1126/science.1142842
57. Palomaki GE, Melillo S, Bradley LA. Association between 9p21 genomic markers and heart disease: a meta-analysis. *JAMA.* 2010;303:648–656. doi: 10.1001/jama.2010.118
- Wu WC, Manson JE, et al. Sex hormone-binding globulin and risk of coronary heart disease in men and women. *Clin Chem.* 2023;69:374–385. doi: 10.1093/clinchem/hvac209
43. Colantonio LD, Richman JS, Carson AP, Lloyd-Jones DM, Howard G, Deng L, Howard VJ, Safford MM, Muntner P, Goff DC Jr. Performance of the atherosclerotic cardiovascular disease Pooled Cohort Risk Equations by social deprivation status. *J Am Heart Assoc.* 2017;6:e005676. doi: 10.1161/JAHA.117.005676
42. Khan SS, Post WS, Guo X, Tan J, Zhu F, Bos D, Sedaghati-Khayat B, van Rooij J, Aday A, Allen NB, et al. Coronary artery calcium score and polygenic risk score for the prediction of coronary heart disease events.

58. van der Harst P, Verweij N. Identification of 64 novel genetic loci provides an expanded view on the genetic architecture of coronary artery disease. *Circ Res*. 2018;122:433–443. doi: 10.1161/CIRCRESAHA.117.312086
59. Tcheandjieu C, Zhu X, Hilliard AT, Clarke SL, Napolioni V, Ma S, Lee KM, Fang H, Chen F, Lu Y, et al; Regeneron Genetics Center. Large-scale genome-wide association study of coronary artery disease in genetically diverse populations. *Nat Med*. 2022;28:1679–1692. doi: 10.1038/s41591-022-01891-3
60. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Coding variation in *ANGPTL4*, *LPL*, and *SVEP1* and the risk of coronary disease. *N Engl J Med*. 2016;374:1134–1144. doi: 10.1056/NEJMoa1507652
44. Mora S, Wenger NK, Cook NR, Liu J, Howard BV, Limacher MC, Liu S, Margolis KL, Martin LW, Paynter NP, et al. Evaluation of the Pooled Cohort Vries Risk Equations for cardiovascular risk prediction in a multiethnic cohort
61. Natarajan P, Pampana A, Graham SE, Ruotsalainen SE, Perry JA, de PS, Broome JG, Pirruccello JP, Honigberg MC, Aragam K, et al; NHLBI

Trans-Omics for Precision Medicine (TOPMed) Consortium. Chromosome Xq23 is associated with lower atherogenic lipid concentrations and favorable cardiometabolic indices. *Nat Commun*. 2021;12:2182. doi: 10.1038/s41467-021-22339-1

62. Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, McConkey M, Gunta N, Gabriel S, Ardissino D, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med*. 2017;377:111–121. doi: 10.1056/NEJMoa1701719

63. Bick AG, Weinstock JS, Nandakumar SK, Fulco CP, Bao EL, Zekavat SM, Szeto MD, Liao X, Leventhal MJ, Nasser J, et al: NHLBI Trans-Omics for Precision Medicine Consortium. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature*. 2020;586:763–768. doi: 10.1038/s41586-020-2819-2

64. Khera AV, Chaffin M, Zekavat SM, Collins RL, Roselli C, Natarajan P, Lichtman JH, D'Onofrio G, Mattera J, Drever R, et al. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with myocardial infarction. *Circulation*. 2019;139:1593–1602. doi: 10.1161/CIRCULATIONAHA.118.035658

65. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016;375:2349–2358. doi: 10.1056/NEJMoa1605086

66. Groenendyk JW, Greenland P, Khan SS. Incremental value of polygenic risk scores in primary prevention of coronary heart disease: a review. *JAMA Intern Med*. 2022;182:1082–1088. doi:

- Assoc. 2021;10:e019305. doi: 10.1161/JAHA.120.019305
81. De Luca G, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Jensen LO, Loh PH, Calmac L, et al; ISACS-STEMI COVID-19. COVID-19 pandemic, mechanical reperfusion and 30-day mortality in ST elevation myocardial infarction. *Heart*. 2022;108:458–466. doi: 10.1136/heartjnl-2021-319750
 82. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024. 10.1001/jamainternmed.2022.3171
 67. Marston NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, Pedersen TR, Keech AC, Wang H, Lira Pineda A, et al. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score: results from the FOURIER trial. *Circulation*. 2020;141:616–623. doi: 10.1161/CIRCULATIONAHA.119.043805
 68. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive accuracy of a polygenic risk score-enhanced prediction model vs a clinical risk score for coronary artery disease. *JAMA*. 2020;323:636–645. doi: 10.1001/jama.2019.22241
 69. Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, Kundu S, Robinson-Cohen C, Psaty BM, Rich SS, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. *JAMA*. 2020;323:627–635. doi: 10.1001/jama.2019.21782
 70. Lu X, Liu Z, Cui Q, Liu F, Li J, Niu X, Shen C, Hu D, Huang K, Chen J, et al. A polygenic risk score improves risk stratification of coronary artery disease: a large-scale prospective Chinese cohort study. *Eur Heart J*. 2022;43:1702–1711. doi: 10.1093/eurheartj/ehac093
 71. Dikilitas O, Schaid DJ, Kosel ML, Carroll RJ, Chute CG, Denny JA, Fedotov A, Feng Q, Hakonarson H, Jarvik GP, et al. Predictive utility of polygenic risk scores for coronary heart disease in three major racial and ethnic groups. *Am J Hum Genet*. 2020;106:707–716. doi: 10.1016/j.ajhg.2020.04.002
 72. Wang M, Menon R, Mishra S, Patel AP, Chaffin M, Tanneeru D, Deshmukh M, Mathew O, Apte S, Devanboo CS, et al. Validation of a genome-wide polygenic score for coronary artery disease in South Asians. *J Am Coll Cardiol*. 2020;76:703–714. doi: 10.1016/j.jacc.2020.06.024
 73. Mahajan S, Valero-Elizondo J, Khera R, Desai NR, Blankstein R, Blaha MJ, Virani SS, Kash BA, Zoghbi WA, Krumholz HM, et al. Variation and disparities in awareness of myocardial infarction symptoms among adults in the United States. *JAMA Netw Open*. 2019;2:e1917885. doi: 10.1001/jamanetworkopen.2019.17885
 74. Mannoh I, Turkson-Ocran RA, Mensah J, Mensah D, Yi SS, Michos ED, Commodore-Mensah Y. Disparities in awareness of myocardial infarction and stroke symptoms and response among United States- and foreign-born adults in the National Health Interview Survey. *J Am Heart Assoc*. 2021;10:e020396. doi: 10.1161/JAHA.121.020396
 75. Cushman M, Shay CM, Howard VJ, Jiménez MC, Lewey J, McSweeney JC, Newby LK, Poudel R, Reynolds HR, Rexrode KM, et al; on behalf of the American Heart Association. Ten-year differences in women's awareness related to coronary heart disease: results of the 2019 American Heart Association national survey: a special report from the American Heart Association. *Circulation*. 2021;143:e239–e248. doi: 10.1161/CIR.0000000000000907
 76. Vallabhajosyula S, Patlolla SH, Miller PE, Cheungpasitporn W, Jaffe AS, Gersh BJ, Holmes DR Jr, Bell MR, Barsness GW. Weekend effect in the management and outcomes of acute myocardial infarction in the United

83. Dixon LK, Di Tommaso E, Dimagli A, Sinha S, Sandhu M, Benedetto U, Angelini GD. Impact of sex on outcomes after cardiac surgery: a systematic review and meta-analysis. *Int J Cardiol.* 2021;343:27–34. doi: 10.1016/j.ijcard.2021.09.011
84. Chang M, Lee CW, Ahn JM, Cavalcante R, Sotomi Y, Onuma Y, Zeng Y, Park DW, Kang SJ, Lee SW, et al. Coronary artery bypass grafting versus drug-eluting stents implantation for previous myocardial infarction. *Am J Cardiol.* 2016;118:17–22. doi: 10.1016/j.amjcard.2016.04.009
85. Thuijs DJFM, Kappetein AP, Serruys PW, Mohr F-W, Morice M-C, Mack MJ, Holmes DR Jr, Curzen N, Davierwala P, Noack T, et al; SYNTAX Extended Survival Investigators. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet.* 2019;394:1325–1334. doi: 10.1016/S0140-6736(19)31997-X
86. Lopez-Sendon JL, Cyr DD, Mark DB, Bangalore S, Huang Z, White HD, Alexander KP, Li J, Nair RG, Demkow M, et al. Effects of initial invasive versus initial conservative treatment strategies on recurrent and total cardiovascular events in the ISCHEMIA trial. *Eur Heart J.* 2021;43:148–149. doi: 10.1093/eurheartj/ehab509
87. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice M-C, Puskas J, Trial Investigators. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med.* 2019;381:1820–1830. doi: 10.1056/NEJMoa1909406
88. Valle JA, Tamez H, Abbott JD, Moussa ID, Messenger JC, Waldo SW, protected left main coronary artery percutaneous coronary intervention Registry Research to Practice Initiative. *JAMA Cardiol.* 2019;4:100–109. doi: 10.1001/jamacardio.2018.4376
89. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks Steering Committee and Investigators. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med.* 2019;381:1411–1421. doi: 10.1056/NEJMoa1907775
90. Shavadia JS, Roe MT, Chen AY, Lucas J, Fanaroff AC, Kochar A, Fordyce ac catheterization laboratory pre-activation and reperfusion timing metrics tion undergoing primary percutaneous coronary intervention: a report from 10.1016/j.jcin.2018.07.020
91. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, ISCHEMIA Research Group. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med.* 2020;382:1395–1407. doi: 10.1056/NEJMoa1915922

B, Di Pasquale G, López-Sendón J, Faxon DP, et al; COMPLETE Trial

Kennedy KF, Masoudi FA, Yeh RW. Contemporary use and trends in un- in the United States: an analysis of the National Cardiovascular Data

CB, Jollis JG, Tamis-Holland J, Henry TD, et al. Association between cardi- and outcomes in patients with ST-segment elevation myocardial infarction the ACTION Registry. *JACC Cardiovasc Interv.* 2018;11:1837–1847. doi:

al;

92. Elbadawi A, Elgendy IY, Ha LD, Mahmoud K, Lenka J, Olorunfemi O, Reyes A, Ogunbayo GO, Saad M, Abbott JD. National trends and outcomes of percutaneous coronary intervention in patients ≥ 70 years of age with acute coronary syndrome (from the National Inpatient Sample Database). *Am J Cardiol.* 2019;123:25–32. doi: 10.1016/j.amjcard.2018.09.030
93. McCarthy CP, Kolte D, Kennedy KF, Vaduganathan M, Wasfy JH, Januzzi JL Jr. Patient characteristics and clinical outcomes of type 1 versus type 2 myocardial infarction. *J Am Coll Cardiol.* 2021;77:848–857. doi: 10.1016/j.jacc.2020.12.034
94. Mohammad MA, Persson J, Buccheri S, Odenstedt J, Sarno G, Angerås O, Völz S, Tödt T, Götberg M, Isma N, et al. Trends in clinical practice and outcomes after percutaneous coronary intervention of left main coronary artery. *J Am Heart Assoc.* 2022;11:e024040. doi: 10.1161/JAHA.121.024040
95. Shields GE, Rowlandson A, Dalal G, Nickerson S, Cranmer H, elevation myocardial infarction. *Am J Cardiol.* 2021;147:23–32. doi: 10.1016/j.amjcard.2021.02.015
110. Minhas AMK, Awan MU, Raza M, Virani SS, Sharma G, Blankstein R, Blaha MJ, Al-Kindi SG, Kaluksi E, Nasir K, et al. Clinical and economic burden of percutaneous coronary intervention in hospitalized young adults in the United States, 2004-2018. *Curr Probl Cardiol.* 2022;47:101070. doi: 10.1016/j.cpcardiol.2021.101070
111. Joseph JJ, Rajwani A, Roper D, Zhao S, Kline D, Odei J, Brock G, Echouffo-Tcheuui JB, Kalvani RR.

- J, Jacobs AK. Sex-based differences in discharge disposition and out-comes for ST-segment elevation myocardial infarction patients within a regional network. *J Womens Health (Larchmt)*. 2018;27:1001–1006. doi: 10.1089/jwh.2017.6553
- Capobianco L, Doherty P. Cost-effectiveness of home-based cardiac rehabilitation: a systematic review. *Heart*. 2023;109:913–920. doi: 10.1136/heartjnl-2021-320459
96. Widmer RJ, Allison TG, Lennon R, Lopez-Jimenez F, Lerman LO, Lerman A. Digital health intervention during cardiac rehabilitation: a randomized controlled trial. *Am Heart J*. 2017;188:65–72. doi: 10.1016/j.ahj.2017.02.016
97. Krishnamurthi N, Schopfer DW, Shen H, Rohrbach G, Elnaggar A, Whooley MA. Association of home-based cardiac rehabilitation with lower mortality in patients with cardiovascular disease: results from the Veterans Health Administration Healthy Heart Program. *J Am Heart Assoc*. 2023;12:e025856. doi: 10.1161/JAHA.122.025856
98. Khaloo P, Ledesma PA, Nahlawi A, Galvin J, Ptaszek LM, Ruskin JN. Outcomes of patients with Takotsubo syndrome compared with type 1 and type 2 myocardial infarction. *J Am Heart Assoc*. 2023;12:e030114. doi: 10.1161/JAHA.123.030114
99. Wang S, Zhu R, Zhang C, Guo Y, Lv M, Zhang C, Bian C, Jiang R, Zhou W, Guo L. Effects of the pre-existing coronary heart disease on the prognosis of COVID-19 patients: a systematic review and meta-analysis. *PLoS One*. 2023;18:e0292021. doi: 10.1371/journal.pone.0292021
100. Goel A, Malik AH, Bandyopadhyay D, Isath A, Gupta R, Hajra A, Shrivastav R, Virani SS, Fonarow GC, Lavie CJ, et al. Impact of COVID-19 on outcomes of patients hospitalized with STEMI: a nationwide pro-pensity-matched analysis. *Curr Probl Cardiol*. 2023;48:101547. doi: 10.1016/j.cpcardiol.2022.101547
101. Mirna M, Berezin A, Schmutzler L, Demirel O, Hoppe UC, Lichtenauer M. Early beta-blocker therapy improves in-hospital mortality of patients with non-ST-segment elevation myocardial infarction: a meta-analysis. *Int J Cardiol*. 2023;389:131160. doi: 10.1016/j.ijcard.2023.131160
102. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
103. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.
104. Krumholz HM, Normand ST, Wang Y. Twenty-year trends in outcomes for older adults with acute myocardial infarction in the United States. *JAMA Netw Open*. 2019;2:e191938. doi: 10.1001/jamanetworkopen.2019.1938
105. Sidney S, Go AS, Jaffe MG, Solomon MD, Ambrosy AP, Rana JS. Association between aging of the US population and heart disease mortality from 2011 to 2017. *JAMA Cardiol*. 2019;4:1280–1286. doi: 10.1001/jamacardio.2019.4187
106. Landon BE, Anderson TS, Curto VE, Cram P, Fu C, Weinreb G, Zaslavsky AM, Ayanian JZ. Association of Medicare Advantage vs traditional Medicare with 30-day mortality among patients with acute myocardial infarction. *JAMA*. 2022;328:2126–2135. doi: 10.1001/jama.2022.20982

113. Langabeer JR 2nd, Champagne-Langabeer T, Fowler R, Henry T. Gender-based outcome differences for emergency department presentation of non-STEMI acute coronary syndrome. *Am J Emerg Med*. 2019;37:179–182. doi: 10.1016/j.ajem.2018.05.005
114. Huded CP, Johnson M, Kravitz K, Menon V, Abdallah M, Gullett TC, Hantz S, Ellis SG, Podolsky SR, Meldon SW, et al. 4-Step protocol for disparities in STEMI care and outcomes in women. *J Am Coll Cardiol*. 2018;71:2122–2132. doi: 10.1016/j.jacc.2018.02.039
115. Enumah ZO, Canner JK, Alejo D, Warren DS, Zhou X, Yenokyan G, Matthew T, Lawton JS, Higgins RSD. Persistent racial and sex disparities in outcomes after coronary artery bypass surgery: a retrospective clinical registry review in the drug-eluting stent era. *Ann Surg*. 2020;272:660–667. doi: 10.1097/SLA.0000000000004335
116. Kosmidou I, Leon MB, Zhang Y, Serruys PW, von Birgelen C, Smits PC, Ben-Yehuda O, Redfors B, Madhavan MV, Maehara A, et al. Long-term outcomes in women and men following percutaneous coronary intervention. *J Am Coll Cardiol*. 2020;75:1631–1640. doi: 10.1016/j.jacc.2020.01.056
117. Shah NS, Ning H, Petito LC, Kershaw KN, Bancks MP, Reis JP, Rana JS, Sidney S, Jacobs DR, Kiefe CI, et al. Associations of clinical and social risk factors with racial differences in premature cardiovascular disease. *Circulation*. 2022;146:201–210. doi: 10.1161/CIRCULATIONAHA.121.058311
118. Post WS, Watson KE, Hansen S, Folsom AR, Szklo M, Shea S, Barr RG, Burke G, Bertoni AG, Allen N, et al. Racial and ethnic differences in all-cause and cardiovascular disease mortality: the MESA study. *Circulation*. 2022;146:229–239. doi: 10.1161/CIRCULATIONAHA.122.059174
119. Liao NS, Sidney S, Deosaransingh K, Van Den Eeden SK, Schwartz J, Alexeeff SE. Particulate air pollution and risk of cardiovascular events among adults with a history of stroke or acute myocardial infarction. *J Am Heart Assoc*. 2021;10:e019758. doi: 10.1161/JAHA.120.019758
120. Dugani SB, Fabbri M, Chamberlain AM, Bielinski SJ, Weston SA, Manemann SM, Jiang R, Roger VL. Premature myocardial infarction: a community study. *Mayo Clin Proc Innov Qual Outcomes*. 2021;5:413–422. doi: 10.1016/j.mayocpiqo.2021.01.011
121. Rathod KS, Jones DA, Jain AK, Lim P, McCarthy PA, Rakhit R, Lockie T, Kalra S, Dalby MC, Malik IS, et al. The influence of biological age and sex on long-term outcome after percutaneous coronary intervention for ST-elevation myocardial infarction. *Am J Cardiovasc Dis*. 2021;11:659–678.
122. Desai R, Mishra V, Chhina AK, Jain A, Vyas A, Allamneni R, Lavie CJ, Sachdeva R, Kumar G. Cardiovascular disease risk factors and outcomes of acute myocardial infarction in young adults: evidence from 2 nation-wide cohorts in the United States a decade apart. *Curr Probl Cardiol*. 2023;48:101747. doi: 10.1016/j.cpcardi.2023.101747
123. Masoudi FA, Ponirakis A, de Lemos JA, Jollis JG, Kremers M, Messenger JC, Moore JW, Moussa I, Oetgen WJ, Varosy PD, et al. Trends in cardiovascular care: 2016 report from 4 ACC National Cardiovascular Data Registries. *J Am Coll Cardiol*. 2017;69:1427–1450. doi: 10.1016/j.jacc.2016.12.005
107. Reynolds HR, Shaw LJ, Min JK, Page CB, Berman DS, Chaitman BR, Picard MH, Kwong RY, O'Brien SM, Huang Z, et al. Outcomes in the ISCHEMIA trial based on coronary artery disease and ischemia severity. *Circulation*. 2021;144:1024–1038. doi: 10.1161/CIRCULATIONAHA.120.049755
108. Hochman JS, Anthonopolos R, Reynolds HR, Bangalore S, Xu Y, O'Brien SM, Mavromichalis S, Chang M, Contreras A, Rosenberg Y, et al; ISCHEMIA-EXTEND Research Group. Survival after invasive or conservative management of stable coronary disease. *Circulation*. 2023;147:8–19. doi: 10.1161/CIRCULATIONAHA.122.062714
109. Shah T, Haimi I, Yang Y, Gaston S, Taoutel R, Mehta S, Lee HJ, Zambahari R, Baumbach A, Henry TD, et al. Meta-analysis of gender disparities in in-hospital care and outcomes in patients with ST-segment

124. Udell JA, Desai NR, Li S, Thomas L, de Lemos JA, Wright-Slaughter P, Zhang W, Roe MT, Bhatt DL. Neighborhood socioeconomic disadvantage and care after myocardial infarction in the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004054. doi: 10.1161/CIRCOUTCOMES.117.004054
125. Mahmoud AN, Taduru SS, Mentias A, Mahtta D, Barakat AF, Saad M, Elgendy AY, Mojadidi MK, Omer M, Abuzaid A, et al. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: a population-based analysis. *JACC Cardiovasc Interv*. 2018;11:80–90. doi: 10.1016/j.jcin.2017.08.016

126. Smilowitz NR, Mahajan AM, Roe MT, Reynolds HR. Mortality of myocardial infarction by coronary artery disease status in the Coronary Treatment and Intervention With the Guidelines). *Circ Cardiovasc Qual Outcomes*. doi: 10.1161/CIRCOUT.2017.000000
127. Abdullah A, Eidi G, Salama A, Wahab A, R. Impact of delirium on patients' prognosis: a score analysis of the National Inpatient Sample. *Am J Geriatr Psychiatry*. 2018;41:910–915. doi: 10.1002/gps.22972
128. Giustino G, Redfors B, Brener SJ, Kirtane DJ, Dudek D, Neunteufl T, Metzger DC. Prognostic impact of new-onset heart failure after myocardial infarction treated with primary percutaneous coronary intervention: insights from the INFUSE-AMI trial. *Eur Heart J Acute Cardiovasc Care*. 2018;7:339–347. doi: 10.1177/2048872617719649
129. Wang Y, Leifheit E, Normand ST, Krumholz HM. Association between sub-
142. Likosky DS, Van Parys J, Zhou W, JS. Association between Medicare reimbursement rates in patients with acute myocardial infarction from 1999 through 2014. *JAMA*. 2017;317:4771–4779. doi: 10.1001/jama.2017.4771
143. Cowner PA, Knight JD, Davidson-Ray T, TRANSLATE-ACS Investigators. Results from the TRANSLATE-ACS Investigators for acute myocardial infarction treated with primary percutaneous coronary intervention: results from the TRANSLATE-ACS Investigators. *Am J Geriatr Psychiatry*. 2019;8:e011322. doi: 10.1002/gps.22972
144. Teman NR, Hawkins RB, Charles EJ, Ailawadi G. Investigators for the TRANSLATE-ACS Investigators. Results from the TRANSLATE-ACS Investigators for acute myocardial infarction treated with primary percutaneous coronary intervention: results from the TRANSLATE-ACS Investigators. *Am J Geriatr Psychiatry*. 2018;7:339–347. doi: 10.1177/2048872617719649

- sis of cost and outcomes. *Ann Thorac Surg.* 2021;111:1478–1484. doi: 10.1016/j.athoracsur.2020.06.136
145. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation.* University of Washington. Accessed July 1, 2024.
- sequent hospitalizations and recurrent acute myocardial infarction within 1 year after acute myocardial infarction. *J Am Heart Assoc.* 2020;9:e014907. doi: 10.1161/JAHA.119.014907
130. Fordyce CB, Giugliano RP, Cannon CP, Roe MT, Sharma A, Page C, White JA, Lokhnygina Y, Braunwald E, Blazing MA. Cardiovascular events and long-term risk of sudden death among stabilized patients after acute coronary syndrome: insights from IMPROVE-IT. *J Am Heart Assoc.* 2022;11:e022733. doi: 10.1161/JAHA.121.022733
131. Gaudino M, Di Franco A, Alexander JH, Bakaeen F, Egorova N, Kurlansky P, Boening A, Chikwe J, Demetres M, Devereaux PJ, et al. Sex differences in outcomes after coronary artery bypass grafting: a pooled analysis of individual patient data. *Eur Heart J.* 2021;43:18–28. doi: 10.1093/eurheartj/ehab504 132.
- Yandrapalli S, Malik A, Pemmasani G, Aronow W, Shah F, Lanier G, Cooper H, Jain D, Naidu S, Frishman W, et al. Sex differences in heart failure hospitalisation risk following acute myocardial infarction. *Heart.* 2021;107:1657–1663. doi: 10.1136/heartjnl-2020-318306
133. Conradie A, Atherton J, Chowdhury E, Duong M, Schwarz N, Worthley S, Eccleston D. The association of sex with unplanned cardiac readmissions

146. Quashie NT, D'Este C, Agrawal S, Naidoo N, Kowal P. Prevalence of angina and co-morbid conditions among older adults in six low- and middle-income countries: evidence from SAGE wave 1. *Int J Cardiol.* 2019;285:140–146. doi: 10.1016/j.ijcard.2019.02.068
147. Georgiopoulos G, Kraler S, Mueller-Hennessen M, Delialis D, Mavraganis G, Sopova K, Wenzl FA, Räber L, Biener M, Stähli BE, et al. Modification of the GRACE risk score for risk prediction in patients with acute coronary syndromes. *JAMA Cardiol.* 2023;8:946–956. doi: 10.1001/jamacardio.2023.2741
148. Alharbi A, Franz A, Alfathawi H, Wazzan M, Alsughayer A, Eltahawy E, Assaly R. Impact of COVID-19 pandemic on the outcomes of acute coronary syndrome. *Curr Probl Cardiol.* 2023;48:101575. doi: 10.1016/j.cpcardiol.2022.101575
149. Piccolo R, Bruzzese D, Mauro C, Aloia A, Baldi C, Boccalatte M, Bottiglieri G, Briguori C, Caiazzo G, Calabro P, et al; Collaborators. Population trends in rates of percutaneous coronary revascularization for acute coronary syndromes associated with the following COVID-19 outbreak. *Circulation.* 2020;141:2035–2037. doi: 10.1161/CIRCOUTCOMES.121.008861
- multicentre outcomes registry (GenesisCare Cardiovascular Outcomes Registry). *J Clin Med.* 2022;11:6866. doi: 10.3390/jcm11226866
- Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed May 1, 2024.
135. Velagapudi P, Kolte D, Ather K, Khera S, Gupta T, Gordon PC, Aronow HD, Kirtane AJ, Abbott JD. Temporal trends and factors associated with prolonged length of stay in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol.* 2018;122:185–191. doi: 10.1016/j.amjcard.2018.03.365
136. Lee MT, Mahtta D, Ramsey DJ, Liu J, Misra A, Nasir K, Samad Z, Itchhaporia D, Khan SU, Schofield RS, et al. Sex-related disparities in cardiovascular health care among patients with premature atherosclerotic cardiovascular disease. *JAMA Cardiol.* 2021;6:782–790. doi: 10.1001/jamacardio.2021.0683
137. Zheutlin AR, Derington CG, Herrick JS, Rosenson RS, Poudel B, Safford MM, Brown TM, Jackson EA, Woodward M, Reading S, et al. Lipid-lowering therapy use and intensification among United States veterans following myocardial infarction or coronary revascularization between 2015 and 2019. *Circ Cardiovasc Qual Outcomes.* 2022;15:e008861. doi: 10.1161/CIRCOUTCOMES.117.004397
138. White HD, O'Brien SM, Alexander KP, Boden WE, Bangalore S, Li J, Manjunath CN, Lopez-Sendon JL, Peteiro J, Gosselin G, et al. Comparison of days alive out of hospital with initial invasive vs conservative management: a prespecified analysis of the ISCHEMIA trial. *JAMA Cardiol.* 2021;6:1023–1031. doi: 10.1001/jamacardio.2021.1651
139. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2024.
140. Moore BJ, Liang L. Medicare Advantage versus the traditional Medicare program: costs of inpatient stays, 2009-2017. HCUP Statistical Brief #262. August 2020. Accessed April 9, 2024.
141. Wadhera RK, Joynt Maddox KE, Wang Y, Shen C, Bhatt DL, Yeh RW. Association between 30-day episode payments and acute myocardial infarction outcomes among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes.* 2018;11:e004397. doi: 10.1161/CIRCOUTCOMES.117.004397

10.1161/CIRCULATIONAHA.120.047457

150. Peck KY, Andrianopoulos N, Dinh D, Roberts L, Duffy SJ, Sebastian M, Clark D, Brennan A, Oqueli E, Ajani AE, et al. Role of beta blockers following percutaneous coronary intervention for acute coronary syndrome. *Heart*. 2021;107:728–733. doi: 10.1136/heartjnl-2020-316605

151. Qureshi WT, Kakouros N, Fahed J, Rade JJ. Comparison of prevalence, presentation, and prognosis of acute coronary syndromes in ≤35 years, 36 - 54 years, and ≥ 55 years patients. *Am J Cardiol*. 2021;140:1–6. doi: 10.1016/j.amjcard.2020.10.054

152. Chakraborty S, Bandyopadhyay D, Amgai B, Sidhu JS, Paudel R, Koirala S, Hajra A, Ghosh RK, Lavie CJ. Does insurance effect the outcome in patients with acute coronary syndrome? An insight from the most recent National Inpatient Sample. *Curr Probl Cardiol*. 2021;46:100411. doi: 10.1016/j.cpcardiol.2019.02.003

153. de Abreu M, Zylberman M, Vensentini N, Villarreal R, Zaidel E, Antonietti L, Mariani J, Gagliardi J, Doval H, Tajer C. Sex differences in the clinical presentation of acute coronary syndromes. *Curr Probl Cardiol*. 2022;47:101300. doi: 10.1016/j.cpcardiol.2022.101300

154. Batra G, Lindbäck J, Becker RC, Harrington RA, Held C, James SK, Kempf T, Lopes RD, Mahaffey KW, Steg PG, et al. Biomarker-based prediction of recurrent ischemic events in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2022;80:1735–1747. doi: 10.1016/j.jacc.2022.08.767

155. Kaura A, Hartley A, Panoulas V, Glampson B, Shah ASV, Davies J, Mulla A, Woods K, Omigie J, Shah AD, et al. Mortality risk prediction of high-sensitivity C-reactive protein in suspected acute coronary syndrome: a cohort study. *PLoS Med*. 2022;19:e1003911. doi: 10.1371/journal.pmed.1003911

156. Will JC, Yuan K, Ford E. National trends in the prevalence and medical history of angina: 1988 to 2012. *Circ Cardiovasc Qual Outcomes*. 2014;7:407–413. doi: 10.1161/CIRCOUTCOMES.113.000779

157. Blumenthal DM, Howard SE, Searl Como J, O'Keefe SM, Atlas SJ, Horn DM, Wagle NW, Wasfy JH, Yeh RW, Metlay JP. Prevalence of angina among primary care patients with coronary artery disease. *JAMA Netw Open*. 2021;4:e2112800. doi: 10.1001/jamanetworkopen.2021.12800

158. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, Fryar CD, Gu S, Hales CM, Hughes JP, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files: development of files and prevalence estimates for selected health outcomes. *Natl Health Stat Rep*. 2021;158:10.15620/cdc:106273. doi: https://dx.doi.org/10.15620/cdc:106273

22. CARDIOMYOPATHY AND HEART FAILURE

See Tables 22-1 through 22-3 and Charts 22-1 through 22-4

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Cardiomyopathy

ICD-9 425; ICD-10 I42

2022, United States: Underlying cause mortality—19 739. Any-mention mortality—45 314.

Cardiomyopathy diagnoses account for a substantial number of inpatient and outpatient encounters annually.¹ According to HCUP 2021 data² for inpatient hospitalizations, cardiomyopathy was the principal diagnosis for 14 770, and it was included among all-listed diagnoses for 1 154 769.

Hypertrophic Cardiomyopathy

- HCM is a monogenic disorder with primarily autosomal dominant inheritance that is caused by 1 of hundreds of variants in >30 genes that primarily encode components of the sarcomere, with variants in *MYH7* and *MYBPC3* (cardiac myosin-binding protein C) being the most common.^{3,4} A variant is identifiable in 30% to 60% of cases of familial HCM.

versus 0.09% ($P<0.05$); 40 to 49 years of age, 0.66% versus 0.28% ($P=0.09$); and 60 to 69 years of age, 3.99% versus 1.33% ($P<0.01$). Risk for adverse events (ie, any ventricular years of age (cumulative incidence, 77% [95% CI, 72%–80%] by 60 years of age versus were also higher in patients with versus without pathogenic sarcomere variants (HR, 1.98 [95% CI,

- A meta-analysis of prior GWASs found a strong correlation between common genetic variants associated with several LV traits, including increased LV mass, mean LV wall thickness, and radial strain, and HCM.⁵ Two-sample mendelian randomization suggests a causal link between increased LV contractility and risk of developing HCM.
- The Sarcomeric Human Cardiomyopathy Registry studied 4591 patients with HCM contributing >24 000 PY of follow-up and observed a higher mortality rate in patients with HCM compared with unaffected individuals of a similar age in the US general population: 20 to 29 years of age, 0.39%

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

1.72–2.28]). AF (HR, 2.41 [95% CI, 1.98–2.94]) and HF (HR, 2.03 [95% CI, 1.68–2.45]) accounted for a substantial proportion of the adverse events despite typically not manifesting until years to decades after the initial diagnosis. Compared with males, females with HCM were at lower risk for ventricular arrhythmia (HR, 0.69 [95% CI, 0.51–0.94]; $P<0.05$) and AF (HR, 0.72 [95% CI, 0.60–0.87]; $P<0.001$) but higher risk for HF (HR, 1.28 [95% CI, 1.07–1.52]; $P<0.01$). There was no statistically significant difference in risk of each outcome for patients from underrepresented racial groups (all $P>0.05$).⁶

- A meta-analysis of 98 studies encompassing 70 510 patients with HCM from 1985 to 2020 demonstrated an overall incidence rate of SCD of 0.43%/y (95% CI, 0.37%/y–0.50%/y).⁷ This rate decreased over time from 0.73%/y (95% CI, 0.53%/y–1.02%/y) in 1985 to 2000 to 0.32%/y (95% CI, 0.20%/y–0.52%/y) in 2015 to 2020.
- Sex disparities exist in the treatment of HCM. Among 9306 patients with obstructive HCM in the MarketScan database, females were less likely to be prescribed β -blockers (42.7% versus 45.2%; $P=0.600$) or to receive an ICD (1.7% versus 2.6%; $P=0.005$).⁸

Genetic Testing

- The NIH-funded Clinical Genome Resource framework identified that of the 33 speculated HCM genes, 8 genes (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, *MYL2*, and *MYL3*) have definitive evidence, 3 genes (*CSRP3*, *TNNC1*, and *JPH2*) have moderate evidence, and the remaining genes have limited to no evidence supporting an association with HCM.⁹
- Given the heterogeneous nature of the underlying genetics, manifestation of the disease is highly variable, even in cases for which the causal variant has been identified.¹⁰ Among clinically unaffected individuals with pathogenic sarcomere variants discovered as part of cascade testing, 46% developed HCM over 15 years of follow-up.¹¹

Dilated Cardiomyopathy

- DCM has a prevalence of 1 in 2500, but it is likely underestimated.¹²

- Potential causes of DCM of reversibility include after an identifiable exposure mia, stress, neurohormonal chemotherapy, infection, (see the Peripartum
- Among 23 341 participants tries in the G-CHF registry, DCM.¹⁴
- Many cases of DCM have a familial DCM.¹⁵ Familial DCM has an estimated prevalence of 30% to 50% among all cases of DCM, and a causal genetic variant has been identified in 10% to 14% of cases.^{3,15}
- In a cross-sectional survey of 1220 probands with confirmed DCM and 1693 first-degree relatives who underwent clinical screening, including trans-thoracic echocardiography, the
 - In 186 families who underwent inq because of having a (95% CI, 30%–45%) were likely pathogenic or DCM.²⁰
 - In an appraisal of the 51 genes associated with DCM, the Resource framework panel genes from 8 gene ontologies (*BAG3*, *DES*, *FLNC*, *LMNA*, prevalence of famil- ial DCM was 11.6%.¹⁶
 - If all living first-degree relatives had been screened, the estimated prevalence of familial DCM was 29.7% (95% CI, 23.5%–36.0%).

SCN5A, *TNNC1*, *TNNT2*, and *TTN*) or strong (*DSP*) evidence and only 7 genes from the additional 2 ontologies (*ACTC1*, *ACTN2*, *JPH2*, *NEXN*, *TNNI3*, *TPM1*, and *VCL*) have moderate evidence supporting a robust association with DCM.²¹ Because DCM is often the final disease manifestation of several cardiomyopathies, it shares genetic architecture with other inherited cardiomyopathies. Among the previously mentioned 19 genes linked to DCM, the Clinical Genome Resource panel noted that 6 had a similar classification for HCM and 3 had a similar classification for arrhythmogenic right ventricular

- The estimated prevalence of familial DCM cardiomyopathy.²¹ was higher in Black probands compared with White probands (difference, 11.3% [95% CI,

- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy, as well as to DCM, with incomplete penetrance [1.9%–20.8%]).
- With the use of an expanded definition of familial DCM, which included the presence of DCM, LV enlargement, or LV systolic dysfunction without a known cause in at least 1 first-degree relative, the estimated prevalence was 56.9% (95% CI, 44.9%–68.9%).

penetrance in the general population.¹⁷ Analysis of sequence data in 7855 cases with cardiomyopathy and >60 000 controls revealed the variance in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of

50.8%–63.0%).

- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy and to DCM with incomplete penetrance in the general population.¹⁷ Analysis of sequence data in 7855 cases with cardiomyopathy and >60 000 controls revealed a

variation in mendelian disease genes.¹⁸

range in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of genetic variation in cardiomyopathy-associated genes.¹⁸

- A recent GWAS has identified common genetic variants associated with HCM (16 loci identified) and DCM (13 loci identified), indicating a potential oligogenic pattern (instead of a conventionally understood monogenic pattern) for the genetic risk of HCM and DCM.^{5,22} It is notable that 2 HCM loci (chromosome 1 near *HSPB7* and chromosome 10 near *BAG3*) have opposite directions of effect for DCM and require further evaluation in subsequent investigations.

Genetic Testing

- Among patients with DCM, a recent multisite nationwide cross-sectional study indicates an estimated familial prevalence of ≈30% in first-degree relatives and an estimated 19% risk of developing DCM by 80 years of age.¹⁶ This study also indicates that first-degree relatives of NH

Black probands (index patients with DCM) or probands diagnosed at a young age have a higher risk of DCM. These findings suggest a potential yield of phenotypic

Peripartum Cardiomyopathy

- PPCM is a global problem with significant geo-incidence (1 in 102 births) is seen in Nigeria, and Japan.²⁴ Accordingly, worldwide and in the United States, females with Black ancestry appear to have highest risk, especially females with Nigerian (1 per screening of first-degree relatives of index DCM cases, especially those identified at a young age. The clinical outcomes in familial DCM have been described recently.¹⁹

graphic variation in its incidence.²³ The highest the lowest incidence (1 in 15 533 births) is seen in States, females with Black ancestry appear to have 100 live births) and Haitian (1 per 300 live births) background.^{23,25}

- In the United States, according to NIS data, the incidence of PPCM increased between 2004 and 2011 from 8.5 to 11.8 per 10 000 live births

($P_{\text{trend}} < 0.001$), likely related to rising average maternal age and prevalence of PPCM risk factors such as obesity, hypertension, pregnancy-related hypertension, and diabetes.²⁶ Stratified by race and ethnicity, incidence of PPCM was lowest in Hispanic females (3.6 per 10 000 live births) and highest in Black females (22.8 per 10 000 live births). Stratified by region, incidence was lowest in the West (6.5 [95% CI, 6.3–6.7] per 10 000 live births) and highest in the South

- In a cohort of 55 804 hospitalized patients with PPCM in the United States, Black individuals (OR, 1.17 [95% CI, 1.15–1.57]; $P < 0.001$) and Hispanic individuals (OR, 1.37 [95% CI, 1.17–1.59]; $P < 0.001$) were more likely to develop cardiogenic shock than White individuals.²⁷ Similarly, Black individuals (OR, 1.67 [95% CI, 1.21–2.23]; $P = 0.002$) and Hispanic individuals (OR, 2.20 [95% CI, 1.45–3.33]; $P < 0.001$) were more likely to have in-hospital mortality than White individuals.
- In a UK case-control study of women with PPCM from 1998 to 2017, the incidence was 2.02 (95% CI, 1.76–2.29) per 10 000 deliveries in Scotland, which was similar to the incidence rate of 2.12 (95% CI, 2.03–2.21) per 10 000 deliveries in England from 2003 to 2017.²⁸ From 1998 to 2017 in Scotland, 7.7% of women with PPCM died over a median follow-up of 8.3 years, and 30-day mortality was 2.3% (95% CI, 0.9%–5.3%).²⁸
- In a global prospective PPCM registry, which

Genetics of PPCM

- Genetic analyses suggest that ~15% of individuals with PPCM have rare truncating variants in genes also linked to idiopathic DCM. The majority of these are truncating variants in *TTN*, which encodes the sarcomeric protein titin, and truncating variants in *TTN* in females with PPCM are associated with lower EF after 1 year of follow-up.³⁴

included 739 women enrolled between 2012 and 2018 from 49 countries, the 6-month maternal mortality rate was 5.9% overall but negatively correlated with the health expenditure of the countries, defined as a proportion of GDP allocated to health care expenses.²⁹ Maternal mortality rates at 6 months ranged from 2.0% in high-health-expenditure (>8% GDP) countries, 5.5% in medium-health-expenditure (5%–8% GDP) countries, and 10.0% in low-health-expenditure (<5% GDP) countries ($P = 0.002$).

- In a registry of 535 women with PPCM from 51 countries from 2012 to 2018, overall 1-year mortality was 8.4% with rates varying by region: Europe, 4.9%; Africa, 6.5%; Asia Pacific, 9.2%; and the Middle East, 18.9% ($P < 0.001$).³⁰ Within 1 year of diagnosis, 14.0% of women had at least 1 rehospitalization, and 3.5% had ≥ 2 rehospitalizations.
- In many cases of PPCM (47%–66%), LVEF recovers to at least near-normal ($\geq 50\%$) function and often within 6 months.^{30–33} However, an initial LVEF <30%, LV end-diastolic dimension ≥ 6.0 cm, Black race, and initial presentation >6 weeks after delivery are associated with lower LVEF at 1 year.³⁴

African descent was positively correlated with mortality (weight correlation coefficient, 0.29 [95% CI, 0.13–0.52]).³⁵

Youths

- Since 1996, the Pediatric Cardiomyopathy Registry has collected prospective data on children with cardiomyopathy in New England and central southwestern states.^{36,37}
 - Overall incidence of cardiomyopathy is 1.13 cases per 100 000 in children <18 years of age.
 - Incidence is 8.34 (95% CI, 7.21–9.61) per 100 000 in children <1 year of age.
 - Annual incidence (cases per 100 000) is higher in Black children (1.47) than in White children (1.06; $P=0.02$), in male (1.32) than in female (0.92) children ($P<0.001$), and in New England (1.44) than in the central Southwest (0.98; $P<0.001$).
- The annual incidence of HCM in children is ≈ 4.7 per 1 million (95% CI, 4.1–5.3) with higher incidence in New England (5.9 per 1 million [95% CI, 4.8–7.2]) than in the central Southwest region (4.2 per 1 million [95% CI, 3.5–4.9]) and in males (5.9 per 1 million [95% CI, 5.0–6.9]) than in females (3.4 per 1 million [95% CI, 2.8–4.2]).³⁸ Approximately 9% progress to HF and 12% to SCD over a median follow-up of 6.5 years.³⁹ Chapter 18 (Disorders of Heart Rhythm) provides statistics on SCD. Data from the NIS indicate that hospitalization is more likely with increasing age (OR, 5.59 [95% CI, 2.03–15.37] for ≥ 10 years of age versus 1–9 years of age) and in Black individuals compared with White individuals (OR, 2.78 [95% CI, 1.19–6.47]).⁴⁰
- The annual incidence of DCM in children is ≈ 0.57 per 100 000 (95% CI, 0.52–0.63) with a higher incidence in males than females (0.66 versus 0.47; $P<0.001$) and in Black children than White children (0.98 versus 0.46; $P<0.001$). Commonly recognized causes include myocarditis (46%) and neuromuscular disease (26%).⁴¹ The 5-year incidence rate of SCD is 3% at the time of DCM diagnosis.⁴² • For all cardiomyopathies seen in children, 5-year transplantation-free survival rate of DCM, HCM, restrictive cardiomyopathy, and LV noncompaction is 50%, 90%, 30%, and 60%, respectively.⁴³

- Data from the Childhood Cancer cohort of 14 358 survivors of cent cancers showed a 5.9-increased risk for HF ally preceded by sisting up to 30 years after the especially in patients treated anthracycline chemotherapy.

*Global Burden of Cardiomyopathy
(See Table 22-1 and Charts 22-1*

- Based on 204 countries and
 - There were 0.40 (95% UI, total deaths estimated for mvocarditis and an age-rate of 4.89 (95% UI, 4.47–(Table 22-1).
 - The highest age-regions estimated for carditis were for Eastern Europe followed by cen-tral sub-Saharan Africa and Central Asia. Rates were lowest for Andean Latin America (Chart 22-1).
 - Globally, there were 5.26 (95% UI, 4.36–6.09) million prevalent cases of cardiomyopathy and myocarditis and an age-standardized prevalence rate of 65.90 (95% UI, 54.98–76.83) per 100 000 (Table 22-1).
 - Age-standardized prevalence of cardiomyopathy and myocarditis among regions was highest for high-income North America followed by Australasia and Eastern Europe. The lowest prevalence rates were for East Asia and Oceania (Chart 22-2).
- Rates of SCD in patients with HCM vary by geographic region. In a meta-analysis of data from 2015 to 2020, the reported incidence rate per

in 2015 to 2018 (NHLBI using NHANES). The by age and sex is shown in

- Based on temporal trends, the projected to increase further. people ≥ 18 years of age by centage of the population with rise from 2.4% in 2012 to
- Overall, 1.9% to 2.6% of adults have HF.⁴⁶

Incidence

- Of 1 799 027 unique Medicare risk for HF (median, 73 years range, 68–79 years): 56% a new diagnosis of HF.⁴⁷ HF cases per 1000 beneficiaries tent across subgroups based ethnicity.
 - 100 PY was highest in Asia (0.67% [95% CI, 0.54%–0.84%]) followed by Europe (0.37% [95% CI, 0.31%–0.46%]) and North America (0.28% [95% CI, 0.18%–0.43%]).⁷

Heart Failure

ICD-9 428; ICD-10 I50. For hospital discharges, ICD-10 I50, I11.0, I13.0, I13.2, I09.81

2022, United States: Underlying cause mortality—87 941. Any-mention mortality—425 147.

2021, United States: Hospital discharges, principal diagnosis—1 200 188

Risk Factors

- Hypertension, smoking, diabetes, and obesity account for 52% of incident HF with PARs as follows⁴⁸: CHD, 20% (23% in males versus 16% in females); hypertension, 20% (28% in females versus 13% in males); cigarette smoking, 14%; obesity, 12%; and diabetes, 12%.
- Data from NHANES show that one-third of US adults have at least 1 HF risk factor.⁴⁹
- Risk factors differ by HF subtype: among 4 community-based studies (CHS, FHS, PREVENT, MESA)⁵⁰: incident HFpEF versus HFrEF (subdistribution HR, 1.91 [95% CI, 1.78–2.06] versus 1.69 [95% CI, 1.59–1.81], respectively, per 10-year age increase; *P* for equality=0.02).
 - In contrast, the following risk factors were more strongly associated with incident HFrEF than HFpEF: male sex (subdistribution HR, 1.87 [95% CI, 1.63–2.16] in HFrEF versus 0.91 [95% CI, 0.79–1.05] in HFpEF; *P* for equality <0.0001), previous MI (subdistribution HR, 2.70 [95% CI, 2.25–3.24] in HFrEF versus 1.30 [95% CI, 1.02–1.67] in HFpEF; *P* for equality <0.0001), electrocardiographic LVH (subdistribution HR, 2.08 [95% CI, 1.60–2.69] in HFrEF versus 1.16 [95% CI, 0.84–1.60] in HFpEF; *P* for equality=0.009), and left bundle-branch block (subdistribution HR, 3.65 [95% CI, 2.62–5.09] in HFrEF versus 1.30 [95% CI, 0.81–2.09] in HFpEF; *P* for equality=0.0008).

Prevalence

(See Table 22-2 and Chart 22-3)

- According to data from NHANES 2017 to 2020, 6.7 million Americans ≥20 years of age had HF
- Age dependency of risk factors: Although the (Table 22-2), up from the estimate of 6.0 million

absolute risk of HF is lower among younger individuals, the PAR of modifiable risk factors is greater among young (<55 years of age) compared with older (≥ 75 years of age) individuals:

obesity, 21% versus 13%; hypertension, 35% versus 23%; diabetes, 14% versus 7%; and smoking, 32% versus 1%.⁵¹

- Lifestyle factors also affect HF risk. Among WHI, MESA, and CHS participants, individuals with more than twice the minimum guideline-recommended leisure-time PA had lower risk of HFpEF compared with those with no leisure-time PA (HR, 0.81 [95% CI, 0.68–0.97]), whereas no such association
- In the ARIC study, greater alignment with the AHA's Life's Simple 7 guidelines (better profiles in smoking, BMI, PA, diet, cholesterol, BP, and glucose) was associated with lower lifetime risk of HF.⁵³ Specifically, the lifetime risk of HF among those with 5 to 7 ideal components in middle age was 12% (95% CI, 9%–15%), whereas those with 0 ideal components had a lifetime risk of 45% (95% CI, 35%–52%).

Race and Sex Differences

- In 6 US longitudinal population-based cohorts, hypertension had the highest PAR among Black males and females (28% [95% CI, 19%–37%] and 26% [95% CI, 16%–34%], respectively), whereas obesity had the highest PAR among White males and females (21% [95% CI, 15%–27%] and 18% [95% CI, 13%–23%]).⁵⁴
- Sex-specific risk factors for incident HF include disorders of pregnancy (eclampsia/preeclampsia, gestational diabetes), PPCM, polycystic ovarian syndrome, and premature menopause, although

- Multiple GWASs of cardiac structure and function have highlighted the association of genetic architecture of LV phenotypes with the risk of future HF.^{62,63} A transancestry meta-analysis of GWASs including >1 500 000 individuals identified 47 risk loci for all-cause HF. Integrating cardiac MRI intermediary phenotypes into this GWAS led to the identification of the exact contribution of these conditions to the incidence of HF among women is unknown.⁵⁵ The penetrance of genetic cardiomyopathies may be influenced by sex with males often more severely affected.

Family History and Genetics

- In the multigenerational FHS, HF in at least 1 parent was associated with a higher prevalence of asymptomatic LV systolic dysfunction (5.7% versus 3.1%; *P* adjusted for age, sex, and height=0.046) and greater risk of incident HF (age- and sex-adjusted 10-year incidence rate, 2.72% [95% CI, 1.80%–4.11%] versus 1.62% [95% CI, 1.10%–2.39%]; age- and sex-adjusted HR, 1.72 [95% CI, 1.13–2.61]; *P*=0.01).⁵⁶
- Several GWASs have been conducted to identify common variations associated with cardiomyopathy and HF in the general population, albeit with modest results, highlighting a small number of putative loci, including *HSPB7*^{57–59} and *CACNB4*.⁶⁰ In a GWAS of >47 000 cases and >930 000 controls, 11 HF loci were identified, all of which have known relationships with other CVD traits.⁶¹

18 novel loci.⁶⁵ Mendelian randomization and colocalization analyses identified an additional 10 putatively causal loci associated with HF.⁶⁵ According to the GWAS and Mendelian randomization proteomics analysis, 7 potential proteins (*CAMK2D*, *PRKD1*, *PRKD3*, *MAPK3*, *TNFSF12*, *APOC3*, and *NAE1*) were identified as drug targets for HF.⁶⁵ Human induced pluripotent stem cell cardiomyocyte-based functional studies investigating the molecular mechanism of decreased incidence of HF linked to the *BAG3* gene demonstrated that a coding variant (*BAG3*_{C151R}) is responsible for the maintenance of myofibrillary integrity and regulation response to proteotoxic stress.⁶⁶

- A single-cell profiling study showed that HCM and DCM share a common final transcriptional pathway at the cellular level. Furthermore, cardiomyopathy was associated with a shift in the macrophage population and the presence of a unique population of activated fibroblasts.⁶⁷
- The genetic basis of specific cardiomyopathies is summarized in the previous Cardiomyopathy section.

Treatment

- Improvement in survival has been attributed primarily to evidence-based approaches to treat HFrEF, including pharmacotherapies, ICDs, and cardiac resynchronization therapy.⁶⁸
- Based on modeling from clinical trial data, initiation of contemporary GDMT for HFrEF (quadruple therapy with angiotensin receptor/neprilysin inhibitors, ACE inhibitors, or ARBs; β -blockers; mineralocorticoid receptor antagonists; and SGLT-2 inhibitors) may reduce the hazard of cardiovascular death or HF hospitalization in HFrEF by up to 62% (HR, 0.38 [95% CI, 0.30–0.47]) compared with limited conventional therapy, resulting in an estimated 1.4 to 6.3 additional years alive.⁶⁹ Treatment efficacy with these classes for the outcome of death is attenuated as LVEF increases, and there is no clear evidence to support β -blockers in HFpEF.^{70,71}
- Across jurisdictions, there are significant gaps in the use and dose of GDMT, particularly in females.⁷² In an analysis of a US administrative health claims database of 63 759 patients (mean age, 71.3 years;

56.6% male), only 6.2% within 12 months of HFrEF. GDMT was defined as $\geq 50\%$ evidence-based β -blocker dose of ACE inhibitors or tensin receptor/neprilysin mineralocorticoid receptor

aps were wider in female time point at follow-up. In adjusted analyses, female sex was associated with a 23% lower probability of achieving optimal GDMT after diagnosis (HR, 0.77 [95% CI, 0.71–0.83]; $P < 0.001$). Females were also less likely to receive cardiac resynchronization and intracardiac device therapy than males.

- ICD and cardiac resynchronization therapy reduce all-cause mortality in eligible patients with

patients hospitalized for HF alive. 6 discrete phenogroups predominant comorbidity were valvular HD, AF, sleep apnea, tive pulmonary disease, or ties. Phenogroups were LVEF each phenogroup LVEFs. For the composite death or rehospitalization at 6 phenogroups ranged from

HFrEF^{71,72} but remain underused.

Females receive this inter-vention less frequently than males. In a pooled anal-ysis of 98 cohorts who had received CRT with or without ICD, men received the devices at a median

1.58) for AF to 2.04 (95% CI, 1.62–2.57) for chronic obstructive pulmonary disease (log-rank $P<0.001$) relative to the phenogroup with minimal comorbidities. In comparison, LVEF-based classification did not separate patients into different risk categories for composite of all-cause death or rehospitalization at 6 months; ($P=0.69$); relative to patients with LVEF $\leq 40\%$, those with LVEF $\geq 50\%$ had no difference in risk of all-cause death or rehospitalization at 6 months (HR, 1.01 [95% CI, 0.87–1.17]; $P=0.94$).⁷⁸

ratio of 3.16 (25th–75th interquartile range, 2.48–3.62) relative to women.⁷³

CVD Mortality
(See Table 22-2)

Mortality

Secular Trends

- Among adults ≥ 75 years of age with HF in the CDC WONDER dataset⁷⁴:
 - AAMR per 100 000 declined from 141.0 in 1999 to 108.3 in 2012 (annual percent change, -2.1 [95% CI, -2.4 to -1.9]), after which it increased to 121.3 in 2019 (annual percent change, 1.7 [95% CI, 1.2 – 2.2]).
- Across jurisdictions, the COVID-19 pandemic was associated with increased mortality among those with decompensated HF and with a shift in deaths from hospital to community.^{75,76} There was an increase in both in-hospital and postdischarge mortality among patients hospitalized with HF despite similar care quality. In the GWTG–Heart Failure registry, in-hospital mortality increased from 2.5% in 2019 to 2020 to 3.0% during 2020 to 2021, with in-hospital mortality as high as 8.2%

among those with concurrent COVID-19 infection.⁷⁶

Mortality by HF Subtype

- Among 4 community-based cohorts, including CHS, FHS, PREVENT, and MESA, all-cause mortality rates after HF diagnosis were 459 per 10 000 PY among those with HFrEF and 394 per 10 000 PY in individuals with HFpEF.⁷⁷
 - Phenotypes based on clinical comorbidities may stratify all-cause death or readmissions with greater discrimination than LVEF categories after hospitalization for HF.⁷⁸ In an unsupervised machine-learning cluster analysis of 1693

- Among optimally treated clinical trial patients with HF across the LVEF continuum, 53.5% of deaths were ascribed to CVD causes (of which 33.1% were from HF and 50.6% from SCD), 29.9% to non-CVD causes, and 16.5% to undetermined causes.⁷⁹ The proportion of non-CVD death was higher in those with higher EF. In the same analysis, the rate of death per 100 000 patient-years resulting from sudden death, HF, and cardiovascular causes decreased as LVEF increased.
- Data from the CDC WONDER database show that age-adjusted rates of HF-related CVD death declined from 1999 (78.7 per 100 000 [95% CI, 78.2–79.2]) to 2012 (53.7 per 100 000 [95% CI, 53.3–54.1]) and subsequently increased through 2017 (59.3 per 100 000 [95% CI, 58.9–59.6]).⁸⁰ There is geographic variation in HF-related CVD mortality, with the highest increases in annual AAMR after 2011 occurring in the Midwest (1.14 per 100 000 per year [95% CI, 0.75–1.53]) and South (0.96 per 100 000 per year [95% CI, 0.66–1.26]) compared with the Northeast (0.35 per 100 000 per year [95% CI, 0.03–0.68]).⁸¹
- Given improvements in HF survival overall, the number of individuals carrying a diagnosis of HF at death has increased. Mortality associated with HF is substantial such that ≈1 in 8 deaths in 2021 has HF mentioned on the death certificate (unpublished NHLBI tabulation).⁸²
- In 2022, HF was the underlying cause in 87 941 deaths (41 657 males and 46 284 females; Table 22-2).

- The number of deaths attributable to HF was 45.7% higher in 2022 than in 2012 (60 341; unpublished NHLBI tabulation using CDC WONDER).⁸³

Age, Sex, and Race and Ethnicity Differences in Mortality
(See Table 22-2)

- Among older adults in the CDC WONDER dataset between 1999 and 2019⁷⁴:

were rehospitalized (47.4% of these for HF), an additional 34.1% visited the ED without being rehospitalized, and 15.5% died within 6 months of discharge.⁸⁹

Secular Trends

- In the US NIS, hospitalizations for HF increased from 1 060 540 in 2008 to 1 270 360 in 2018 with a females throughout the period, with an AAMR of 141.1 in males and 107.8 in females in 2019.

viduals: 18.4% in 2008, 21.2% in 2018; Hispanic individuals: 7.1% in 2008, 9.0% in 2018; $P < 0.001$

– NH White adults had the highest overall AAMR (127.2) followed by NH Black adults (108.7), NH American Indian/Alaska Native adults (102.0), Hispanic or Latino adults (78.0), and NH Asian or Pacific Islander adults (57.1).

for all).⁹⁰

- In the Southern Community Cohort Study, all-cause mortality after a diagnosis code for HF varied by sex, with HRs of 1.63 (95% CI, 1.27–2.08), 1.38

- Hospitalizations by HF subtype increased from 2008 to 2018 in the United States for both HFrEF (n=283 193 to n=679 815) and HFpEF (n=189 260 to n=495 095).⁹⁰ A greater proportion of HFrEF hospitalizations occurred in males (60.5%), and a greater proportion of HFpEF hospitalizations occurred in females (62.5%; $P<0.001$ for (95% CI, 1.11–1.72), and 0.90 (95% CI, 0.73–1.12) sex difference).

for White males, Black males, and Black females, respectively, compared with White females.⁸⁴ In the ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively, with Black individuals having a greater 5-year case fatality rate than White individuals ($P<0.05$).⁸⁵

- Underlying cause and any-mention age-adjusted HF mortality rates by gender, race, and ethnicity are listed in Table 22-2.

Rural-Urban Disparities

- Among Medicare fee-for-service beneficiaries, 30-day mortality was higher among patients with HF presenting to rural versus urban hospitals (HR, 1.15 [95% CI, 1.13–1.16]).⁸⁶

Health Care Use: Hospital Use

- In 2019, there were 8 054 000 physician office visits with a primary diagnosis of HF (NAMCS,⁸⁷ unpublished NHLBI tabulation). In 2021, there were 1 390 365 ED visits for HF (HCUP,² unpublished NHLBI tabulation). In 2021, there were 1 200 188 principal diagnosis hospital discharges for HF (HCUP,² unpublished NHLBI tabulation).
- In the NCDR PINNACLE, 1 in 6 patients with HFrEF developed worsening HF within 18 months of diagnosis and was more likely to be Black, to be >80 years of age, and to have greater comorbidity burden; overall, the 2-year mortality rate was 22.5%.⁸⁸
- Outcomes remain poor after hospitalization for HF. In a pragmatic trial of 2494 patients discharged alive after hospitalization for HF in Canada in 2015 to 2016, 49.1% of patients

- Among 11 806 679 cases of HF hospitalization in the US NIS 2002 to 2016, there was a decrease in adjusted mortality from 6.8% in 2002 to 4.9% in 2016 ($P_{\text{trend}} < 0.001$), with consistent findings across age, sex, and race.⁹¹ The adjusted mean length of stay decreased from 8.6 to 6.5 days ($P < 0.001$), and discharge to a long-term care facility increased from 20.8% to 25.6% ($P < 0.001$).

Age, Sex, Race, and Socioeconomic Differences

- NIS dataset in the United States, the median age was 73.4 years (interquartile range, 62.4–82.9 years), 51.3% of hospitalizations occurred in male patients, and race and ethnicity composition included White individuals (70.0%), Black individuals (17.5%), Hispanic individuals (7.6%), Asian or Pacific Islander individuals (2.2%), and Native American individuals (0.5%). Among the hospitalizations, 33.1% were patients from zip codes in the lowest quartile of national household income (including 0.6% experiencing homelessness).⁹² In models adjusted for baseline characteristics, male sex (RR, 1.09 [95% CI, 1.07–1.11]) and low SES (RR, 1.02 [95% CI, 1.00–1.05]) were associated with a higher risk of in-hospital mortality relative to female sex and high SES, whereas Black race (RR, 0.79 [95% CI, 0.76–0.81]) and Hispanic ethnicity (RR, 0.90 [95% CI, 0.86–0.93]) were associated with a lower risk of in-hospital mortality than White race.
- Among 4 287 478 weighted hospitalizations in NIS dataset in the United States, the median age was 73.4 years (interquartile range, 62.4–82.9 years), 51.3% of hospitalizations occurred in male patients, and race and ethnicity composition included White individuals (70.0%), Black individuals (17.5%), Hispanic individuals (7.6%), Asian or Pacific Islander individuals (2.2%), and Native American individuals (0.5%). Among the hospitalizations, 33.1% were patients from zip codes in the lowest quartile of national household income (including 0.6% experiencing homelessness).⁹² In models adjusted for baseline characteristics, male sex (RR, 1.09 [95% CI, 1.07–1.11]) and low SES (RR, 1.02 [95% CI, 1.00–1.05]) were associated with a higher risk of in-hospital mortality relative to female sex and high SES, whereas Black race (RR, 0.79 [95% CI, 0.76–0.81]) and Hispanic ethnicity (RR, 0.90 [95% CI, 0.86–0.93]) were associated with a lower risk of in-hospital mortality than White race.
 - Among 767 180 weighted hospitalizations for HF among young adults <50 years of age in the NIS dataset in the US, Black adults (50.1%) accounted for disproportionately higher HF

hospitalizations compared (31.9%) and Hispanic adults of hospitalizations (45.8%) from the lowest quartile of income.⁹³

- Data from the 2005 to 2014 ARIC Surveillance study have shown that hospitalization rates are increasing over annual percentage change CI, 0.7%–3.1%) in White (2.7%–5.9%) in Black females

This increase in HF hospitalizations is driven largely by HFpEF events. Age-adjusted 28-day and 1-year case fatality rates after first-time hospitalized HF were higher among White individuals versus Black individuals. Specifically,

versus 14.3 [95% CI, 13.3–15.3] years, respectively).⁹⁷

Orthotopic Heart Mechanical Circulatory Placement in the United States

*Heart Transplantation
(See Chapter 27 [Medical
additional heart transplantation
Transplant Recipients*

28-day age-adjusted case fatality was 12.1% (White males), 11.7% (White females), 10.2% (Black females), and 9.2% (Black

- The annual number of transplantations in the United States has increased over time from 1676 in 1988 to 4111 in 2022.⁹⁸
- In 2022, the annual transplantation rate was 122.5 per 100 patient-years.⁹⁹
 - Among 3668 adult transplant recipients in 2022, the most common age group (46.6%) was 50 to 64 years of age, 26.9% were female, and 56.4% were White.
- In a pragmatic clinical trial of 2494 patients hospitalized for HF in Canada, females were on average ≈5 years older (mean±SD age, 80.0±10.9 years versus 75.4±12.8 years), more commonly resided in a nursing home (16.2% versus 8.2%), had a 6.89 (5.51–8.28) higher associated mean LVEF,⁷⁸ and experienced worse quality of life as measured by the European Quality of Life 5 Dimensions 5 Level Version scores (range, 0–1; 0.37 [95% CI, 0.30–0.44] females versus 0.62 [95% CI, 0.57–0.67] males).^{89,95} Event rates were high after index hospitalization; at 3 years of follow-up, 51.4% of patients receiving usual care had died, 80.7% were readmitted for any cause,

- The demographic characteristics of the typical heart transplant recipient—50 to 64 years of age, male, White—remained unchanged between 2012 and 2022; however, there has been an increase in the proportion of recipients who are 18 to 34 years of age (10.9% to 12.5%), ≥65 years of age (17.8% to 20.3%), and of Black race (19.7%–27.0%) or Hispanic ethnicity (7.9% to 11.2%); there has been a decrease in private insurance payers (50.9% to 44.8%). The proportion of recipients who are female remained unchanged between 2012 and 2022 (27.7% to 26.9%).⁹⁶
- Among those who die or are rehospitalized for any cause after hospitalization for HF, the proportion of cardiovascular deaths or HF hospitalizations decreases as LVEF increases. In a cohort of 1693 patients hospitalized for HF in 2015 to 2016 and discharged alive in Canadian hospitals, patients with LVEF ≥50% had a similar risk of all-cause death or rehospitalization at 6 months (HR, 1.01 [95% CI, 0.87–1.17]; *P*=0.94), but a lower risk of cardiovas-

- Among 3668 transplant recipients in 2022, the primary diagnosis was cardiomyopathy (64.1%) followed by CAD (25.9%), congenital HD (5.1%), and valvular disease (1.0%), with unknown underlying diagnoses in 3.9%. Coronary disease has become a less common primary diagnosis for heart transplantation over time (38.8% in 2012), and cardiomyopathy remains the most common diagnosis for heart transplantation (54.1% in 2012). cular death or HF rehospitalization (HR, 0.75 [95% CI, 0.62–0.92]; $P=0.005$) than those with LVEF $\leq 40\%$.⁷⁸ Among those who died or were rehospi- talized for any cause at 6 months, the proportion

- Among 3668 transplant recipients in 2022, a majority lived <50 miles from the transplantation center (59.2%) and in metropolitan areas
 - of cardiovascular deaths or HF hospitalizations was (83.6%).
 - higher in patients with LVEF <40% (61.1%) than
 - in those with LVEF >50% (48.4%).

- A ventricular assist device was present in 35.2% of transplant recipients in 2022, down from 41.4% in 2012.⁹⁹
- In the CHARM program, rates of cardiovascular hospitalization were higher among those with LVEF $\leq 40\%$ (23.6 [95% CI, 22.6–24.7] per 100 patient-years) versus LVEF $> 40\%$ (19.3 [95% CI, 18.2–20.5] per 100 patient-years; $P < 0.001$ for difference), whereas rates of noncardiovascular hospitalization were similar (14.3 [95% CI, 13.5–15.2]

- The proportion of transplant recipients who waited <90 days for a transplantation increased from 47.6% in 2012 to 65.9% in 2022.
- Multiorgan transplantation has increased more rapidly than heart transplantation alone. In 2012, 6.0% of heart transplantations were combined

with transplantation of other organs, and this increased to 14.0% in 2022. Between 2012 and 2022, heart-kidney transplantations increased from 3.7% to 10.5% of total heart transplantations, heart-liver transplantations increased from 0.9% to 2.0%, and heart-lung transplantations changed from 1.3% to 1.2%; the absolute numbers of each type of multiorgan transplantations increased

• Five-year survival was modestly lower in those 18 to 34 years of age (78.9%) and ≥65 years of age (77.8%) compared with the other age groups (35–49 and 50–64 years of age, 82.1% and 81.0%, respectively).⁹⁹• Five-year survival was highest in White transplant recipients (81.9%) followed by recipients identifying as Asian, multiracial, Black,

Transplantation Listings

- In 2022, a total of 7519 adults were awaiting heart transplantation in the United States, a 28.1% increase from 2011.⁹⁹
- A majority (61.6%) of adult heart transplantation candidates lived <50 miles from the transplantation center in 2022.⁹⁹
- The largest adult age group on the waiting list in 2022 continued to be 50 to 64 years of age (46.7%, followed by 35 to 49 years of age (21.7%), ≥65 years of age (20.3%), and 18 to 34 years of age (11.3%).⁹⁹
- In 2022, more than half of adult heart transplantation candidates were White (56.3%); 28.2% were Black, 10.8% were Hispanic, 3.8% were Asian, 0.4% were Native American, and 0.5% multiracial.⁹⁹
- Among 8747 US adults listed for heart transplantation in the Scientific Registry of Transplant Recipients from 2017 to 2019, 84.7% were from metropolitan, 8.6% were from micropolitan, and 6.6% were from rural settings; >70% were male candidates.¹⁰⁰

- Time on the waiting list, which is determined by the earliest of transplantation, death, removal, or December 31 of the year, has decreased, and the proportion of candidates waiting <90 days increased from 2011 to 45.8% in 2022.⁹⁹
- The proportion of candidates on the waiting list with a ventricular assist device increased from 22.4% in 2012 to 35.0% in 2022.⁹⁹
- Overall pretransplantation mortality declined from 15 deaths per 100 patient-years in 2011 to 8.7 deaths per 100 patient-years in 2019 and remained steady through 2022. The decrease in pretransplantation mortality has been consistent in all age and race or ethnicity groups other than Asian Americans, who experienced a slight increase with 9.7 deaths per 100 patient-years in 2022 compared with 8.5 deaths per 100 patient-years in 2012.⁹⁹

Outcomes After Transplantation

- In 2022, 6-month, 1-year, 3-year, and 5-year mortality after transplantation were 7.3%, 9.2%, 15.3%, and 19.9%, respectively. Mortality after transplantation has decreased since 2009.⁹⁹

portion of Black individuals and Hispanic individuals listed increased from 2011 to 2020 (21.7% to 28.2% [$P=0.003$] and 7.7% to 9.0% [$P=0.002$], respectively).¹⁰¹ Black individuals had a higher risk of death after transplantation (aHR, 1.14 [95% CI, 1.04–1.24]; $P=0.004$) compared with White individuals.

- Among 34 198 heart transplant recipients in the International Society for Heart and Lung Transplantation registry between 2004 and 2014, when matched for recipient and donor characteristics, there was no significant difference in survival between male and female recipients.¹⁰² Data from the Scientific Registry of Heart Transplant Recipients 2015 to 2017 also demonstrate no sex differences in survival through 5 years after transplantation.⁹⁹ Among 15 036 adult candidates for heart transplantation between 2011 and 2016 in the United States, there was significant state-level variation in outcomes, ranging from 1.0 to 7.8 deaths per 1000 wait-list person-days for wait-list mortality.¹⁰³ One-year risk-adjusted graft survival ranged from 87% to 92%.

Mechanical Circulatory Support

- The 14th Annual Report from the STS INTERMACS described outcomes of 27 493 patients with a continuous-flow LVAD from 2013 to 2022.¹⁰⁴ During this period, there was a shift to nearly exclusive use of fully magnetically levitated devices.
- In 2022, of 2517 primary LVADs implanted, 99.8% were fully magnetically levitated devices.¹⁰⁴
- The outcomes of magnetically levitated devices are superior to those of nonmagnetically levitated devices in contemporary (2018–2022) and historical (2013–2017) cohorts.¹⁰⁴
- Patients supported by a magnetically levitated device ($n=10\,920$) had a higher 1-year survival of 86% versus 79% and 81% in contemporary and historical nonmagnetically levitated groups, respectively ($P<0.0001$). They also had a higher 5-year survival of 64% versus 44% and 44% in contemporary and historical nonmagnetically levitated groups, respectively ($P<0.0001$).¹⁰⁴
- Over 5 years, a higher proportion of patients with magnetically levitated devices had freedom from gastrointestinal bleeding (72% versus 60%;

$P < 0.0001$), stroke (87% and device malfunction/pump vs 54%; $P < 0.0001$) but not tion (61% versus 64%; nonmagnetically levitated temporary era).¹⁰⁴

- INTERMACS reported outcomes receiving an FDA-approved circulatory support device During the reported 10-year

significant change in the acuity of illness of patients receiving an implant. INTERMACS profiles 1 and 2 still represented approximately half of the population (51% in 2021 versus 54.9% in 2012), with a minority of patients belonging to INTERMACS profile 4 (12.7% in 2021 versus 14.9% in 2012).

- Among LVAD recipients, destination therapy is now the predominant indication (increased from 56.5% in 2018 to 81.1% in 2021), whereas bridge to transplantation is uncommon (decreased from 18.9% in 2018 to 5.3% in 2021).¹⁰⁵

– 1-year and 5-year survival was 86.5% and 52.9% for bridge to transplantation, 84.7% and 49.4% for bridge to candidacy, and 70.9% and 42.4% for destination therapy in 2012 to 2021. During this period, there was a consistent improvement in survival for all device indications, with the most striking improvement in destination therapy as the predominant implantation strategy.¹⁰⁵

– Improvements in LVAD technology and the use of LVAD as destination therapy have led

- In 2012, total cost for HF was \$30.7 billion (2010 dollars). of two-thirds was attributed to Projections suggest that by HF will increase by 127% to inq to ≈\$244 for every US

- In a systematic review of HF-costs in the United States annual median total cost was per patient. with HF

to more prolonged time on support. Currently, withdrawal from support is the leading cause of death (19.4%), replacing neurological dysfunction (17.9%) in the prior era.¹⁰⁵

- In a study that used the United Network for Organ Sharing registry between 2006 and 2015 and addressed insurance status, among those with bridge to transplantation LVADs, Medicaid insurance was associated with worse survival compared with private insurance (subdistribution HR, 1.57 [95% CI, 1.15–2.16]), although access to transplantation was not different.¹⁰⁶

Sex Differences

- According to INTERMACS data from 2017 to 2019, for patients receiving contemporary centrifugal LVADs, the risk of death appeared to be higher in males (HR, 1.63; $P = 0.01$) relative to females.¹⁰⁷

the majority (\$15 879 per patient).¹⁰⁹

- Data from the US NIS for 4 287 478 primary HF hospitalizations 2014 to 2017 highlight differences in cost of care across demographic groups.⁹² The median direct cost of admission was higher in high- than in low-SES groups (\$10 940.40 versus \$9324.60), male versus female patients (\$10 217.10 versus \$9866.60), and White versus Black individuals (\$10 019.80 versus \$9077.20).

The median costs increased with SES in all demographic groups, related to greater procedural use. • Among 11 806 679 HF hospitalizations in the US NIS database between 2002 and 2016, inflation-adjusted mean cost of stay increased from \$14 301 to \$17 925 ($P<0.001$; average annual increase, 1.52%).⁹¹ This trend may have been related to the temporal increase in procedures (echocardiogram, right-sided heart catheterization, use of ventricular assist devices, CABG) and the higher incidence of HF complications (cardiogenic shock, respiratory failure, ventilator, and renal failure requiring dialysis). • The costs associated with treating HF comorbidities and HF exacerbations in youths are significant, totaling nearly \$1 billion in inpatient costs, and may be rising. The associated cost burden of HF is anticipated to constitute a large portion of total pediatric health care costs.¹¹¹

Global Burden of HF

(See Table 22-3 and Chart 22-4)

- Based on 204 countries and territories in 2021⁴⁵:
 - There were 55.50 (95% UI, 49.00–63.84) million prevalent cases of HF and an age-standardized prevalence rate of 676.68 (95% UI, 598.68–776.84) per 100 000 globally (Table 22-3).
 - Among regions, age-standardized prevalence of HF was highest for high-income North America followed by Central Europe, North Africa and the

Cost

Middle East, and eastern sub-Saharan

Overall Costs

The overall cost of HF continues to rise. See Chapter

28 (Economic Cost of Cardiovascular Disease) for further statistics.

Asia Pacific (Chart 22-4).

- In 2019:

- Adults >70 years of age accounted for 62.2% of the world's HF cases, with female predominance

in this age group and male predominance in younger adults; 50.3% of those living with HF were females, but age-standardized prevalence was greater in males.¹¹²

– 69.2% lived in low- and middle-income countries, although the highest age-standardized prevalence was highest in North America and lowest in South America (993.84 [95% CI, 866.22–1140.37] per 100 000 in females; 1344.62 [95% CI, 1159.53–1556.54] per 100 000 in males) and East Asia (1001.01 [95% CI, 819.06–1245.62] per 100 000 in females; 991.23 [95% CI, 808.02–1228.71] per 100 000 in males) followed by Oceania and eastern sub-Saharan Africa.¹¹³

– There were 5.1 (95% UI, 3.3–7.3) million years lived with disability from HF, distributed equally between the sexes.¹¹²

– In sequence, ischemic, hypertensive, and rheumatic HDs were the most common causes of HF in the world. IHD and hypertensive HD were the top causes of HF in males and females, respectively.¹¹²

56.2 (95% UI, 46.4–67.8) million, with a doubling in both males and females.

– Accounting for population growth, the age-standardized rate of HF per 100 000 people decreased by 7.1% worldwide, from 766.0 (95% UI, 626.3–936.0) in 1990 to 711.9 (95% UI, 591.1–858.3) in 2019. There were 9.1% (from 864.2 to 785.7) and 5.8% (from 686.0 to 646.1) decreases in age-standardized rates (from 877.5 to 736.8), whereas low-income regions experienced a 3.9% increase (from 612.1 to 636.0), largely consistent across sexes.

– There was a temporal increase in age-standardized HF from hypertensive, rheumatic, and calcific aortic valvular HD, as well as a temporal decrease from IHD, with some regional and sex differences.

Age-standardized HF rates from hypertensive HD were largely stable but increased by as much as 22.3% in females in high-middle-SDI regions. Age-standardized prevalence of HF from rheumatic HD increased over time; this was

enced increases ranging from 5% to 25% over time; this trend was consistent in both sexes.

Table 22-1. Global Prevalence and Mortality of Cardiomyopathy and Myocarditis, by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	0.40 (0.37 to	5.26 (4.36 to 6.09)	0.25 (0.22 to	3.03 (2.51 to 3.53)	0.16 (0.14 to	2.22 (1.84 to 2.62)
Percent change (%) in	45.67 (33.04 to 59.51)	77.47 (67.74 to 87.17)	63.31 (46.26 to	82.04 (72.71 to 91.54)	24.63 (11.99 to 39.24)	71.60 (61.49 to 81.79)
Percent change (%) in	−0.53 (−6.38 to 5.73)	20.11 (13.65 to 26.46)	0.85 (−7.51 to 7.93)	20.27 (13.82 to 25.90)	−2.61 (−9.32 to 4.93)	19.90 (13.12 to 27.15)
Rate per 100 000,	4.89 (4.47 to	65.90 (54.98 to 76.83)	6.47 (5.86 to	78.26 (65.37 to 90.93)	3.46 (3.05 to	54.20 (45.01 to 63.96)
Percent change (%) in rate, age	−37.54 (−42.40 to −32.03)	3.22 (−2.63 to 9.13)	−30.30 (−36.37 to −23.64)	5.97 (0.28 to 11.49)	−46.71 (−51.37 to −41.47)	−0.01 (−6.07 to 6.48)
Percent change (%) in rate, age	−25.16 (−29.44 to −20.50)	−0.58 (−5.89 to 4.35)	−23.01 (−28.99 to −17.91)	−0.47 (−5.61 to 4.10)	−27.96 (−32.80 to −22.55)	−0.75 (−6.42 to 4.55)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁴⁵

Table 22-2. HF in the United States

Population group	Prevalence, 2017–2020, ≥20 y of age	Underlying cause mortality, 2022, all ages*	Underlying cause age-adjusted mortality rates per 100 000 (95% CI)
Both sexes	6 700 000 (2.3%) (95% CI, 1.9%–2.8%)	87 941	21.0 (20.8–21.1)
Males	3 700 000 (2.7%)	41 657 (47.4%)†	24.2 (24.0–24.5)
Females	3 000 000 (1.9%)	46 284 (52.6%)†	18.5 (18.3–18.6)
NH White males	2.9%	32 820	25.3 (25.0–25.6)
NH White females	1.6%	37 152	19.6 (19.4–19.8)
NH Black males	3.8%	5101	32.1 (31.2–33.1)
NH Black females	3.3%	5375	22.7 (22.1–23.3)
Hispanic males	1.8%	2434	15.0 (14.3–15.6)
Hispanic females	1.6%	2478	11.0 (10.5–11.4)

HF includes people who answered “yes” to the question of ever having congestive HF. CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading. In March 2020, the COVID-19 pandemic halted NHANES field operations. Because data collected in the partial 2019 to 2020 cycle are not nationally representative, they were combined with previously released 2017 to 2018 data to produce nationally representative estimates.¹¹⁴

COVID-19 indicates coronavirus disease 2019; ellipses (...), data not available; HF, heart failure; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*Mortality data for cause of death listed as HF on death certificates for Hispanic people, NH American Indian or Alaska Native people, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native decedents, Asian and Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses. For reference to all-cause mortality in setting of prevalent HF, please see the Mortality section.

†These percentages represent the portion of total mortality attributable to HF that is for males vs females.

‡ Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.¹¹⁵ Percentages are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2020 US population estimates. These data are based on self-reports. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System⁸² and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.⁸³

Table 22-3. Global Prevalence of Heart Failure, by Sex, 2021

	Prevalence		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	55.50 (49.00 to 63.84)	28.59 (25.35 to 32.83)	26.91 (23.72 to 30.98)
Percent change (%) in	118.21 (112.40 to 124.14)	119.11 (112.83 to 125.49)	117.25 (111.26 to 123.99)
Percent change (%) in	33.28 (30.67 to 36.34)	32.28 (29.62 to 35.21)	34.36 (31.31 to 37.50)
Rate per 100 000, age	676.68 (598.68 to 776.84)	760.78 (673.19 to 874.71)	604.00 (534.95 to 692.29)
Percent change (%) in rate, age standardized,	5.54 (2.70 to 8.49)	4.78 (1.74 to 7.81)	5.57 (2.35 to 8.69)
Percent change (%) in rate, age standardized,	1.02 (−0.54 to 2.73)	0.16 (−1.43 to 1.85)	1.81 (0.00 to 3.59)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁴⁵

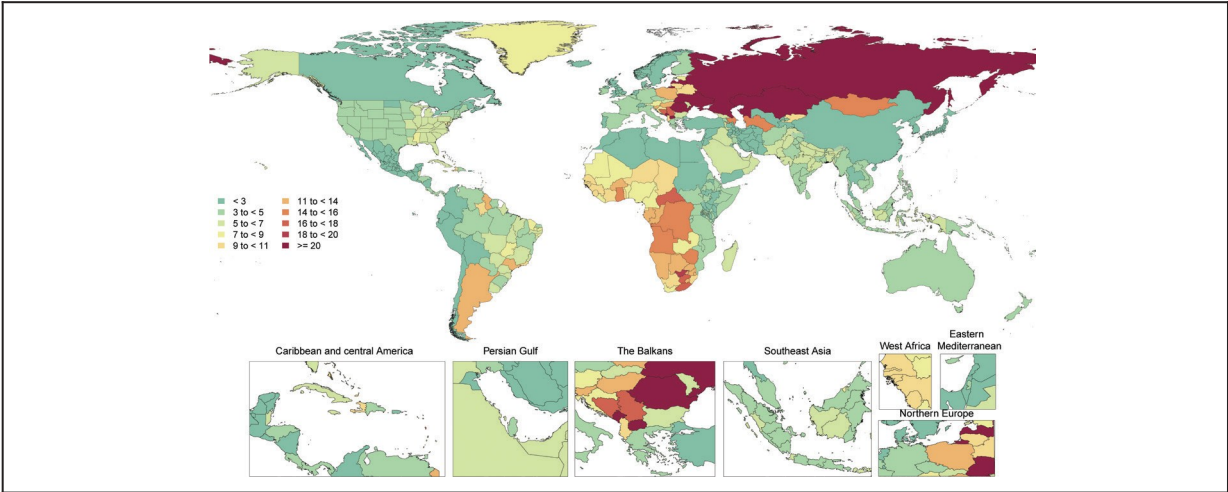


Chart 22-1. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁴⁵

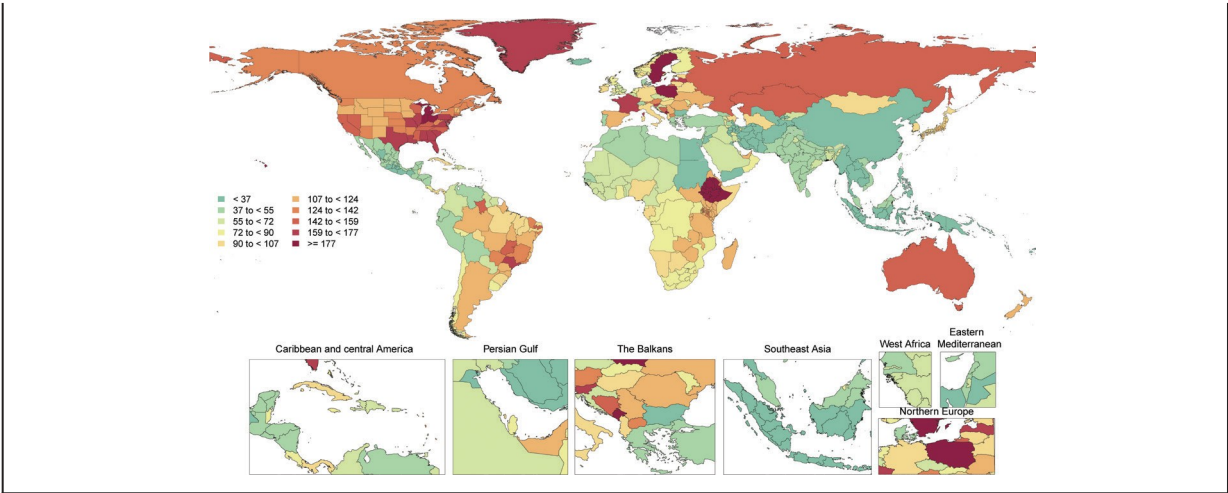


Chart 22-2. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁴⁵

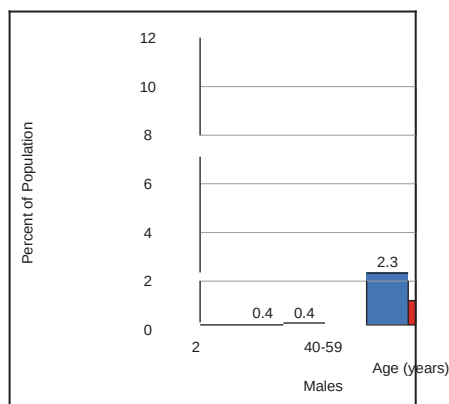


Chart 22-3. Prevalence of HF among US adults ≥ 20 years of age, by sex and age (NHANES, 2017–2020).

HF indicates heart failure; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.¹¹⁵

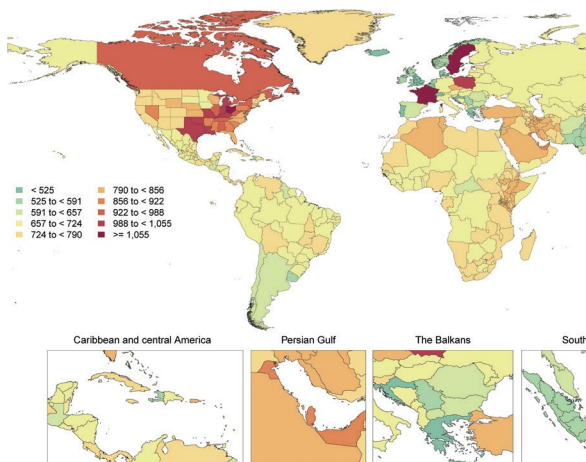


Chart 22-4. Age-standardized global prevalence rates of HF per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. GBD indicates Global Burden of Disease, Injuries, and Risk Factors; and HF, heart failure.

Source: Data courtesy of the GBD Study, Institute for Health

REFERENCES

- Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, Bezzina CR, Biagini E, Blom NA, de Boer RA, et al; ESC Scientific Document Group. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44:3503–3626. doi: 10.1093/eurheartj/ehad194
- Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024.
- Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic evaluation of cardiomyopathy: a Heart Failure Society of America practice guideline. *J Card Fail*. 2018;24:281–302. doi: 10.1016/j.cardfail.2018.03.004
- Jaaskelainen P, Vangipurapu J, Raivo J, Kuulasmaa T, Helio T, Aalto-Setälä K, Kaartinen M, Ilveskoski E, Vanninen S, Hamalainen L, et al. Genetic basis and outcome in a nationwide study of Finnish patients with hypertrophic cardiomyopathy. *ESC Heart Fail*. 2019;6:436–445. doi: 10.1002/ehf2.12420
- Tadros R, Francis C, Xu X, Vermeer AMC, Harper AR, Huurman R, Kelu Bisabu K, Walsh R, Hoorntje ET, Te Rijdt WP, et al. Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect. *Nat Genet*. 2021;53:128–134. doi: 10.1038/s41588-020-00762-2
- Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human

Cardiomyopathy Registry (SHaRe). *Circulation*. 2018;138:1387–1398. doi: 10.1161/CIRCULATIONAHA.117.033200

7. Abdelfattah OM, Martinez M, Sayed A, ElRefaei M, Abushouk AI, Hassan A, Masri A, Winters SL, Kapadia SR, Maron BJ, et al. Temporal and global trends of the incidence of sudden cardiac death in hypertrophic cardiomyopathy. *JACC Clin Electrophysiol*. 2022;8:1417–1427. doi: 10.1016/j.jacep.2022.07.012

8. Butzner M, Leslie D, Cuffee Y, Hollenbeak CS, Sciamanna C, Abraham TP. Sex differences in clinical outcomes for obstructive hypertrophic cardiomyopathy in the USA: a retrospective observational study of administrative claims data. *BMJ Open*. 2022;12:e058151. doi: 10.1136/bmjopen-2021-058151

9. Ingles J, Goldstein J, Thaxton C, Caleshu C, Corty EW, Crowley SB, Dougherty K, Harrison SM, McGlaughon J, Milko LV, et al. Evaluating the clinical validity of hypertrophic cardiomyopathy genes. *Circ Genom Precis Med*. 2019;12:e002460. doi: 10.1161/CIRCGEN.119.002460

10. Page SP, Kounas S, Syrris P, Christiansen M, Frank-Hansen R, Andersen PS, Elliott PM, McKenna WJ. Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome. *Circ Cardiovasc Genet*. 2012;5:156–166. doi: 10.1161/CIRCGENETICS.111.960831

11. Lorenzini M, Norrish G, Field E, Ochoa JP, Cicerchia M, Akhtar MM, Syrris P, Lopes LR, Kaski JP, Elliott PM. Penetrance of hypertrophic cardiomyopathy in sarcomere protein mutation carriers. *J Am Coll Cardiol*. 2020;76:550– 559. doi: 10.1016/j.jacc.2020.06.011

12. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10:531–547. doi: 10.1038/nrcardio.2013.105
13. Schultheiss HP, Fairweather D, Caforio ALP, Escher F, Hershberger RE, Lipshultz SE, Liu PP, Matsumori A, Mazzanti A, McMurray J, et al. Dilated cardiomyopathy. *Nat Rev Dis Primers*. 2019;5:32. doi: 10.1038/s41572-019-0084-1
14. Joseph P, Roy A, Lonn E, Stork S, Floras J, Mielniczuk L, Rouleau JL, Zhu J, Dzudie A, Balasubramanian K, et al; G-CHF Investigators. Global variations in heart failure etiology, management, and outcomes. *JAMA*. 2023;329:1650–1661. doi: 10.1001/jama.2023.5942
15. McNally EM, Mestroni L. Dilated cardiomyopathy: genetic determinants. *Circ Res*. 2016;116:309–326. doi: 10.1161/CIRCRESAHA.116.309396
16. Huggins GS, Kinnamon DD, Haas GJ, Jordan E, Hofmeyer M, Kransdorf E, Ewald GA, Morris AA, Owens A, Lowes B, et al; DCM
29. Sliwa K, van der Meer P, Viljoen C, Jackson AM, Petrie MC, Mebazaa A, Hilfiker-Kleiner D, Maggioni AP, Laroche C, Regitz-Zagrosek V, et al; EURObservational Research Programme, in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Socio-economic factors determine maternal and neonatal outcomes in women with peripartum cardiomyopathy: a study of the ESC EORP PPCM registry. *Int J Cardiol*. 2024;398:131596. doi: 10.1016/j.ijcard.2023.131596
30. Jackson AM, Bauersachs J, Petrie MC, van der Meer P, Laroche C, Farhan HA, Frogoudaki A, Ibrahim B, Fouad DA, Damasceno A, et al; EURObservational Research Programme in Precision Medicine Study of the DCM Consortium. Prevalence and cumulative risk of familial idiopathic dilated cardiomyopathy. *JAMA*. 2022;327:454–463. doi: 10.1001/jama.2022.1111

- partum cardiomyopathy: findings from the ESC EORP PPCM Registry. *Eur J Heart Fail.* 2024;26:34–42. doi: 10.1002/ehf.3055
31. Koerber D, Khan S, Kirubakaran A, Spivak A, Wine R, Matelski J, Sobel M, Harris K. Meta-analysis of long-term (>1 year) cardiac outcomes of peripartum cardiomyopathy. *Am J Cardiol.* 2023;194:71–77. doi: 10.1001/jama.2021.24674
17. Hastings R, de Villiers CP, Hooper C, Ormondroyd L, Pagnamenta A, Lise S, Salatino S, Knight SJ, Taylor JC, Thomson KL, et al. Combination of whole genome sequencing, linkage, and functional studies implicates a missense mutation in titin as a cause of autosomal dominant cardiomyopathy with features of left ventricular noncompaction. *Circ Cardiovasc Genet.* 2016;9:426–435. doi: 10.1161/CIRCGENETICS.116.001431
18. Walsh R, Thomson KL, Ware JS, Funke BH, Woodley J, McGuire KJ, Mazzarotto F, Blair E, Seller A, Taylor JC, et al; Exome Aggregation Consortium. Reassessment of mendelian gene pathogenicity using cardiomyopathy cases and 60,706 reference samples. *Genet Med.* 2017;19:192–203. doi: 10.1038/gim.2016.90
19. Shetty NS, Parcha V, Hasnie A, Pandey A, Arora G, Arora P. Mechanical cir-

32. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, Modi K, Alexis JD, Ramani GV, Semigran MJ, et al; IPAC Investigators. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol*. 2015;66:905–914. doi: 10.1016/j.jacc.2015.06.1309
33. Irizarry OC, Levine LD, Lewey J, Boyer T, Riis V, Elovitz MA, Arany Z. Comparison of clinical characteristics and outcomes of peripartum cardio-myopathy between African American and non-African American women. *JAMA Cardiol*. 2017;2:1256–1260. doi: 10.1001/jamacardio.2017.3574
34. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, et al; IMAC-2 and IPAC Investigators. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med*. 2016;374:233–241. doi: 10.1056/NEJMoa1505517
20. Vissing CR, Espersen K, Mills HL, Bartels ED, Jurlander R, Skriver SV, Ghose J, Thune JJ, Axelsson Raja A, Christensen AH, et al. Family
- culatory support devices among patients with familial dilated cardiomyopathy: insights from the INTERMACS. *Circulation*. 2022;146:1486–1488. doi: 10.1161/CIRCULATIONAHA.122.061143

35. Kerpen K, Koutrolou-Sotiropoulou P, Zhu C, Yang J, Lyon JA, Lima FV, Stergiopoulos K. Disparities in death rates in women with peripartum cardiomyopathy between advanced and developing countries: a systematic review and meta-analysis. *Arch Cardiovasc Dis.* 2019;112:187–198. doi: 10.1016/j.acvd.2018.10.002
- screening in dilated cardiomyopathy: prevalence, incidence, and potential for limiting follow-up. *JACC Heart Fail.* 2022;10:792–803. doi: 10.1016/j.jchf.2022.07.009
21. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, Celeghin R, Edwards M, Fan J, Ingles J, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation.* 2021;144:7–19. doi: 10.1161/CIRCULATIONAHA.120.053033
22. Harper AR, Goel A, Grace C, Thomson KL, Petersen SE, Xu X, Waring A, Ormondroyd E, Kramer CM, Ho CY, et al; HCMR Investigators. Common genetic variants and modifiable risk factors underpin hypertrophic cardio-myopathy susceptibility and expressivity. *Nat Genet.* 2021;53:135–142. doi: 10.1038/s41588-020-00764-0
23. Arany Z. Peripartum cardiomyopathy. *N Engl J Med.* 2024;390:154–164. doi: 10.1056/NEJMra2306667
24. Isogai T, Kamiya CA. Worldwide incidence of peripartum cardiomyopathy and overall maternal mortality. *Int Heart J.* 2019;60:503–511. doi: 10.1016/j.ihj.2019.03.002

36. Lipshultz SE, Law YM, Asante-Korang A, Austin ED, Dipchand AI, Everitt MD, Hsu DT, Lin KY, Price JF, Wilkinson JD, et al; on behalf of the American Heart Association Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Council on Genomic and Precision Medicine. Cardiomyopathy in children: classification and diagnosis: a scientific state-ment from the American Heart Association. *Circulation*. 2019;140:e9–e68. doi: 10.1161/CIR.0000000000000682
37. Wilkinson JD, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ, Cox GF, Canter CE, Hsu DT, Webber SA, et al. The Pediatric Cardiomyopathy Registry and heart failure: key results from the first 15 years. *Heart Fail Clin*. 2010;6:401–413, vii. doi: 10.1016/j.hfc.2010.05.002
38. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific Pediatric Cardiomyopathy Registry. *Circulation*. 2007;115:773–781. doi: 10.1536/ihj.18-729
25. Sliwa K, Mebazaa A, Hilfiker-Kleiner D, Petrie MC, Maggioni AP, Laroche C, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van der Meer P, et al. Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM): EURObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM. *Eur J Heart Fail*. 2017;19:1131–1141. doi: 10.1161/CIRCULATIONAHA.106.621185

39. Ziolkowska L, Turska-Kmiec A, Petryka J, Kawalec W. Predictors of long- term outcome in children with hypertrophic cardiomyopathy. *Pediatr Cardiol.* 2016;37:448–458. doi: 10.1007/s00246-015-1298-y
40. Sakai-Bizmark R, Webber EJ, Marr EH, Mena LA, Chang RR. Patient characteristics and incidence of childhood hospitalisation due to hypertrophic cardiomyopathy in the United States of America 2001-2014. *Cardiol Young.* 2019;29:344–354. doi: 10.1017/S1047951118002421
26. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, Jain D, Gass A, Ahmed A, Panza JA, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nation-

41. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA*. 2006;296:1867–1876. doi: 10.1001/jama.296.15.1867
- wide population-based study. *J Am Heart Assoc*. 2014;3:e001056. doi: 10.1161/JAHA.114.001056
27. Olanipekun T, Abe T, Effoe V, Egbuche O, Mather P, Echols M, Adedinsowo D. Racial and ethnic disparities in the trends and outcomes of cardio-genic shock complicating peripartum cardiomyopathy. *JAMA Netw Open*. 2022;5:e2220937. doi: 10.1001/jamanetworkopen.2022.20937

42. Pahl E, Sleeper LA, Canter CE, Hsu DT, Lu M, Webber SA, Colan SD, Kantor PF, Everitt MD, Towbin JA, et al; Pediatric Cardiomyopathy Registry Investigators. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. *J Am Coll Cardiol*. 2012;59:607–615. doi: 10.1016/j.jacc.2011.10.878
28. Jackson AM, Macartney M, Brooksbank K, Brown C, Dawson D, Francis M, Japp A, Lennie V, Leslie SJ, Martin T, et al. A 20-year population study of peripartum cardiomyopathy. *Eur Heart J*. 2023;44:5128–5141. doi: 10.1093/eurheartj/ehad626
43. Choudhry S, Puri K, Denfield SW. An update on pediatric cardiomyopathy. *Curr Treat Options Cardiovasc Med*. 2019;21:36. doi: 10.1007/s11936-019-0739-y

44. Mulrooney DA, Yeazel MW, Kawashima T, Donaldson SS, Green DM, Sklar CA. in a cohort of adult survivors of childhood snective analysis of the Childhood Cancer 2009;339:b4606. doi: 10.1136/bmi.b4606
45. *Global Burden of Disease Study and Institute Evaluation*. University of Washington.
46. Siontis GC, Bhatt DL, Patel CJ. Secular failure diagnosis over 20 years (from the 2022;172:161–164. doi:
47. Khera R, Kondamudi N, Zhong L, SR Grodin JL, Halm FA, Berry JD, Pandey heart failure incidence among Medicare beneficiaries across risk fac- tor strata, 2011 to 2016. *JAMA Netw Open*. 2020;3:e2022190. doi: 10.1001/jamanetworkopen.2020.22190
48. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart fail- ure: a population-based case-control study. *Am J Med*. 2009;122:1023– 1028. doi: 10.1016/j.amjmed.2009.04.022
49. Kovell LC, Juraschek SP, Russell SD. Stage A heart failure is not adequate- ly recognized in US adults: analysis of the National Health and Nutrition Examination Surveys, 2007–2010. *PLoS One*. 2015;10:e0132228. doi: 10.1371/journal.pone.0132228
50. Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, Bartz TM, Santhanakrishnan R, Lee DS, Chan C, et al. Predicting heart failure with preserved and reduced ejection fraction: the International Collaboration on Heart Failure Subtypes. *Circ Heart Fail*. 2016;9:e003116. doi: 10.1161/CIRCHEARTFAILURE.115.003116
51. Tromp J, Paniagua SMA, Lau ES, Allen NB, Blaha MJ, Gansevoort RT, Hillege HL, Lee DE, Levy D, Vasan RS, et al. Age dependent associations of risk factors with heart failure: pooled population based cohort study. *BMJ*. 2021;372:n461. doi: 10.1136/bmj.n461
52. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, et al. Relationship between phys- ical activity, body mass index, and risk of heart failure. *J Am Coll Cardiol*. 2017;69:1129–1142. doi: 10.1016/j.jacc.2016.11.081
53. Folsom AR, Shah AM, Lutsey PL, Roetker NS, Alonso A, Avery CL, Miedema MD, Konety S, Chang PP, Solomon SD. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *Am J Med*. 2015;128:970–976. doi: 10.1016/j.amjmed.2015.03.027
54. Sinha A, Ning H, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM, Khan SS. Race- and sex-specific population attributable frac- tions of incident heart failure: a population-based cohort study from the Lifetime Risk Pooling Project. *Circ Heart Fail*. 2021;14:e008113. doi: 10.1161/CIRCHEARTFAILURE.120.008113
55. Sullivan K, Doumouras BS, Santema BT, Walsh MN, Douglas PS, insights into the pathogenesis of heart doi: 10.1038/s41467-019-13690-5
62. Aune N, Vargaas JD, Yano C, Cabrera Tzanis E, Barnes MR, Rottler JL. analysis of left ventricular image- fies fourteen loci associated with heart failure development. *Circulation*. 10.1161/
63. Moslev JD, Levinson RT, Farber-Ener AM, Giri A, Shuev MM, Shaffer CM. ture of left ventricular mass mirrors the 2020;10:7561. doi: 10.1038/s41598-
64. Levin MG, Tsao NI, Singhal P, Liu C, Voors AA, Van Spall HGC. Sex-specific differences in heart failure: pathophysiology, risk factors, management, and outcomes. *Can J Cardiol*. 2021;37:560– 571. doi: 10.1016/j.cjca.2020.12.025
56. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ, Nam BH, Larson MG, D'Agostino RB, Vasan RS. Association of parental heart failure with risk of heart failure in offspring. *N Engl J Med*. 2006;355:138– 147. doi: 10.1056/NEJMoa052948
57. Cappola TP, Li M, He J, Ky B, Gilmore J, Qu L, Keating B, Reilly M, Kim CE, Glessner J, et al. Common variants in *HSPB7* and *FRMD4B* associated with advanced heart failure. *Circ Cardiovasc Genet*. 2010;3:147– 154. doi: 10.1161/CIRCGENETICS.109.898395
58. Matkovich SJ, Van Booven DJ, Hindes A, Kang MY, Druley TE, Vallania FL, Mitra RD, Reilly MP, Cappola TP, Dorn GW 2nd. Cardiac signaling genes exhibit unexpected sequence diversity in sporadic cardiomyopathy, revealing *HSPB7* polymorphisms associated with disease. *J Clin Invest*. 2010;120:280–289. doi: 10.1172/JCI39085
59. Stark K, Esslinger UB, Reinhard W, Petrov G, Winkler T, Komajda M, Isnard R, Charron P, Villard E, Cambien F, et al. Genetic association study identifies *HSPB7* as a risk gene for idiopathic dilated cardiomyopathy. *PLoS Genet*. 2010;6:e1001167. doi: 10.1371/journal.pgen.1001167
60. Xu H, Dorn li GW, Shetty A, Parihar A, Dave T, Robinson SW, Gottlieb SS, Donahue MP, Tomaselli GF, Kraus WE, et al. A genome-wide association study of idiopathic dilated cardiomyopathy in African Americans. *J Pers Med*. 2018;8:E11. doi: 10.3390/jpm8010011
61. Shah S, Henry A, Roselli C, Lin H, Sveinbjornsson G, Fatemifar G, Hedman AK, Wilk JB, Morley MP, Chaffin MD, et al; Regeneron Genetics Center. Genome-wide association and mendelian randomisation analysis provide

- Bellomo TR, Bone WP, Biddinger KJ, et al; Regeneron Genetics Center. Genome-wide association and multi-trait analyses characterize the com-mon genetic architecture of heart failure. *Nat Commun.* 2022;13:6914. doi: 10.1038/s41467-022-34216-6
65. Rasooly D, Peloso GM, Pereira AC, Dashti H, Giambartolomei C, Wheeler E, Aung N, Ferlito BR, Pietzner M, Farber-Eger EH, et al. Genome-wide association analysis and Mendelian randomization proteomics identify drug targets for heart failure. *Nat Commun.* 2023;14:3826. doi: 10.1038/s41467-023-39253-3
66. Perez-Bermejo JA, Judge LM, Jensen CL, Wu K, Watry HL, Truong A, Ho JJ, Carter M, Runyon WV, Kaake RM, et al. Functional analysis of a com-mon allele associated with protection from heart failure. *Nat Cardiovasc Res.* 2023;2:615–628. doi: 10.1038/s44161-023-00288-w
67. Chaffin M, Papangeli I, Simonson B, Akkad AD, Hill MC, Arduini A, Fleming SJ, Melanson M, Hayat S, Kost-Alimova M, et al. Single-nucleus profiling of human dilated and hypertrophic cardiomyopathy. *Nature.* 2022;608:174–180. doi: 10.1038/s41586-022-04817-8
68. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, Di Lenarda A, Sinagra G. Long-term prognostic impact of therapeutic strategies in pa-tients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. *Eur J Heart Fail.* 2014;16:317–324. doi: 10.1002/ehf.16
69. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JCW, Pedro Ferreira C, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharma-cological therapies in patients with heart failure with reduced ejection frac-tion: a comparative analysis of three randomised controlled trials. *Lancet.* 2020;396:121–128. doi: 10.1016/s0140-6736(20)30748-0
70. Gevaert AB, Kataria R, Zannad F, Sauer AJ, Damman K, Sharma K, Shah SJ, Van Spall HGC. Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management. *Heart.* 2022;108:1342–1350. doi: 10.1136/heartjnl-2021-319605
71. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/ HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published corrections ap-pear in *Circulation.* 2022;144:e1033, *Circulation.* 2022;146:e185, and *Circulation.* 2023;147:e674]. *Circulation.* 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063
72. Sumarsono A, Xie L, Keshvani N, Zhang C, Patel L, Alonso WW, Thibodeau JT, Fonarow GC, Van Spall HGC, Messiah SE, et al. Sex dis-parities in longitudinal use and intensification of guideline-directed medical therapy among patients with newly diagnosed heart failure with reduced ejection fraction. *Circulation.* 2024;149:510–520. doi: 10.1161/CIRCULATIONAHA.123.067489
73. Dewidar O, Dawit H, Barbeau V, Birnie D, Welch V, Wells GA. Sex differ-ences in implantation and outcomes of cardiac resynchronization therapy in real-world settings: a systematic review of cohort studies. *CJC Open.* 2022;4:75–84. doi: 10.1016/j.cjco.2021.09.003
74. Siddiqi TJ, Khan Minhas AM, Greene SJ, Van Spall HGC, Khan SS, Pandey A, Mentz RJ, Fonarow GC, Butler J, Khan MS. Trends in heart failure-re-lated mortality among older adults in the United States from 1999-2019. *JACC Heart Fail.* 2022;10:851–859. doi: 10.1016/j.jchf.2022.06.012
75. Shoaib A, Van Spall HGC, Wu J, Cleland JGF, McDonagh TA, Rashid M, Mohamed MO, Ahmed FZ, Deanfield J, de Belder M, et al. Substantial de-cline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. *Eur Heart J Qual Care Clin Outcomes.* 2021;7:378–387. doi: 10.1093/ehjqcco/qcab040
76. Keshvani N, Mehta A, Alger HM, Rutan C, Williams J, Zhang S, Young R, Alhanti B, Chiswell K, Greene SJ, et al. Heart failure quality of care and in-hospital outcomes during the COVID-19 pandemic: findings from

- the Get With The Guidelines-Heart Failure Registry. *Eur J Heart Fail*. 2022;24:1117–1128. doi: 10.1002/ehjhf.2484
77. Bhamhani V, Kizer JR, Lima JAC, van der Harst P, Bahrami H, Naylor M, de Filippi CR, Enserro D, Blaha MJ, Cushman M, et al. Predictors and outcomes of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2018;20:651–659. doi: 10.1002/ehjhf.1091
78. Gevaert AB, Tibebe S, Mamas MA, Ravindra NG, Lee SF, Ahmad T, Ko DT, Januzzi JL Jr, Van Spall HGC. Clinical phenogroups are more effective than left ventricular ejection fraction categories in stratifying heart failure outcomes. *ESC Heart Fail*. 2021;8:2741–2754. doi: 10.1002/ehf2.13344
- gliflozin on cause-specific mortality in patients with heart failure across the spectrum of ejection fraction: a participant-level pooled analysis of DAPA-HF and DELIVER. *JAMA Cardiol*. 2022;7:1227–1234. doi: 10.1001/jamacardio.2022.3736
80. Glynn P, Lloyd-Jones DM, Feinstein MJ, Carnethon M, Khan SS.
94. Chang PP, Wruck LM, Shahar E, Rossi JS, Loehr LR, Russell SD, Agarwal SK, Konety SH, Rodriguez CJ, Rosamond WD. Trends in hospitalizations and survival of acute decompensated heart failure in four US communities (2005-2014): ARIC Study Community Surveillance. *Circulation*. 2018;138:12–24. doi: 10.1161/CIRCULATIONAHA.117.027551
95. Blumer V, Gayowsky A, Xie F, Greene SJ, Graham MM, Ezekowitz JA, Perez R, Ko DT, Thabane L, Zannad F, et al. Effect of patient-centered transitional care services on patient-reported outcomes in Disparities in cardiovascular mortality related to heart failure in the United States. *J Am Coll Cardiol*. 2019;73:2354–2355. doi: 10.1016/j.jacc.2019.02.042
81. Glynn PA, Molsberry R, Harrington K, Shah NS, Petit LC, Yancy CW, Carnethon MR, Lloyd-Jones DM, Khan SS. Geographic varia-

- in Heart Failure (PACT-HF) randomized controlled trial. *Eur J Heart Fail*. 2024;26:652–660. doi: 10.1002/ehhf.3134
97. Desai AS, Claggett B, Pfeffer MA, Bello N, Finn PV, Granger CB, hospitalization for cardiovascular versus noncardiovascular reasons on the spectrum of ejection fraction. *Circ Heart Fail*. 2014;7:895–902. doi: 10.1161/CIRCHEARTFAILURE.114.001567
98. US Department of Health and Human Services. Organ Procurement and Transplantation Network website. Accessed April 18, 2024.
99. US Department of Health and Human Services. Organ Procurement and Transplantation Network website. Accessed April 18, 2024.
100. Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
82. Centers for Disease Control and Prevention and National Center for
83. Centers for Disease Control and Prevention and National Center for

99. Colvin MM, Smith JM, Ahn YS, Handarova DK, Martinez AC, Lindblad KA, Israni AK, Snyder JJ. OPTN/SRTR 2022 annual data report: heart. *Am J Transplant*. 2024;24:S305–S393. doi: 10.1016/j.ajt.2024.01.016
100. Breathett K, Knapp SM, Addison D, Johnson A, Shah RU, Flint K, Van Spall HGC, Sweitzer NK, Mazimba S. Relationships between 2018 UNOS heart policy and transplant outcomes in metropolitan, micropolitan, and rural settings. *J Heart Lung Transplant*. 2022;41:1228–1236. doi: 10.1016/j.healun.2022.06.015
- Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.
84. Akwo EA, Kabagambe EK, Wang TJ, Harrell FE Jr, Blot WJ, Mumma M, Gupta DK, Lipworth L. Heart failure incidence and mortality in the

101. Chouairi F, Fuery M, Clark KA, Mullan CW, Stewart J, Caraballo C, Clarke JD, Sen S, Guha A, Ibrahim NE, et al. Evaluation of racial and ethnic disparities in cardiac transplantation. *J Am Heart Assoc.* 2021;10:e021067. doi: 10.1161/CIRCHEARTFAILURE.116.003553
85. Loefer LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol.* 2008;101:1016–1022. doi: 10.1016/j.amjcard.2007.11.061
86. Loefer EC, Joynt Maddox KE, Wang Y, Kazi DS, Yeh RW, Wadhera RK. Rural-urban disparities in outcomes of myocardial infarction, heart failure, and stroke in the United States. *J Am Coll Cardiol.* 2022;79:267–279. doi: 10.1161/JAHA.120.021067

102. Moayed Y, Fan CPS, Cherikh WS, Stehlik J, Teuteberg JJ, Ross HJ, Khush KK. Survival outcomes after heart transplantation: does recipient sex matter? *Circ Heart Fail*. 2019;12:e006218. doi: 10.1161/CIRCHEARTFAILURE.119.006218
103. Akintoye E, Shin D, Alvarez P, Briasoulis A. State-level variation in wait-list mortality and transplant outcomes among patients listed for heart transplantation in the US from 2011 to 2016. *JAMA Netw Open*. 2020;3:e2028459. doi: 10.1001/jamanetworkopen.2020.28459
10.1016/j.jacc.2021.10.045
87. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed May 1, 2024.
104. Jorde UP, Saeed O, Koehl D, Morris AA, Wood KL, Meyer DM, Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, Givertz MM. Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;73:935–944. doi:

- Cantor R, Jacobs JP, Kirklin JK, Pagani FD, et al. The Society of Thoracic Surgeons Intermacs 2023 annual report: focus on magnetically levitated devices. *Ann Thorac Surg.* 2024;117:33–44. doi: 10.1016/j.athoracsur.2023.11.004
105. Yuzefpolskaya M, Schroeder SE, Houston BA, Robinson MR, Gosev I, Reyentovich A, Koehl D, Cantor R, Jorde UP, Kirklin JK, et al. The Society of Thoracic Surgeons Intermacs 2022 annual report: focus on the 2018 Heart Transplant Allocation System. *Ann Thorac Surg.* 2023;115:311–327. doi: 10.1016/j.athoracsur.2022.11.023
89. Van Spall HGC, DeFilippis EM, Lee SF, Oz UE, Perez R, Healey JS, Allen LA, Voors AA, Ko DT, Thabane L, et al. Sex-specific clinical outcomes of the PACT-HF randomized trial. *Circ Heart Fail.* 2021;14:e008548. doi:

106. Emani S, Tumin D, Foraker RE, Hayes D Jr, Smith SA. Impact of insurance status on heart transplant wait-list mortality for patients with left ventricular assist devices. *Clin Transplant*. 2017;31:10.1111/ctr.1287. doi: 10.1161/CIRCHEARTFAILURE.121.008548
90. Clark KAA, Reinhardt SW, Chouairi F, Miller PE, Kay B, Fuery M, Guha A, Ahmad T, Desai NR. Trends in heart failure hospitalizations in the US from 2008 to 2018. *J Card Fail*. 2022;28:171–180. doi: 10.1016/j.cardfail.2021.08.020
91. Khan SU, Khan MZ, Alkhouli M. Trends of clinical outcomes and health care resource use in heart failure in the United States. *J Am Heart Assoc*. 2020;9:e016782. doi: 10.1161/JAHA.120.016782
92. Averbuch T, Mohamed MO, Islam S, Defilippis EM, Breathett K, Alkhouli MA, Michos ED, Martin GP, Kontopantelis E, Mamas MA, et al. The association between socioeconomic status, sex, race/ethnicity and in-hospital mortality among patients hospitalized for heart failure. *J Card Fail*. 2022;28:697–709. doi: 10.1016/j.cardfail.2021.09.012
93. Jain V, Minhas AMK, Khan SU, Greene SJ, Pandey A, Van Spall HGC, Fonarow GC, Mentz RJ, Butler J, Khan MS. Trends in HF hospitalizations among young adults in the United States From 2004 to 2018. *JACC Heart Fail*. 2022;10:350–362. doi: 10.1016/j.jchf.2022.01.021

107. Teuteberg JJ, Cleveland JC Jr., Cowger J, Higgins RS, Goldstein DJ, Keebler M, Kirklin JK, Myers SL, Salerno CT, Stehlik J, et al. The Society of Thoracic Surgeons Intermacs 2019 annual report: the changing land-scape of devices and indications. *Ann Thorac Surg.* 2020;109:649–660. doi: 10.1016/j.athoracsur.2019.12.005
108. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, et al; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Arteriosclerosis, Thrombosis, and Vascular Biology, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6:606–619. doi: 10.1161/HHF.0b013e318291329a
109. Urbich M, Globe G, Pantiri K, Heisen M, Bennison C, Wirtz HS, Di Tanna GL. A systematic review of medical costs associated with heart failure in

23. VALVULAR DISEASES

See Tables 23-1 through 23-4 and Charts 23-1 through 23-7

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Mortality data in this section are for 2022 and based on unpublished NHLBI tabulations using the NVSS¹ and CDC WONDER.² Prevalence data are for 2016 and 2017. Hospital discharge data are from HCUP³ 2021; data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2021 are

Valvular HD

ICD-9 424; ICD-10 I34 to I38.

2022, United States: Underlying cause mortality—24 102. Any-mention mortality—59 139.
2021, United States: Hospital discharges—145 495.

Prevalence

- The global prevalence of nonrheumatic VHD in 2021 was 28.4 million with a 95% UI of 26.3 million to 30.6 million.⁴
- Older adults in the ARIC study, a prospective community-based cohort study, underwent protocol echocardiography to

- In a US population-based study conducted between October 2011 and June 2014, the prevalence of VHD in 1818 Hispanic/Latino people (mean age 55 years, 53% female) was 3.1%. Regurgitant lesions of moderate or greater severity were present in 2.4% of the population. Aortic stenosis was present in 0.2%.⁶ There is variation in the cause of VHD across the world. In a prospective cross-sectional study across all 31 provinces in China between 2012 and 2015, the weighted prevalence of VHD based on an analysis of 31 499 adults >35 years of age was 11.1%. Rheumatic disease was the most common cause of VHD (5.1%), followed by degenerative disease and 21.3% had degenerative dis-

classify their aortic and mitral lesions according to ACC/AHA guidelines.⁵ Among 6118 ARIC participants with mean±SD age of 76±5 years (42% male, 22% Black race), at-risk (stage A) left-sided VHD was present in 39%, progressive (stage B) and advanced (stage C/D) in 17%, and advanced (stage C/D) in 1.1%; 0.7% had previously undergone valve replacement or repair. A graded association was observed between stages A, B, and C/D VHD and risk of all-cause mortality, incident HF, incident CHD but not incident stroke. During the 6.6 years of follow-up, the prevalence of stage C/D VHD increased from 1% to 7%.

ease. The prevalence of VHD increased with age ($P<0.001$) and was not different between males and females ($P=0.308$). VHD was more prevalent in participants with hypertension (5.6% versus 2.8%; $P<0.001$) or CKD (9.2% versus 3.5%; $P<0.001$).

Aortic Valve Disorders

ICD-9 424.1; ICD-10 I35.

2022, United States: Underlying cause mortality—15 817. Any-mention mortality—38 260.

2021, United States: Hospital discharges—110 740.

Prevalence

- In the MESA study of 6814 participants 45 to 84 years of age free of known CVD in the United States,⁷ 77 participants (1.1%) had aortic stenosis on echocardiography; the age-adjusted prevalence of aortic stenosis was highest in White participants (3.5% [95% CI, 2.6%–4.7%]) and Hispanic participants (3.7% [95% CI, 2.5%–5.6%]) with lower prevalence in Black participants (1.8% [95% CI, 1.1%–3.1%]) and Chinese participants (0.3% [95% CI, 0.04%–2.0%]).

- Globally, there was a 443% increase in the prevalence of calcific aortic valve disease from 1 732 988 (95% CI, 1 431 470–2 074 810) in 1990 to 9 404 080 (95% CI, 8 079 600–10 889 730) in 2019.⁹

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- In a random sample of Swedish males from the general population born in 1943 (n=798) and followed up for 21 years, prevalence of aortic stenosis was 2.6%.¹⁰
- In younger age groups, the most prevalent cause of aortic stenosis is bicuspid aortic valve, the most common form of congenital HD:
 - In the Copenhagen Baby Heart Study, which involved 25 556 newborns (51.7% male; mean±SD age, 12±8 days) in Denmark born

between 2016 and 2018 transthoracic of bicuspid aortic valve was 0.67%–0.88%), with a 2.1:1.¹¹

- A meta-analysis of 11 revealed that among 1177 syndrome, the prevalence identified by cardiac MRI or CI, 21.3%–26.1%).¹²

Risk Factors

- In the CGPS, among 108 275 of developing aortic stenosis BMI was $\geq 35.0 \text{ kg/m}^2$ (HR, 2.6
- In the Swedish General BMI, obesity, cholesterol, and heredity for stroke were tic stenosis.¹⁶ The HRs of in males with a baseline BMI to 30, and $>30 \text{ kg/m}^2$ were

2012 and 2015 reported an aortic regurgitation incidence of 1.2% (95% CI, 0.7%–2.1%) and an aortic stenosis incidence of 0.7% (95% CI, 0.4%–1.1%).¹⁵

Lifetime Risk and Cumulative Incidence

- Global incidence and prevalence of calcific aortic valve disease are positively correlated with age.

There are 2 peaks in incidence: 1 peak at 70 to 74 years of age and the other at >95 years of age. The prevalence of calcific aortic valve disease peaks at 90 to 94 years of age globally.⁹

- In a randomly selected group of male participants (N=9998) born from 1915 to 1925 in Gothenburg, Sweden, 7494 were examined and followed up until a diagnosis of aortic stenosis or death (maximum follow-up time, 42.8 years).¹⁶ The lifetime cumulative incidence of aortic stenosis in the middle-aged male population was 3.2%.

Incidence

- In a population-based cohort study of inpatient, out-patient, and professional claims from a 20% sample of Medicare beneficiaries in the United States between 2010 and 2018, 1 513 455 patients were diagnosed with aortic stenosis.¹³
 - The aortic stenosis incidence rate for the overall group increased from 13.5 to 17.0 per 1000 between 2010 and 2018 ($P<0.001$).
 - In addition, beneficiaries from underrepresented racial and ethnic groups had significantly lower incidence rates compared with White beneficiaries throughout the study period (91.3% White, 4.5% Black, 1.1% Hispanic, and 3.1% Asian and North American Native).
- Globally, the incident cases of calcific aortic valve disease have increased by 351% from 130 821 cases (95% CI, 110 700–156 020) in 1990 to 589 637 cases (95% CI, 512 900–677 060) in 2019.⁹
- In a retrospective cohort study of 1507 patients from 9 institutions in Japan undergoing hemodialysis, 251 or 17% of patients developed aortic stenosis within a median follow-up of 3.2 years.¹⁴
- A prospective cross-sectional study of 31 499 people across all 31 provinces in China between

- 3.55), 2.98 (95% CI, 1.65–5.40), and 3.55 (95% CI, 1.84–6.87), respectively, with BMI of 20 to 22.5 kg/m² used as reference.
- In a prospective cohort study of 361 930 people with genetic data in the UK Biobank, a total of 1602 participants developed aortic valve stenosis during an 8.4-year follow-up.¹⁸ Cox proportional risk regression models were used to estimate the HRs between 28 modifiable risk factors and aortic valve stenosis.
 - Modifiable risk factors associated with a higher risk of aortic valve stenosis included the following: adiposity (HR, 1.04 [95% CI, 1.05–1.07]), waist-to-hip ratio (HR, 1.03 [95% CI, 1.03–1.04]), BP (HR, 1.10 [95% CI, 1.07–1.14]), pulse pressure (HR, 1.23 [95% CI, 1.19–1.26]), resting heart rate (HR, 1.06 [95% CI, 1.02–1.10]), LDL (HR, 1.10 [95% CI, 1.03–1.18]), urate (HR, 1.02 [95% CI, 1.02–1.03]), CRP (HR, 1.03 [95% CI, 1.02–1.04]), creatinine (HR, 1.04 [95% CI, 1.03–1.05]), glycated hemoglobin (HR, 1.07 [95% CI, 1.06–1.08]), smoking (HR, 1.35 [95% CI, 1.21–1.50]), and insomnia (HR, 1.19 [95% CI, 1.05–1.35]).
 - Genetically predicted 1-SD higher levels of BMI (HR, 1.09 [95% CI, 1.03–1.16]), body fat percentage (HR, 1.17 [95% CI, 1.03–1.33]), LDL (HR, 1.15 [95% CI, 1.08–1.21]), and serum TC (HR, 1.13 [95% CI, 1.02–1.25]) were associated with a higher risk of aortic valve stenosis.
 - The CGPS recruited 69 988 randomly selected individuals between 2003 and 2015 to evaluate the association between high lipoprotein(a) and high BMI and risk of calcific aortic valve disease.¹⁹
 - Compared with individuals in the 1st to 49th percentiles for both lipoprotein(a) and BMI, the aHRs for calcific aortic valve disease were 1.6 (95% CI, 1.3–1.9) for the 50th to 89th percentiles of both, and 3.5 (95% CI, 2.5–5.1) for the 90th to 100th percentiles of both.
 - The 10-year absolute risk of calcific aortic valve disease was higher in males than in females. The 10-year absolute risk of calcific aortic valve disease in females 70 to 79 years of age with BMI ≥30.0 kg/m² was 5% for lipoprotein(a) ≤42 mg/dL, 7% for lipoprotein(a) 42 to 79 mg/dL, and 9% for lipoprotein(a) ≥80 mg/dL.

- The 10-year absolute risk of calcific aortic valve disease in males 70 to 79 years of age with BMI ≥ 30.0 kg/m² was 8% for lipoprotein(a) ≤ 42 mg/dL, 11% for lipoprotein(a) 42 to 79 mg/dL, and 14% for lipoprotein(a) ≥ 80 mg/dL.
- In a retrospective registry based observational study comprising 23 298 individuals who had their lipoprotein(a) measured between 2003 and 2017 at stenosis.²⁰ The cohort was divided into deciles of lipoprotein(a) levels.
 - Those with calcific aortic stenosis had significantly higher lipoprotein(a) (117 mg/dL) than those with-out calcific aortic stenosis (89 mg/dL; $P < 0.001$).
 - For individuals at the 90th percentile for lipoprotein(a) levels, the sex- and age-adjusted

Genetics and Family History

- Bicuspid aortic valve is thought to be highly heritable with 47% of the phenotypic variance being explained by genetic variation.²³ Variants in *NOTCH1*, *GATA4*, *GATA5*, *GATA6*, *EXOC4*, *PALMD*, *TEX41*, *FBN1*, *ROBO4*, *MYH6*, and *SMAD6* have been associated with bicuspid aortic valve.^{24–31}

HR for development of calcific aortic stenosis was 1.53 (95% CI, 1.08–2.15; $P = 0.016$) compared with those below the 50th percentile.

- A comparison of 2786 patients on dialysis with and without aortic stenosis from 58 hospitals in the Tokai region of Japan between 2017 and 2018 was

with an HR of 3.41 (95% CI, 2.23–5.21) for being
cate an overall familial aggregation of this disease

- A GWAS for bicuspid aortic valve including 2236
at *MUC4* and replicated previously reported loci at
bicuspid aortic valve.³³ Approximately 20% of the
attributed to a polygenic basis.
- A GWAS in 34 287 individuals of European ancestry for functional aortic area (estimated using cardiac
conducted.²¹
 - Multivariable logistic regression analysis
revealed that age (aOR, 1.93 [95% CI, 1.71–
2.19]; $P<0.001$), long-term dialysis (aOR, 1.41

diagnosed with aortic stenosis. These findings indi-
beyond bicuspid aortic valve alone.³²

cases and 11 604 controls identified a novel locus
PALMD, *GATA4*, and *TEX41* to be associated with
observed heritability of bicuspid aortic valve may be

MRI) showed significant associations for variants in
[95% CI, 1.21–1.64]; $P<0.001$), and elevated serum
phosphorus levels (aOR, 1.16 [95% CI, 1.06–1.28];
 $P=0.001$) were associated with mild aortic

DLEU1, *CRADD*, and *GOSR2*.³⁴ A polygenic score developed from this GWAS was shown to be associated with the development of aortic stenosis in an independent population of 308 683 individuals (HR, 1.14 per 1-SD decrease polygenic score; $P=0.002$). • A GWAS in 6942 individuals identified an SNP

- Similarly, age (aOR, 2.51 [95% CI, 2.02–3.12]; $P<0.001$), long-term dialysis (aOR, 1.35 [95% CI, 1.06–1.71]; $P=0.01$), and elevated serum phosphorus levels (aOR, 1.24 [95% CI, 1.07–1.44]; $P=0.005$) were associated with moderate to severe aortic stenosis.
- In an observational case-control study of 3 812 588 people in the Utah Population Database, age and sex-matched controls without aortic or aortic valve disease were identified for individuals with bicuspid aortic valve, TAA, or thoracic aortic dissection.²² Compared with

located in an intron of the lipoprotein(a) gene that controls without aortic or aortic valve disease, the risk of concordant diagnosis was elevated in first-degree relatives of individuals with bicuspid aortic valve (HR, 6.88 [95% CI, 5.62–8.43]), first-degree relatives of individuals with TAA (HR, 5.09 [95% CI, 3.80–6.82]), and first-degree relatives of individuals with thoracic aortic dissection (HR, 4.15 [95% CI, 3.25–5.31]). The risk of aortic dissection was higher in first-degree relatives of individuals with bicuspid aortic valve (HR, 3.63 [95% CI, 2.68–4.91]) and in first-degree relatives of patients with thoracic aneurysm (HR, 3.89 [95% CI, 2.93–5.18]) compared with controls.

was significantly associated with the presence of lipoprotein(a) levels, and the development of aortic stenosis.³⁵

- In a GWAS of 1009 individuals undergoing cardiac surgery in Quebec and across Europe between 1993 and 2018,³⁶ a weighted GRS in each individual, estimated by adding the number of lipoprotein(a)-raising alleles weighted by the effect of each variant on lipoprotein(a) levels, was associated with a higher risk of calcific aortic stenosis (OR, 1.35 [95% CI, 1.10–1.660]; $P=0.003$).
- To investigate the association of hepatic *LPA* expression with calcific aortic valve stenosis, 80 SNPs strongly associated with the expression of *LPA* were examined in 408 403 individuals in the UK Biobank.³⁷ Of the total cohort, 2574 had calcific aortic valve stenosis (1659 males and 915 females). There was a causal association between hepatic *LPA* expression and calcific aortic valve stenosis in males (OR, 1.27 [95% CI, 1.13–1.43]) and females (OR, 1.22 [95% CI, 1.04–1.44]).
- A GWAS meta-analysis of 5115 cases and 354 072 controls identified *IL6*, *ALPL*, and *NAV1* as susceptibility genes for calcific aortic valve stenosis,³⁸ adding

to knowledge from previous genome studies of aortic valve stenosis established several loci. *TEX41*.^{35,36,39,40} A meta-analysis of 67 individuals identified 6 novel loci *CEP85L*, *MECOM*, *CDAN1*, *CEP85L*, *MECOM*, *CDAN1*, analysis assessing the association of aortic valve stenosis with lipid metabolism.

cellular senescence.⁴¹

- A recent GWAS meta-analysis for calcific aortic stenosis comprising 14 819 cases and 927 044 controls of European ancestry identified 32 loci, of which 20 loci were novel.⁴² Transcriptomics-based approaches led to the identification of 5 additional genes associated with calcific aortic stenosis.
- Multiple SNPs that encode for LDL-C have been combined to form a GRS that has been associated with prevalent aortic valve calcification (OR, 1.38 [95% CI, 1.09–1.74] per GRS increment) and incident aortic valve stenosis (HR, 2.78 [95% CI, 1.22–6.37] per GRS increment) by use of a mendelian randomization design.⁴³
- PCSK9, a key regulator of plasma LDL-C, binds to LDL receptors, leading to their degradation in the liver. Inhibition of PCSK9 leads to an increase in LDL receptors and a decrease in LDL in the blood.
A meta-analysis of 10 studies found that the loss-of-function R46L variant in *PCSK9* is associated with a reduced risk of calcific aortic valve stenosis (OR, 0.80 [95% CI, 0.70–0.91]; $P=0.0011$).⁴⁴
- To evaluate the association between SBP and risk of valvular disease, 502 602 individuals 40 to 96 years of age in the UK Biobank between 2006 and 2010 were evaluated through mendelian randomization.⁴⁵ Each genetically predicted 20-mm Hg increment in SBP was associated with

stenosis.⁴⁶ One hundred fifty-67 years of age; 57% men) countries between 2015 and allocated to early surgery treatment ($n=79$). At a median months, patients randomized to a significantly lower incidence of the primary end point of all-cause unplanned hospitalization for conservative arm (HR, 0.46

an increased risk of aortic stenosis (OR, 3.26 [95% CI, 1.50–7.10]) and aortic regurgitation (OR, 2.59 [95% CI, 0.75–8.92]).

- To investigate the genetic association of obesity with incident aortic valve stenosis and aortic valve replacement, a mendelian randomization study using 5 genetic variants associated with obesity and including 108 211 individuals from the Copenhagen General Population Study was conducted. The study found that each 1-kg/m² increase in BMI was associated with causal RRs for aortic valve stenosis and replacement of 1.52 (95% CI, 1.23–1.87) and 1.49 (95% CI, 1.07–2.08), respectively.¹⁷

Treatment

Randomized Controlled Trials

- The AVATAR is prospective RCT that evaluated the safety and efficacy of early SAVR in the treatment of asymptomatic patients with severe aortic

$P=0.02$). Kaplan-Meier estimates of the individual end points of all-cause mortality and HF hospitalization tended to be higher in the conservative compared with the early surgery group but did not reach statistical significance.

- A propensity-matched comparison of pulmonary autograft (Ross procedure; $n=434$) and bioprosthetic and mechanical aortic valve replacement ($n=434$) was performed in individuals between 18 and 50 years of age in the mandatory California and New York databases between 1997 and 2014.⁴⁷ At 15 years, the actuarial survival after the Ross procedure was 93.1% (95% CI, 89.1%–95.7%), significantly higher than actuarial survival after bioprosthetic aortic valve replacement (HR, 0.42 [95% CI, 0.23–0.75]; $P=0.003$) or mechanical aortic valve replacement (HR, 0.45 [95% CI, 0.26–0.79]; $P=0.006$). At 15 years, the Ross procedure was associated with a lower cumulative risk of reoperation ($P=0.008$) and endocarditis ($P=0.01$) than bioprosthetic aortic valve replacement. In contrast, the Ross procedure was associated with a higher cumulative incidence of reoperation ($P<0.001$). At 15 years, the Ross procedure also had lower risks of stroke ($P=0.03$) and major bleeding ($P=0.016$) compared with mechanical aortic valve replacement.
- A meta-analysis examined mortality and morbidity in 4812 patients ≥ 16 years of age undergoing the Ross procedure ($n=1991$) or mechanical ($n=2019$) or bioprosthetic ($n=802$) aortic valve replacement.⁴⁸ At a mean follow-up of 7.4 years, all-cause mortality was significantly lower in the Ross procedure group compared with the mechanical aortic valve replacement (HR, 0.58 [95% CI, 0.35–0.97]; $P=0.035$) and bioprosthetic aortic valve replacement (HR, 0.32 [95% CI, 0.18–0.59]; $P<0.001$) groups.
- The CAVIAAR prospective cohort study enrolled 130 patients who underwent aortic valve remodeling root repair with expansible aortic ring annuloplasty and 131 patients who underwent mechanical composite valve and graft replacement.⁴⁹ At 4 years, there was no statistically significant difference in the primary composite outcome of mortality, reoperation, thromboembolic or major bleeding events, endocarditis or operating site infections, pacemaker implantation, and HF between patients

who underwent aortic valve repair and those who had mechanical composite valve and graft replacement (HR, 0.66 [95% CI, 0.39–1.12]). However, there were significantly fewer valve-related deaths (HR, 0.09 [95% CI, 0.02–0.34]) and major bleeding events (HR, 0.37 [95% CI, 0.16–0.85]) in patients who underwent aortic valve repair compared with those who underwent mechanical composite valve and graft replacement.

- SAVR can be performed through either a mini- of 358 patients enrolled in the PARTNER 3 low-risk trial underwent isolated SAVR at 68 centers through either a minimally invasive or full sternotomy approach.⁵⁰ The composite end point of death, stroke, or rehospitalization was similar between both groups (16.9% for minimally invasive versus 14.9% for full sternotomy; HR, 1.15 [95% CI, 0.66–

and 30 deaths (6.6%) in the SAVR group, with an adjusted absolute risk difference of –2.0% (1-sided 97.5% CI, $-\infty$ to 1.2%; $P<0.001$ for noninferiority). At 1 year, there were significantly fewer major bleeding events after TAVR compared with surgery (aHR, 0.33 [95% CI, 0.24–0.45]) but significantly more vascular complications (aHR, 4.42 [95% CI, 2.54–7.71]), conduction disturbances

2.03]; $P=0.618$). At 1 year, there were no significant differences in mortality (2.8% in both minimally invasive and full sternotomy groups; $P>0.05$), stroke (1.9% for minimally invasive versus 3.6% for full sternotomy; $P>0.05$), or rehospitalization (13.3% for minimally invasive versus 10.6% for full sternotomy; $P>0.05$ for all). Quality of life, as assessed

- Despite the increase in TAVR procedures, racial disparities observed in SAVR also exist with TAVR.⁵⁴ Among the 70 221 patients in the STS/ACC TVT Registry who underwent TAVR between 2011 and 2016, 91.3% were White, 3.8% were Black, 3.4% were Hispanic, and 1.5% were Asian/Native American/Pacific Islander. Among the 4 racial groups, no difference was noted in the rates of in-hospital mortality, MI, stroke, major bleeding, vascular complications, or new pacemaker requirements. Among the 29 351 Medicare and Medicaid patients in this cohort, 1-year adjusted mortality rates were similar in Black individuals and Hispanic individuals compared with White individuals but lower among Asian/Native American/Pacific individuals of Asian/Native American/Pacific by the Kansas individuals of Asian/Native American/Pacific

score at 30 days or 1 year, was comparable in both groups ($P=0.351$).

- Between 2014 and 2016, 270 patients from a single center in the United Kingdom were enrolled and randomized to undergo ministernotomy aortic valve replacement ($n=135$) or conventional median sternotomy aortic valve replacement ($n=135$).⁵¹ At a median follow-up of 6.1 years, the composite outcome of all-cause mortality and reoperation occurred in 25 patients (18.5%) in the conventional sternotomy group and in 23 patients (17%) in the ministernotomy group ($P=0.72$).
- The annual volume of TAVR has increased each year since 2011.⁵² After the US FDA approval of TAVR for low-risk patients in 2019, the TAVR volume exceeded all forms of SAVR ($n=72\,991$ versus $57\,626$).⁵² From 2011 through 2018, extreme-risk and high-risk patients remained the largest cohort

Islander race (aHR, 0.71 [95% CI, 0.55–0.92]; $P=0.028$). Black individuals and Hispanic individuals had more HF hospitalizations compared with White individuals (aHR, 1.39 [95% CI, 1.16–1.67]; $P<0.001$; and aHR, 1.37 [95% CI, 1.13–1.66]; $P=0.004$, respectively). These differences remained after further adjustment for SES.

- The 276 316 patients treated with TAVR who entered the STS/ACC TVT Registry between 2011 and 2019 demonstrated improved temporal trends, with 2018 or 2019 cohorts demonstrating lower event rates than more historic cohorts⁵²:

- Expected risk of 30-day operative mortality (STS Predicted Risk of Mortality score) is 2.5%.

- The 1-year mortality is 12.6%, with mortality differing according to risk group and intermediate-risk patients experiencing in-hospital, 30-day, and 1-year mortality about half that of high- and undergoing TAVR, but in 2019, intermediate-risk extreme-risk patients.

patients were the largest cohort, and the low-risk stenosis were randomized to either TAVR with any valve and any access route (n=458) or SAVR (n=455).⁵³ The median STS mortality risk score of all study patients with a median of 75 years of age increased to 8395, making up 11.5% of all participants was 2.6% (interquartile range, 2.0%– patients with TAVR. • Between 2014 and 2018, 913 patients ≥ 70 years of age at 34 centers in the 3.4%). At 1 year, there were 21 deaths (4.6%) in the United Kingdom with severe, symptomatic aortic TAVR group

- Overall in-hospital and 30-day stroke rates are 1.6% and 2.3%, respectively.
- Incidence of permanent pacemaker implantation at 30 days is 10.8%.
- A study to determine the 5-year outcomes in 18 010 patients treated by isolated TAVR or SAVR in the German Aortic Valve Registry between 2011 and 2012⁵⁵ showed that patients treated with TAVR (n=8942) were significantly older (80.9 ± 6.1 years versus 68.5 ± 11.1 years; $P < 0.001$) and had a higher STS score (6.3 ± 4.9 versus 2.6 ± 3.0 ; $P < 0.001$) and

higher 5-year all-cause 16.5%; $P<0.0001$) than (n=9068). There was no hospital stroke, in-hospital MI, use of propensity score—total sample size of 3640 deaths (41.9%) among 1820 TAVR compared with 552 treated with SAVR during the (HR, 1.51 [95% CI, 1.35–

patients who received TAVR had a higher rate of new pacemaker implantation compared with those who received SAVR (448 [24.6%] versus 201 [11.0%]; $P<0.0001$, respectively).

High-Risk Patients

- Two RCTs, PARTNER 1A and US CoreValve High Risk, using balloon-expandable and self-expanding devices, respectively, have shown that TAVR compares favorably with SAVR in terms of mortality in high-risk patients at 1 and 5 years.

- In the PARTNER 1A trial, risk of death at 5 years was 67.8% in the TAVR group compared with 62.4% in the SAVR group (HR, 1.04 [95% CI, 0.86–1.24]; $P=0.76$).⁵⁶

- The 5-year follow-up results in the US CoreValve High Risk trial revealed similar midterm survival and stroke rates in high-risk patients after TAVR (55.3% all-cause mortality, 12.3% major stroke) and SAVR (55.4% all-cause mortality, 13.2% major stroke rates).⁵⁷

Intermediate-Risk Patients

- In a cohort of 1746 patients from 87 centers in Europe and North America with severe aortic stenosis at intermediate surgical risk in the SURTAVI trial, the estimated incidence of the primary end point (death

of the primary SURTAVI entv-five patients enrolled in underwent an attempted the 5-year follow-up, the rate or disabling stroke was 29.9% 29.2%; disabling stroke, ventation and new permanent tion were 1.1% and 27.6%. no cases of clinical valve valve endocarditis (1.2%).

attributable to any cause or debilitating stroke) was 12.6% in the TAVR group (using a self-expanding

device) and 14.0% in the SAVR group (95% credible interval [Bayesian analysis] for difference, –5.2% to 2.3%; posterior probability of noninferiority >0.999) at

24 months.⁵⁸ At the 5-year follow up, the primary end point was 31.3% in the TAVR group and 30.8%

in the SAVR group (HR, 1.02 [95% CI, 0.85–1.22]; $P=0.85$).⁵⁹ Moderate to severe paravalvular leak was

more common with TAVR than surgery (11 [3.0%] versus 2 [0.7%]; risk difference, 2.37% [95% CI,

0.17%–4.85%]; $P=0.05$). Pacemaker implantation rates were higher after TAVR (289 [39.1%] versus 94 [15.1%]; HR, 3.30 [95% CI, 2.61–4.17]; $P<0.001$).

Last, valve reintervention rates were higher after TAVR (27 [3.5%] versus 11 [1.9%]; HR, 2.21 [95% CI, 1.10–4.45]; $P=0.02$).

- SURTAVI Continued Access Study was the single-arm prospective, multicenter, nonrandomized phase

ent was 9.16 mm Hg, and the 5-year mean effective orifice area was 2.06 cm². Most patients had no or trace aortic regurgitation (87.9%) and no or trace paravalvular leak (89.4%).

- In the PARTNER 2 trial using a balloon-expandable device, the Kaplan-Meier event rates of the same end point were 19.3% in the TAVR group and 21.1% in the SAVR group (HR in the TAVR group, 0.89 [95% CI, 0.73–1.09]; $P=0.25$) at the 2-year follow-up. At 5 years, the incidence of death resulting from any cause or disabling stroke in the PARTNER 2 trial was 47.9% and 43.4% in the TAVR (transfemoral access) group and SAVR group, respectively (HR, 1.09 [95% CI, 0.95–1.25]; $P=0.21$).¹ Overall, these findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.^{61,62}
- In a propensity score–matched analysis of 783 matched pairs of intermediate-risk patients who underwent either TAVR from the PARTNER 2 trial or SAVR from the PARTNER 2A trial,⁶³ all-cause death and disabling stroke at 5 years was 40.2% in patients undergoing TAVR and 42.7% in patients undergoing SAVR (HR, 0.87 [95% CI, 0.74–1.03]; $P=0.10$).

Low-Risk Patients

- In 1000 patients with severe aortic stenosis at low surgical risk randomized in the PARTNER 3 trial to either balloon-expandable TAVR or SAVR, the primary composite end point (death, stroke, or rehospitalization) rate was significantly lower in the TAVR than the SAVR group (8.5% versus 15.1%; absolute difference, –6.6 percentage points [95% CI, –10.8 to –2.5]; $P<0.001$ for noninferiority; HR, 0.54 [95% CI, 0.37–0.79]; $P=0.001$ for superiority).⁶⁴ At 2 years, the primary end point was significantly reduced after TAVR compared with SAVR (11.5% versus 17.4%; HR, 0.63 [95% CI, 0.45–0.88]; $P=0.007$), although TAVR valve thrombosis at 2 years was increased (2.6%; 13 events) compared with surgery (0.7%; 3 events; $P=0.02$). At 5 years, the Kaplan-Meier estimates for outcomes were as follows: death, 10.0% in the TAVR group and 8.2% in the surgery group; stroke, 5.8% and 6.4%, respectively; and rehospitalization, 13.7% and 17.4%, respectively.⁶⁵ The

hemodynamic performance of the according to the mean $\pm$ SD valve 12.8 $\pm$ 6.5 mm Hg in the TAVR group mm Hg in the surgery group. A first primary end point (death, stroke, ization) occurred in 111 of 496 group (22.8%) and in 117 of 454 surgery group (27.2%; difference, points [95% CI, -9.9 to 1.3]; primary end point was a hierarchical included death, stroke, and the talization days, analyzed with the analysis. The win ratio for the point was 1.17 (95% CI, 0.90–1.51];

- In the Medtronic Evolut Replacement in Low Risk 1414 patients with severe aortic surgical risk were randomized to TAVR (n=730) or SAVR (n=684) between 2016 and 2019.⁶⁶ After 1 year of follow-up, Bayesian statistical inference was used to predict that the 2-year incidence of composite death or disabling stroke was 5.3% in the TAVR group and 6.7% in the SAVR group (difference, -1.4 percentage points [95% Bayesian credible interval for difference, -4.9 to 2.1]; posterior probability of noninferiority >0.999). After the 2-year follow-up, the primary end point of death or disabling stroke was 4.3% in the TAVR group and 6.3% in the surgery group ($P=0.084$).⁶⁷ At 3 years, all-cause mortality or disabling stroke occurred in 7.4% of TAVR patients and 10.4% of surgery patients (HR, 0.70 [95% CI, 0.49–1.00]; $P=0.051$).⁶⁸ The incidence of mild paravalvular regurgitation was 20.3% in patients undergoing TAVR and 2.5% in surgical patients. The incidence of pacemaker placement was 23.2% in patients undergoing TAVR and 9.1% in higher proportion of aortic valve TAVR than in SAVR (RR, 3.16 [95% heterogeneity $P=0.60$; $I^2=0\%$ at 2
- Among 96 256 transfemoral TAVR adjusted 30-day mortality was higher tions with low procedural volume 2.78%–3.67%]) than at institutions dural volume (2.66% [95% CI, 1.21; $P=0.02$]).⁷¹

Additional Patient Groups

- In a retrospective observational registry of 923 patients from 12 centers, reductions in LVEF were associated with greater 1-year mortality.⁷² The cohort included 146 patients (16%) with LVEF <25%, 425 (46%) with LVEF 25% to 30%, and 352 (38%) with LVEF 31% to 35%.
 - In-hospital mortality was similar in the 3 groups: 7 deaths in patients with LVEF <25% (4.8%), 18 deaths in patients with LVEF 25% to 30% (4.2%), and 7 deaths in patients with LVEF 31% to 35% (2.0%; $P=0.661$). One year mortality was increased in those patients with decreased left ventricular function. There were 21 deaths in patients with LVEF <25% (14%), 49 deaths in patients with LVEF 25% to 30% (12%), and 25 deaths in patients with LVEF 31% to 35% (7.1%; $P=0.024$).

TAVR Techniques

- Although most TAVR valves are implanted using transfemoral access, alternative access techniques for TAVR have been examined. A meta-analysis including 22 observational studies (N=11 896) compared outcomes of patients with transcatheter TAVR access with those of patients with other TAVR access.⁷³ Compared with transfemoral access, the transcatheter approach had higher mortality at 1 month (3.7% versus 2.6%; $P=0.02$) but lower major vascular complications (1.5% versus 3.4%; $P=0.04$).
 - Compared with transaxillary or subclavian artery access, the transcatheter approach had lower major vascular complications (2% versus 2.3%; $P=0.04$) but higher major bleeding (5.3% versus 2.6%; $P=0.03$).
 - Compared with transaortic access, the transcatheter approach had lower in-hospital (11.7% versus 1.9%; $P=0.02$) and 1-month (14.4% versus 3.9%; $P=0.007$) mortality.
 - Compared with transapical access, the transcatheter approach reduced mortality and risk of major vascular complications or major bleeding; however, this did not reach statistical significance.

Comparison of Aortic Valve Replacement Techniques

- A meta-analysis compared postoperative outcomes after minimally invasive SAVR using ministernotomy or minithoracotomy with outcomes after conventional SAVR with full sternotomy and TAVR.⁶⁸
 - Fifty-six studies including 27 117 patients were analyzed with a random-effects model: 10 397 patients had undergone conventional SAVR with

- full sternotomy; 9523 had invasive SAVR with undergone minimally racotomy; and 1710 had
- Compared with notomy, minimally invasive notomy was associated mortality (RR, 0.76 [95% (RR, 0.84 [95% CI, 0.72–injury (RR, 0.76 [95% CI, term mortality (RR, 0.84 weighted mean follow-up
 - Compared with conventional SAVR with full sternotomy, minimally invasive SAVR with mini-
- 0.86 [95% CI, 0.60–1.22]) for of all-cause mortality, stroke.
- Mortality*
- Calcific aortic valve disease—increased worldwide from 53 47 760–59 730) in 1990 to 105 600–141 390) in 2019.⁹
 - Mortality in patients with ease increases having higher mortality than years of age.

- Calcific aortic valve disease accounted for 24 826 (95% CI, 20 354–27 718) deaths in the United States in 2019.^{9a}
thoracotomy was associated with higher rates
of 30-day paravalvular leak (RR, 3.76 [95% CI,
1.31–10.85]) and major bleeding (RR, 1.45
[95%

- In 145 asymptomatic patients with severe aortic stenosis, the cumulative incidence of a combined outcome of 30-day operative mortality or cardio-pacemaker implantation (RR, 2.50 [95% CI, 1.60–3.91]) and 30-day paravalvular leak (RR, 12.85 [95% CI, 1.08–1.94]).
- Compared with conventional SAVR with full sternotomy, TAVR was associated with lower rates of 30-day acute kidney injury (RR, 0.49 [95% CI, 0.31–0.77]) but higher permanent

vascular death was significantly lower in patients undergoing early surgery compared with those using watchful waiting (1% at both 4 and 8 years versus 6% at 4 years and 26% at 8 years; $P=0.003$).⁷⁷ In a study of 2429 patients with severe aortic stenosis, of whom 49.5% were female, the 5-year survival was lower especially in females compared with

- In a review of 14 RCTs (with 1395 participants) assessing the effects of minimally invasive aortic valve replacement through a limited sternotomy versus conventional aortic valve replacement through median sternotomy, upper hemisternotomy⁷⁴:

- had no clear association with mortality (RR, 0.93 [95% CI, 0.45-1.94]);
- was associated with modest increases in cardio-

expected survival ($62\pm 2\%$ versus 71% for females and $69\pm 1\%$ versus 71% for males) and compared with 5-year survival in males despite females having longer life expectancy than males ($66\pm 2\%$ [expected, 75%] versus $68\pm 2\%$ [expected, 70%]; $P<0.001$) after controlling for age.⁷⁸ Females also were more symptomatic ($P=0.004$) and used aortic valve replacement therapy less often (64.4% versus 69.1% ; $P=0.018$).

pulmonary bypass time (mean difference, 10.63 minutes [95% CI, 3.39 – 17.88]) and aortic cross-clamp time slightly (mean difference, 6.07 minutes [95% CI, 0.79 – 11.35]);

operative blood loss (mean difference, -153 mL)

– was associated with a modest decrease in post-

- In a single-center study of 5994 adults with and without aortic stenosis between 2015 and 2016, the Vmax on transthoracic echocardiography was linearly related to 5-year all-cause mortality (HR, 1.26 [95% CI, 1.19–1.33] for every 100 cm/s of [95% CI, –246 to –60]); and Vmax).⁷⁹
 - was associated with a modest difference in quality of life as measured by the 36-item Short Form Health Survey or any other validated scale (mean difference, 0.03 [95% CI, 0–0.06] and no change in pain scores (SMD, –0.19 [95% CI, –0.43 to

- A meta-analysis of 25 studies comprising 12 143 individuals found that, compared with patients with moderate aortic stenosis, the incidence rate difference of all-cause mortality was -3.9 (95% CI, -6.7 to -1.1) in patients with no or mild aortic stenosis (0.04]).
- The WATCH-TAVR trial is a multicenter randomized trial evaluating the safety and effectiveness of concomitant TAVR and LAO with the WATCHMAN device in patients with AF.⁷⁵ Patients were randomized 1:1 to either TAVR with a WATCHMAN device and 2.2 (95% CI, 0.8–3.5) in patients with severe aortic stenosis.⁷⁹ (n=177) or TAVR with medical therapy (n=172) between December 2017 and November 2020 at

- In an observational echocardiographic multicenter cohort study of 98 565 males and 99 357 females ≥ 65 years of age in Australia from 2003 to 2017, 21.0% of males and 18.7% of females had aortic stenosis.⁸⁰ The actual 5-year mortality in males and females with normal aortic valves was 32.1% and 34 US centers. 26.1%, respectively. In males and females with mild
- At 24 months, TAVR with a WATCHMAN device was noninferior to TAVR with medical therapy (HR,

aortic stenosis, this increased to 40.9% and 35.9%, respectively. In males and females with severe

aortic stenosis, this increased 52.2% and 55.3%, respectively.

- A multicenter study of 30 865 US and 217 599 Australian individuals between 2003 and 2017 found that moderate aortic stenosis conferred an increased risk of mortality after adjustment for age and sex (US individuals: HR, 1.66 [95% CI, 1.52–1.80]; Australian individuals: HR, 1.37 [95% CI, 1.34–1.41]).⁸¹
- Echocardiographic data, including Vmax, from years of age were linked to all-cause deaths in Australia and the United States between 2003 and 2018.⁸² Compared with those with Vmax of 1.0 to 1.49 m/s, those with Vmax of 2.50 to 2.99

or arrhythmias, poor functional class or cyanosis, high-risk valve disease/left ventricular outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions), 4 lesion-specific predictors (mechanical valves, high-risk aortopathies, PH, CAD), and 1 delivery-of-care predictor (late pregnancy assessment). These 10 predictors were incorporated into a m/s and 3.0 to 3.49 m/s had HRs of 1.22 (95% CI, 1.12–1.32) and 1.59 (95% CI, 1.36–1.86), respectively, for mortality within 10 years after adjustment for age, sex, left-sided HD, and LVEF.

meta-analysis of RCTs of TAVR versus SAVR, TAVR was significantly associated with a lower risk of acute kidney injury (RR, 0.27 [95% CI, 0.13–0.54]; $P=0.0002$), new-onset AF (RR, 0.26 [95% CI, 0.18–0.39]; $P<0.00001$), and life-threatening or disabling bleeding (RR, 0.35 [95% CI, 0.22–0.55]; $P<0.00001$) but a higher risk of moderate to severe paravalvular regurgitation (RR, 4.40 [95% CI, 1.22–15.86]; $P=0.02$) and permanent pacemaker inser-

Complications

- Sex differences in the complications of bicuspid aortic valve were examined in 992 patients with an echocardiographic diagnosis of bicuspid aortic valve hospitalized at a single center in Beijing between 2008 and 2017.⁸³ The following complications of bicuspid aortic valve were more common in males than females: aortic regurgitation ($\geq 2+$; 39.0% versus 12.8%; $P<0.001$), only aortic root dilation (3.8% versus 0.8%; $P=0.014$), and diffuse aortic dilation (25.3% versus 4.3%; $P<0.001$). The following complications of bicuspid aortic valve were more common in females: moderate to severe aortic stenosis (21.3% versus 45.7%; $P<0.001$) and only ascending aortic dilation (46.2% versus 61.2%; $P<0.001$). Sex did not predict early adverse events after aortic valve replacement ($n=90$; HR, 1.21 [95% CI, 0.74–1.98]; $P=0.44$). • In a systematic review and meta-analysis of patients with bicuspid aortic valve disease including 8 cohort studies with 5351 patients, bicuspid aortic valve IE occurred with an incidence rate of 48.13 per 10 000 patient-years (95% CI, 22.24–74.02)⁸⁴ and a 12-fold increased risk compared with the general population (RR, 12.03 [95% CI, 5.45–26.54]).
- In a prospective study of pregnant individuals with HD from 2 large Canadian tertiary care hospitals in Toronto and Vancouver including 1938 pregnancies, outcomes were examined from 1994 to 2014, and a new risk index to predict maternal cardiac complications was developed.⁸⁵ Cardiac complications occurred in 16% of pregnancies and were related primarily to arrhythmias and HF. The overall rates of cardiac complications during pregnancy did not change over the years. In addition, 10 predictors of maternal cardiac complications were identified: 5 general predictors (prior cardiac events

- In the multicenter UK TAVR registry of 8652 TAVR procedures performed from 2007 to 2015, there were 205 in-hospital strokes (incidence, 2.4%).⁸⁷ Factors associated with increased risk of in-hospital stroke were previous cerebrovascular disease (OR, 1.51, [95% CI, 1.05–2.17]; $P=0.03$), advanced age (OR, 1.02 [95% CI, 0.10–1.04]; $P=0.05$), coronary stenting at the time of TAVR (OR, 5.94 [95% CI, 2.03–17.39]; $P=0.008$), and earlier year of procedure (OR, 0.93 [95% CI, 0.87–1.00]; $P=0.04$); factors associated with lower risk included no prior cardiac surgery (OR, 0.62 [95% CI, 0.41–0.93]; $P=0.01$) and deployment of a first-generation self-expandable transcatheter heart valve (OR, 0.72 [95% CI, 0.53–0.97]; $P=0.03$). Having a stroke during hospitalization for a TAVR procedure significantly increased 30-day mortality (OR, 5.22 [95% CI, 3.49–7.81]; $P<0.001$) and 1-year mortality (OR, 3.21 [95% CI, 2.15–4.78]; $P<0.001$).
- In a study of all hospitalizations in patients ≥ 18 years of age who underwent TAVR from 2016 to 2017 in the Nationwide Readmission Database, a total of 54 317 unweighted hospitalizations for TAVR were identified, of which 5639 (10.4%) required permanent pacemaker implantation.⁸⁸ The risk of pericardial effusion was significantly greater in patients who required permanent pacemaker (2.4% versus 1.6%; aOR, 1.39 [95% CI, 1.15–1.70]; $P<0.001$), and risk of cardiac tamponade nearly doubled (1.6% versus 0.8%; $P<0.001$; aOR, 1.90 [95% CI, 1.48–2.40]; $P<0.001$). Pericardial complications after permanent pacemaker implantation were associated with increased in-hospital mortality, length of stay, hospital costs, and risk of 30-day readmission after TAVI ($P<0.01$ for all comparisons).

- Duration of RV pacing may be **Cost**

risk of cardiovascular death or
The PACE-TAVI trial is an
registry of all patients with
permanent pacemaker
days of their procedure.⁸⁹ The
try is to evaluate the
centage of RV pacing with
patients after TAVR. A total of
enrolled. 158 with <40%
219 with ≥40% ventricular
variable adjustment. those

RV pacing had a higher incidence of the primary
end point, a composite of cardiovascular mortal-
ity or hospitalization for HF (HR, 2.76 [95% CI,
1.39–5.51]; $P=0.004$) and cardiovascular death
(HR, 3.77 [95% CI, 1.02–13.88]; $P=0.04$). The
incidence of all-cause death was not significantly

- In an Australian study, aortic
with 8 more premature deaths
premature deaths in females
investigated.⁸⁰ Per 1000
32.5 more OALYs lost in
etal cost of Australian \$1.40
OALYs lost in females.
of Australian \$2.48 million.
societal cost of premature
aortic stenosis was Australian
and Australian \$735 million in
different between the 2 groups (HR,
2.17 [95% CI, 0.80–5.90]; $P=0.13$).
- In OBSERVANT-II, an observational,
prospec- tive, multicenter cohort
study, 2753 consecutive

- In a European study of patients with severe aortic stenosis and intermediate surgical risk, TAVR was associated with an increase of 0.42 years and 0.41 QALYs and lifetime cost savings of €439 compared with SAVR.⁹²
 - In patients undergoing TAVR with low surgical risk in the Danish health care system, the incremental cost-effectiveness ratios (range, 334 200–904 100 Danish kroner per QALY gained) were all below the country-specific willingness to pay of 1.13 million Danish kroner.⁹³
- patients undergoing TAVR were followed up to investigate the incidence and predictors of 30-day and 6-month postprocedural stroke.⁹⁰ The occurrence of a 30-day and 6-month stroke was 1.3% and 2.4%, respectively. Aortic valve predilatation (OR, 2.28 [95% CI, 1.12–4.65]; $P=0.023$), diabetes (OR, 3.10 [95% CI, 1.56–6.18]; $P=0.001$), and LVEF <50% (OR, 2.15 [95% CI, 1.04–4.47]; $P=0.04$) were independently associated with 30-day stroke. Diabetes (subdistribution HR, 2.07 [95% CI, 1.25–3.42]; $P=0.004$), preexisting neuro-logical dysfunction (subdistribution HR, 3.92 [95% CI, 1.54–10]; $P=0.004$), bicuspid valve (subdistri-

- An economic study of 929 patients with aortic stenosis and low surgical risk randomized to TAVR or SAVR between 2016 and 2017 in the PARTNER 3 trial was conducted.⁹⁴ Procedural costs were approximately \$19 000 higher with TAVR; total index hospitalization costs were \$591 more with TAVR compared with SAVR. However, the study found that follow-up costs were lower with TAVR. They found that TAVR led to 2-year cost savings of \$2030 per patient compared with SAVR (95% CI, -\$6222 to \$1816).

bution HR, 4.75 [95% CI, 1.44–15.7]; $P=0.011$),
and critical status (subdistribution HR, 3.05 [95%
CI, 1.21–7.72]; $P=0.018$) were associated with

Global Burden

(See Table 23-1 and Charts 23-1 and 23-2)

- In 204 countries and territories in 2021, there were 13.32 (95% UI, 11.42–15.25) million prevalent moderate or severe paravalvular leak occurred in patients receiving EVOLUT PRO and SAPIEN 3 at similar rates of 5.3% and 5.8% before hospital discharge, 4% and 3.1% at 1 month, and 3.2% and 4.9% at 1 year, respectively. There was no significant difference in 1-year survival (HR, 0.73 [95% CI, 0.33–1.63]; *P*=0.442).
- An observational retrospective study of 1481 patients with TAVR from 6 different European centers aimed to compare the incidence and severity of paravalvular leak and 1-year survival after TAVR with either the EVOLUT PRO or SAPIEN 3 valve.⁹¹ Paravalvular leak occurred more frequently in patients undergoing TAVR with the EVOLUT PRO at prehospital discharge (55.1% versus 37.3%), at 1 month (51% versus 41.4%), and at 1 year (51.3% versus 39.3%).

lent cases of calcific aortic valve disease and 0.14 (95% UI, 0.12–0.16) million total deaths attribut-able to calcific aortic valve disease (Table 23-1).

The age-standardized prevalence and death rates were 158.35 (95% UI, 135.92–181.00) and 1.83 (95% UI, 1.54–2.00) per 100 000, respectively.⁴ The highest age-standardized death rates of non-rheumatic calcific aortic valve disease among regions were for Western Europe and high-income North America. The lowest rates were for East Asia (Chart 23-1). Among regions, nonrheumatic cal-cific aortic valve disease prevalence was highest for Western Europe, high-income North America, Central Europe, and Australasia (Chart 23-2).

- Among the causes of HF between 1990 and 2019, calcific aortic valve disease increased by >90% in both males and females.⁹⁵

Mitral Valve Disorders

ICD-9 424.0; ICD-10 I34.

2022, United States: Underlying cause mortality—2950. Any-mention mortality—7473.

2021, United States: Hospital discharges—31 725.

Primary MR includes Carpentier functional classification system types I, II, and IIIa with the most common cause being mitral valve prolapse dysfunction, or DCM (type IIIb MR).

Prevalence

- See Global Burden section.

Subclinical Disease

- Milder, nondiagnostic forms of mitral valve prolapse, first described in the familial context, are also present in the community and are associated with a higher likelihood of mitral valve prolapse in offspring (OR, 2.52 [95% CI, 1.25–5.10]; $P=0.01$). Up to

3.57 (95% CI, 2.21–5.76; $P<0.001$)

for the development of MR.¹¹⁰

- Among 3679 young to middle-aged third-generation participants in the FHS with available parental data, 49 (1%) had mitral valve prolapse.¹¹¹ Parental mitral valve prolapse was associated with a higher prevalence of mitral valve prolapse in offspring (10/186 [5.4%]) compared to 80% of nondiagnostic morphologies can progress to diagnostic mitral valve prolapse.^{96,97}

ress

Genetics and Family History

- A number of genetic variants have been identified for the rare X-linked valvular dystrophy and the most common form of autosomal dominant mitral valve prolapse through pedigree investigations and GWASs. Genes implicated in mitral valve prolapse include *GLIS1*, *FLNA*, *DCHS1*, *DZIP1*, *TNS1*, and *LMCD1*.^{98–102} An updated GWAS meta-analysis using dense imputation coverage revealed several

- An exome sequencing study identified potential myopathy genes (*DSP*, *HCN4*, *MYH6*, *TMEM67*, *TRPS1*, and *TTN*) and mitral valve prolapse.^{.112}
- A meta-analysis of 6 GWASs for mitral valve pro-identified 14 loci.^{.113} Transcriptomics-, epigenomics-, and proteomics-based gene prioritization identified *LMCD1*, *SPTBN1*, *LTBP2*, *TGFB2*, *NMB*, and *ALPK3* as candidate genes. A mitral valve prolapse PRS including 1.1 million variants from GWAS meta-analysis was developed. Individuals in the highest quintile had 20% higher odds of mitral valve prolapse compared with individuals in the lower 4 quintiles after accounting for clinical risk factors (OR, 1.20; $P=2.85\times10^{-11}$).
- A GWAS of mitral annular diameter obtained from a 4-chamber view from 32 220 cardiac MRIs identified 10 loci.^{.114} The identified loci included possible novel loci (*GOSR2*, *ERBB4*, *MCTP2*, and *MCPH1*) and genes associated with cardiac contractility (*BAG3*, *TTN*, and *RBFOX1*).
- risk loci (*SYT2*, *SRR*, *TSR1*, *SGSM2*, *SIX5*, *DMPK*, and *DMWD*) warranting further functional analysis for these loci.^{.103}

Treatment

(See Chart 23-3)

- Mitral valve prolapse may be seen in syndromes associated with connective tissue diseases such as Marfan syndrome (*FBN1* gene), Loeys-Dietz syndrome (*TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3* genes), and Ehler-Danlos syndrome (*COL5A1*, *COL5A1*, *COL1A1*, *TNXB* genes).^{.104,105}
- Mitral valve prolapse may also be seen in patients with a specific syndrome not associated with connective tissue disease (Edward syndrome, Patau syndrome, and trisomy of chromosome 15).^{.105,106}

Nonsyndromic mitral valve prolapse may be seen in carriers of variants in the *MMVP1*, *MMVP2*, *MMVP3*, and *FLNA* genes.^{.107–109}

- Familial clustering exists across different MR subtypes, including both primary (ie, related to mitral valve prolapse) and nonprimary MR. Heritability of MR in the FHS was estimated at 15% (95% CI, 7%–23%), 12% (95% CI, 4%–20%) excluding mitral valve prolapse, and 44% (95% CI, 15%–73%) for moderate or greater MR only (all $P<0.05$).^{.110} In Sweden, sibling MR was associated with an HR of

- The 2 main percutaneous mitral valve interventions in the United States are TEER and transcatheter mitral valve replacement. Data from the STS/ACC TVT Registry between 2014 and 2020 are reported.¹¹⁵ A total of 37 475 patients underwent a mitral transcatheter procedure, including 33 878 TEERs and 3597 transcatheter mitral valve replacements. Annual procedure volumes for TEER increased from 1152 per year in 2014 to 10 460 per year in 2019 at 403 sites and for transcatheter mitral valve replacement from 84 per year to 1120 per year at 301 centers. Mortality rates have decreased for TEER at 30 days (from 5.6% to 4.1%) and 1 year (from 27.4% to 22.0%). The 30-day mortality rate was 3.9%, reflecting overall improvements in outcomes over the past several years.
- In the EVEREST II trial, which included mostly patients with primary MR (73%) and compared MitraClip with surgical mitral valve repair, the respective rates of the components of the primary

end point at 12 months were in each group: surgery for 20% versus 2%; and grade 3+ vs 20%.¹¹⁶

- In the United States, the MitraClip started in 2013, with number of procedures at the trend of mitral valve to 2016 performed in the procedures increased from 2016, an increase of ≈90%.¹¹⁷

- Use of MitraClip procedures has also increased in Asia, although at a slower pace, with the highest increase seen in Japan from 18 procedures in 2011 to 439 procedures in 2018.¹¹⁸
- The role of MitraClip in secondary MR has been investigated in 2 published randomized clinical trials, COAPT and MITRA-FR, with divergent results that may be related to differences in sample characteristics, including sample size (614 versus 304, respectively), duration of follow-up (5 years versus 1 year, respectively), and primary end point (rehospitalization versus combined death and rehospitalization for HF; Chart 23-3).^{119–121a}

- The COAPT trial included 614 patients with HF and moderate to severe or severe secondary MR who were symptomatic (New York Heart Association functional class II–IV) despite optimal medical therapy and cardiac resynchronization therapy.^{120,121a}

With MitraClip, there was a significant reduction in the primary end point of rehospitalization for HF at 2 years (35.8% versus 67.9%; HR, 0.53 [95% CI, 0.40–0.70]; $P<0.001$). There was also a significant reduction in all-cause mortality at 2 years (29% versus

patients from the CHOICE-MI secondary MR undergoing either valve repair or goal-directed 2-year rate of HF

lower in the transcatheter (32.8%) compared with the therapy group (54.4%; HR, 0.99; $P=0.04$). There was no in 2-year mortality between patients with transcatheter vs 40.8% in patients with

46.1%; HR, 0.62 [95% CI, 0.46–0.82]; $P<0.001$). All-cause mortality at 5 years was 57.3% in the MitraClip group and 67.2% in the medical therapy alone group (HR, 0.72 [95% CI, 0.58–0.89]). Death or hospitalization for HF within 5 years occurred in 73.6% of the MitraClip patients and in 91.5% of the medical therapy alone group (HR, 0.53 [95% CI, 0.44–0.64]). At 5 years, hospitalization for HF was 33.1% per year in the MitraClip group and 57.2% per year in the medical therapy alone group (HR, 0.53 [95% CI, 0.41–0.68]).

- MITRA-FR included 304 patients with HF, severe secondary MR, and LVEF of 15% to 40% on optimal medical therapy and cardiac resynchronization therapy as indicated. There was no difference in the combined end point of death or rehospitalization for HF at 12 months (83/152 patients

therapy (HR, 1.01 [95% CI, 0.62–1.64]; $P=0.98$).• In a meta-analysis of 15 RCTs and comparative cohort studies, 16 879 patients <70 years of age undergoing mitral valve replacement with either mechanical mitral valve or bioprosthetic mitral valve were compared.¹²³ Bioprosthetic mitral valve replacement was associated with significantly higher rates of 30-day mortality (RR, 1.53 [95% CI, 1.28–1.83]; $P=0.0006$) but no difference in 30-day stroke (RR, 0.70 [95% CI, 0.23–2.12]; $P=0.428$).

Bioprosthetic valve replacement was associated with higher rates of long-term mortality (RR, 1.28 [95% CI, 1.09–1.50]; $P=0.0054$) at a weighted mean follow-up of 14.1 years. No difference was seen between mechanical and bioprosthetic mitral valve replacement for risk of long-term stroke (RR, 0.92 [95% CI, 0.56–1.52]; $P=0.668$), reoperation (RR, 1.72 [95% CI, 0.83–3.56]; $P=0.121$), or major bleeding (RR, 0.57 [95% CI, 0.28–1.15]; $P=0.10$) at a weighted mean follow-up of 11.7, 11.3, and 11.9 years, respectively.

- A systematic review and meta-analysis of 13 RCTs including 1089 patients compared patients who underwent either isolated mitral valve repair or replacement with patients who underwent mitral valve repair or replacement with concomitant sur-gical ablation for AF.¹²⁴ The odds of sinus rhythm were higher in the patients who underwent mitral valve repair or replacement with concomitant sur-gical ablation at discharge (OR, 9.62 [95% CI, 4.87–19.02]; $I_2=55\%$), at 6 months (OR, 7.21 [95% CI, 4.30–12.11]; $I_2=34\%$), and at 1 year (OR, 8.41 [95% CI, 5.14–13.77]; $I_2=48\%$). Although there was no difference in all-cause mortality, stroke, or thromboembolic events between the 2 groups, the odds of permanent pacemaker implantation were higher in patients who underwent mitral valve repair or replacement with concomitant surgical ablation (OR, 1.87 [95% CI, 1.11–3.17]; $I_2=0\%$).

[54.6%] versus 78/152 [51.3%] for interventional **Mortality** and conservative management, respectively).

- The outcomes of transcatheter mitral valve repair versus goal-directed medical therapy were com-

pared using 97 propensity-matched pairs of

- According to data from Mayo Clinic electronic health records and the Rochester Epidemiology Project to identify all cases of moderate or severe iso-lated MR diagnosed during a 10-year period in the

community setting in Olmsted County, Minnesota, at 15 years of follow-up, females with no or mild MR had better survival than males (87% versus 77%; aRR, 0.82 [95% CI, 0.76–0.89]). In contrast, in individuals with severe MR, females had worse survival than males (60% versus 68%; aRR, 1.13 [95% CI, 1.01–1.26]). Survival 10 years after surgery was similar in females and males (77% versus 79%;

MR secondary to ischemic cardiomyopathy have a higher mortality at 2 years (27.1% versus 17.4%; absolute risk increase, 9.7%; aHR, 1.86 [95% CI, 1.05–3.29]; $P=0.03$) and a trend toward higher surgical failure (57.0% versus 43.2%; absolute risk increase, 13.8%; aOR, 1.78 [95% CI, 0.98–3.23]; $P=0.06$) compared with males.¹²⁶

- A propensity-matched study was conducted examining patients with MR undergoing either transcatheter mitral valve repair or surgical mitral valve repair between January 1, 2015, and December 31, 2020, from the TriNetX Analytics Research

injury (aOR, 3.57 [95% CI, 2.85–4.48]; $P<0.001$), AMI (aOR, 1.80 [95% CI, 1.37–2.36]; $P<0.001$), cardiogenic shock (aOR, 2.55 [95% CI, 1.82–3.57]; $P<0.001$), 30-day all-cause readmissions (OR, 2.12 [95% CI, 1.69–2.65]; $P<0.001$), and 30-day HF readmissions (OR, 1.33 [95% CI, 1.05–1.68]; $P<0.01$)

compared with patients without

Data Network, a global federated database of electronic health records from 58 health care organizations.¹²⁷

During this time period, 1392 patients underwent surgical mitral valve repair and 960 underwent transcatheter mitral valve repair. After 1:1 propensity score matching, a total of 550 patients undergoing surgical mitral valve repair were compared with 550 patients undergoing transcatheter mitral valve repair. Compared with patients undergoing transcatheter mitral valve repair, patients undergoing surgical mitral valve repair had lower risk of mortality at 3 years (HR, 0.42 [95% CI, 0.31–0.56];

- At 1 year after TEER, as many as 30% of patients have moderate to severe mitral valve regurgitation and an additional 25% have mitral stenosis, which affect survival, symptomatic congestive HF, and need for reintervention.^{120,131} The STS Adult Cardiac Surgery Database was used to identify 524 adults who underwent first mitral surgery after TEER from 2014 to 2021.¹³² Median time from TEER to mitral valve surgery was 3.5 months. Only 4.5% of mitral valves (n=22) could be repaired with >90% (n=438) of cases requiring mitral valve replacement. Concomitant tricuspid repair or replacement was performed in 32.8% (n=152) with moderate or severe tricuspid regurgitation, and CABG was performed in 12.3% (n=57). The 30-day or in-hospital mortality was 10.6% (n=49).
- A study of 11 396 Medicare patients who underwent TEER between July 2013 and November 2017 revealed that 548 patients (4.8%) required reintervention after a median time interval of 4.5 months¹³³: 294 (53.7%) underwent repeat TEER, and 254 (46.3%) underwent mitral valve surgery. Overall 30-day mortality was 8.6%, and the 30-day composite morbidity was 48.2%. Reintervention with mitral valve surgery after TEER was associated with

Complications

- In 2017, there were 35 700 (95% CI, 30 500–42 500) degenerative mitral valve deaths globally.¹²⁸
 - AF is a common occurrence of severe primary regurgitation and is associated with persistence of excess risk after mitral valve repair. In MIDA, 10-year postsurgical survival in sinus rhythm and in paroxysmal and persistent AF was 82±1%, 70±4%, and 57±3%, respectively (P<0.0001).¹²⁹
- In a study using the Nationwide Readmission Database to identify adult patients who underwent TEER from 2014 to 2018,¹³⁰ of the 21 323 patients identified, 1615 (7.5%) had major bleeding. Coagulopathy, ESKD, nonelective admission, week-end admission, weight loss, cancer, CKD, anemia, and female sex were identified as independent predictors of major bleeding.
 - Patients with major bleeding had significantly higher rates of in-hospital mortality (aOR, 2.70 [95% CI, 1.70–4.10]; P<0.001), acute kidney

higher 30-day morbidity (aOR, 4.76 [95% CI, 3.17–7.14]) compared with repeat TEER. Requirement for reintervention was an independent risk factor for long-term mortality (HR, 3.26 [95% CI, 2.53–4.20]).

Cost

- In the COAPT trial comparing MitraClip plus optimal medical therapy with optimal medical therapy alone in symptomatic patients with HF with moderate to severe or severe secondary MR, MitraClip increased life expectancy by 1.13 years and QALYs by 0.82 years at a cost of \$45 648. This translated into an incremental cost-effectiveness ratio of \$40 361 per life-year and \$55 600 per QALY gained.¹³⁴

Global Burden

(See Table 23-2 and Charts 23-4 and 23-5)

- Based on 204 countries and territories in 2021, there were 15.49 (95% UI, 14.46–16.70) million prevalent cases of degenerative mitral valve disease and 0.04 (95% UI, 0.03–0.04) million total deaths

attributable to degenerative
The age-standardized
were 182.13 (95% UI,
(95% UI, 0.39–0.51) per 100
(Table 23-2). In 2021, the
ized mortality rates of
mitral valve disease among
Europe, Oceania and East
the lowest mortality rates
among regions, nonrheumatic

valve disease prevalence was highest for high-income North America and Central Asia. The lowest prevalence rates were for regions in sub-Saharan Africa (Chart 23-5).

Pulmonary Valve Disorders

ICD-9 424.3; ICD-10 I37.

2022, United States: Underlying cause mortality—17.
Any-mention mortality—96.

2021, United States: Hospital discharges—970.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in ≈10% of children with congenital HD.¹³⁵ Among 44 neonates with critical pulmonic stenosis who underwent balloon pulmonary valvuloplasty from 1990 to 2017, 15 (34.1%) needed reintervention. At a median follow-up of 8.2 years (interquartile range, 3.4–13.1 years), moderate or severe pulmonary regurgitation was seen in 22 children (half of the sample), 3 of whom required pulmonary valve repair/replacement.¹³⁶
- In an observational registry of 82 adults with either congenital pulmonic stenosis or subpulmonic stenosis associated with TOF, percutaneous pulmonic valve implantation with a SAPIEN valve was demonstrated to be feasible and safe.¹³⁷

pulmonic valve replacement
mortality (OR, 0.18 [95% CI,
term mortality (OR, 0.43 [95%
pared with surgical pulmonic
However, postprocedural IE
[95% CI, 0.07–0.42])
replacement. The risk of
the group treated with
replacement, although it was
cant (OR, 2.19 [95% CI, 2.03–

- The most common cause of severe pulmonic regurgitation is iatrogenic, resulting from surgical valvotomy/valvectomy or balloon pulmonary valvuloplasty performed for RV outflow tract obstruction as part of TOF repair.¹³⁸ Transcatheter pulmonic valve implantation of either a Melody or a SAPIEN valve is effective and relatively safe,^{138,139} with serious complications occurring in only 3 patients (One-third died and two-thirds required surgical intervention in a study using the NIS database, which included 57 transcatheter pulmonic valve implantation procedures performed in 2012).¹⁴⁰ Surgical pulmonary valve replacement is preferred for native pulmonic valve regurgitation (caused by endocarditis, carcinoid) and is associated with <1% periprocedural mortality and excellent long-term outcome, with >60% freedom from reoperation at 10 years.¹⁴¹ In a meta-analysis including 4364 patients with either pulmonic stenosis or regurgitation, transcatheter

Tricuspid Valve Disorders

ICD-9 424.2; ICD-10 I36.

2022, United States: Underlying cause mortality—91. Any-mention mortality—395.

2021, United States: Hospital discharges—1195.

- From January 2006 to September 2015, tricuspid valve disease was present in 3 235 292 or 1.7% of US hospitalized patients >50 years of age.¹⁴³
 - The prevalence of tricuspid valve disease was higher in females than males and increased with increasing age.
 - From 2006 to 2015, the prevalence of tricuspid valve disease in all hospitalizations increased from 1.7% to 2.0%.
- The characteristics of patients with HF and MR with or without tricuspid regurgitation were examined in a prospective, multicenter observational study of 11 298 patients with HF from 133 participating centers across 21 European and European Society of Cardiology–affiliated countries in the ESC-HFA EORP HF Long-Term Registry.¹⁴⁴ Within this group, 7541 (67%) had no MR or tricuspid regurgitation, 1931 (17%) had isolated MR, 616 (5.5%) had isolated tricuspid regurgitation, and 1210 (11%) had combined mitral and tricuspid regurgitation. HFpEF was associated with an increased risk of isolated tricuspid regurgitation (OR, 1.94 [95% CI, 1.61–2.33]). Those with isolated tricuspid regurgitation had a higher risk of all-cause death or first HF hospitalization (aHR, 1.43 [95% CI, 1.18–1.73]; $P<0.001$), cardiovascular death or first HF hospitalization (aHR, 1.54 [95% CI, 1.25–1.89]; $P<0.001$), first HF hospitalization (aHR, 1.54 [95% CI, 1.23–1.93]; $P<0.001$), and cardiovascular death (aHR, 1.79 [95% CI, 1.25–2.58]; $P=0.002$).
- A meta-analysis of 29 RCTs and prospective and retrospective observational studies published from inception to January 2023 that reported the incidence of tricuspid regurgitation from echocardiography sought to identify the overall incidence of tricuspid regurgitation after pacemaker or ICD implantation.¹⁴⁵ Patients who underwent device implantation (n=1008) were significantly more

likely to develop worsening tricuspid regurgitation than control subjects who did not undergo device implantation ($n=58\ 605$; OR, 3.18 [95% CI, 1.58–6.39]; $P<0.01$). Worsening tricuspid regurgitation after device implantation significantly increased mortality (HR, 1.42 [95% CI, 1.05–1.92]; $P=0.02$). Larger right atrial area was significantly associated with an increased risk of worsening tricuspid regurgitation after device implantation (OR, 1.11 [95% CI, 1.06– $P<0.01$). There was no statistically significant difference in tricuspid regurgitation after either pacemaker or ICD implantation (OR, 1.12 [95% CI, 0.57–2.18]; $P=0.71$).

- In a meta-analysis of 52 studies (3 RCTs, 18 prospective, and 31 retrospective studies) published from inception to March 2023 including 130 759 patients reporting the incidence or prognosis of cardiac implantable device–associated tricuspid regurgitation, the incidence of cardiac implantable device–associated tricuspid regurgitation was 24% (95% CI, 20%–28%; OR, 2.44 [95% CI, 1.58–3.77]; $P<0.001$).¹⁴⁶ Cardiac implantable device–associated tricuspid regurgitation–associated tricuspid regurgitation was associated with an increased risk of all-cause mortality (aHR, 1.52 [95% CI, 1.36–1.69]; $P<0.001$), HF hospitalizations (aHR, 1.82 [95% CI, 1.19–2.78]; $P=0.006$), and the composite of mortality and HF hospitalizations (aHR, 1.96 [95% CI, 1.33–2.87]; $P=0.001$).
- Outcomes of transcatheter tricuspid valve interventions were analyzed in 317 high-risk

tricuspid regurgitation) than those who underwent mitral valve surgery alone (3.9% versus 10.2%; RR, 0.37 [95% CI, 0.16–0.86]; $P=0.02$).

- In TRILUMINATE Pivotal, patients with severe tri-cuspid regurgitation in 65 centers in the United States, Canada, and Europe were randomized to either transcatheter tricuspid valve repair ($n=175$) or patients with severe tricuspid regurgitation from the international Trivalve registry.¹⁴⁷ Such patients were treated either with transcatheter repair at the level of the leaflets (MitraClip, PASCAL), annulus (Cardioband, TriCinch, Trialign), or coaptation (FORMA) or with transcatheter replacement (Caval Implants). Procedural success, defined as successful device implantation with moderate or less tricuspid regurgitation, was 72.8%. Thirty-day mortality was significantly lower among patients with procedural success (1.9% versus 6.9%; $P=0.04$). Actuarial survival at 1.5 years was $82.8\pm4\%$ and was significantly higher among patients who had procedural success ($70.3\pm8\%$ versus $90.8\pm4\%$; $P<0.0002$).
- Four hundred one patients from 39 clinical centers in the United States, Canada, and Germany undergoing mitral valve surgery for degenerative MR were randomly assigned to receive mitral valve surgery with or without tricuspid annuloplasty.¹⁴⁸ At 2 years, patients who underwent mitral valve surgery with tricuspid annuloplasty had fewer primary end-point events (death, reoperation for tricuspid regurgitation, progression of tricuspid regurgitation by 2 grades from baseline, or presence of severe

from any cause or tricuspid valve surgery, hospital-ization for HF, and an improvement in health sta-tus measured by the Kansas City Cardiomyopathy Questionnaire. The results for the primary end point favored the TEER group (win ratio, 1.48 [95% CI, 1.06–2.13]; $P=0.02$), driven entirely by improve-ments in health status in this unblinded study. Transcatheter tricuspid valve repair significantly improved health status at 1 month (mean between-group difference in Kansas City Cardiomyopathy Questionnaire overall summary score, 9.4 points [95% CI, 5.3–13.4]), with a small additional improvement at 1 year (mean between-group dif-ference, 10.4 points [95% CI, 6.3–14.6]).¹⁵⁰ Despite improvement in self-reported health status, there was no improvement in 6-minute walk distance with intervention (17.1; 95% CI, –12.0 to 46.1).

Rheumatic Fever/Rheumatic HD

ICD-9 390 to 398; ICD-10 I00 to I09.

2022, United States: Underlying cause mortality—4294. Any-mention mortality—9310.

2021, United States: Hospital discharges—25 030.

Prevalence

- Rheumatic HD remains a leading cause of HF across the world.⁹⁵
- A total of 1680 students between 6 and 18 years of age in eastern Egyptian Governorates were screened for rheumatic HD clinically or by echo-cardiography.¹⁵¹ From the total screened students, 1560 studies (92.9%) were adequate and inter-pretable. Rheumatic HD prevalence was 2.3%. MR was the most prevalent lesion detected by echocar-diography in students with rheumatic HD. Of stu-dents with rheumatic HD, mild MR was present in 29 students (90.6%), moderate MR was present in 2 patients (6.3%), and severe MR was present in 1 patient (3.1%).

Subclinical Disease

- Few echocardiographic screening studies for rheumatic HD have been conducted in adults, for whom the criteria are not well validated. In a study from Uganda, the prevalence of rheumatic HD

in adults >20 years of age
1.49%–3.49%).¹⁵²

- Latent rheumatic HD appears more common among youths living with the general Ugandan 0.88%–2.54% versus 3% possibly related to improved care or nearly universal zole prophylaxis among

Treatment

- A meta-analysis of 13 studies valve repairs and 3598 mitral mitral valve disease revealed ity of repair versus 4.3% (OR, 0.68 [95% CI, Mitral valve repair also mortality (OR, 0.41 [95% CI, and reoperation (OR, 3.02 $P<0.001$).
- There are limited data on matic HD. One study procedures¹⁵⁵ from the US Database for hospitalizations 2018. A total of 18 240 in the analysis, including 1779 matic HD. Mitral TEER in HD was associated with in- to that in patients without [95% CI, 0.94–2.30]; matic HD was associated with [95% CI, 1.07–2.56]), acute [95% CI, 1.30–1.94]),

1.50 [95% CI, 1.12–2.01]), high-degree heart block (OR, 1.67 [95% CI, 1.25–2.23]), and conversion to open surgical repair or replacement (OR, 2.53 [95% CI, 1.02–6.30]). Mitral TEER in rheumatic HD was also associated with higher 90-day all-cause readmission (HR, 1.19 [95% CI, 1.04–1.47]; $P=0.012$).

as 46.8% of the patients had symptoms and repeat patients were deemed eligible. However, only 18.1% (17/94)

Global Burden of Rheumatic HD (See Table 23-4 and Charts 23-6)

- Based on 204 countries and
 - There were 0.37 (95% UI, deaths estimated for of 10.76% (95% UI, 1990 to 2021 (Table 23-4).
 - Among regions, mortality matic HD was substantially and Oceania than any other
 - The number of prevalent was 54.79 (95% UI, 43.33–an increase of 69.43% 73.38%) compared with
 - Rheumatic HD prevalence highest for sub-Saharan Latin America, and the
- Among 56.2 million people 204 countries and territories rheumatic HD was the third. The age-standardized matic HD increased between was driven by increasing increase) and low-middle–regions, most notably in (16.7% increase). HF from in middle-, high-middle–, and high-income regions.

Mortality

(See Table 23-3)

- In the United States in 2022, mortality attributable to rheumatic fever/rheumatic HD was 4294 for all ages (2772 females and 1522 males; Table 23-3).

Infective Endocarditis

ICD-9 421.0; ICD-10 I33.0.

2022, United States: Underlying cause mortality—1734. Any-mention mortality—3834.

2021, United States: Hospital discharges—11 620.

Prevalence and Incidence

- In US commercial and Medicaid health insurance
13.8 cases per 100 000 among individuals 18 to

Complications

- In a study at 2 Gambian referral hospitals
involving 255 registered patients with rheumatic

databases, the weighted incidence rate of IE was
64 years of age with commercial insurance and
78.7 per 100 000 among those with Medicaid.¹⁵⁷
HD, the case fatality rate in 2017
was estimated at 19.6%.¹⁵⁶

Incidence was higher in males versus females (16.9 versus 10.8 per 100 000 among those with commercial insurance; 104.6 versus 63.5 per 100 000

The median age at first presentation was 13 years (interquartile range, 9–18 years); 57% of patients had late-stage HF, and 84.1% had a pathological heart murmur. A history suggestive of acute rheumatic fever was reported by 48.7% of patients; only

with Medicaid).

15.8% were adequately treated, and 65.5% of those prescribed penicillin were fully adherent. As many

- Data from the GBD Study show that the incidence of IE has continued to rise over the past 30 years globally.¹⁵⁸ In North America, age-standardized incidence rates went from 10.11 (95% CI, 8.32–12.27) per 100 000 in 1990 to 12.54 (95% CI, 10.35–15.15) per 100 000 in 2019.

Secular Trends

• Data from the North Carolina Hospital Discharge Database show rates of drug use–associated IE rising from 0.08 per 100 000 residents in 2013 to 1.38 per 100 000 residents in 2016 to 2017.¹⁵⁹ In the final year (2016–2017), 42% of IE valve surgeries were for drug use–associated IE.

Risk Factors

• The 15-year cohort risk (through 2006) of IE after diagnosis of mitral valve prolapse (between 1989 and 1998) among Olmsted County, Minnesota, residents was $1.1 \pm 0.4\%$

26.6%; $P=0.016$) and 1-year mortality (53.5% versus 37.8%; $P<0.001$) decreased over these 2 study periods. In the Swiss TAVI Registry, IE after TAVR occurred most frequently in the early period (<100 days; 2.59 events per 100 PY) and

the combined outcome of all-cause mortality, unplanned surgery, embolic events, or relapse of bacteremia was similar in those treated with continuous intravenous antibiotic drugs compared with those switched from intravenous to oral antibiotic drugs after 10 days (24 cases [12.1%] versus 18 cases [9%]; between-group difference, 3.1 percentage points [95% CI, -3.4 to 9.6]; $P=0.40$).¹⁶⁴ After a median follow-up of 3.5 years, the primary composite end point had occurred in 38.2% of patients in the intravenous group and 26.4% in the oral antibiotic group (HR, 0.64 [95% CI, 0.45–0.91]).¹⁶⁵

• A single-center retrospective observational study of 413 patients (25.4% female) who received surgery for IE showed that females had a higher 30-day mortality than males (26.7% versus 14.9%; $P=0.007$).¹⁶⁶ Female sex was predictive for 30-day mortality (OR, 2.090 [95% CI, 1.077–4.053]; $P=0.029$).

• The ESC-HFA EORP European Infective Endocarditis is a prospective, multicenter registry of patients diagnosed with definite or possible IE from 2016 to 2018.¹⁶⁷ Of 2171 patients with left-sided IE, 459 (21.1%) had a new embolic event or died within 30 days. The cutoff value of vegetation size for predicting embolic events or 30-day mortality was >10 mm (HR, 1.38 [95% CI, 1.13–1.69]; $P=0.0015$). Other adjusted predictors of risk of embolic event or death were embolic event on admission (HR, 1.89 [95% CI, 1.54–2.33]; $P<0.0001$), history of HF (HR, 1.53 [95% CI, 1.21–1.93]; $P=0.0004$), creatinine >2 mg/dL (HR, 1.59 [95% CI, 1.25–2.03]; $P=0.0002$), *Staphylococcus aureus* (HR, 1.36 [95% CI, 1.08–1.70]; $P=0.008$), congestive HF (HR, 1.40 [95% CI, 1.12–1.75]; $P=0.003$), presence of hemorrhagic stroke (HR, 4.57 [95% CI, 3.08–6.79]; $P<0.0001$), alcohol abuse (HR, 1.45 [95% CI, 1.04–2.03]; $P=0.03$), presence of cardiogenic shock (HR, 2.07 [95% CI, 1.29–3.34]; $P=0.003$), and not performing left-sided surgery (HR, 1.30 [95% CI, 1.05–1.61]; $P=0.016$).

was most commonly caused by *Enterococcus* species (30.1% of cases).¹⁶³

Awareness, Treatment, and Control

• In a randomized, noninferiority multicenter trial of 400 stable cases with left-sided native IE,

Mortality

- According to the GBD Study 2020, the age-standardized death rate of endocarditis in 2020 was 0.93 (95% UI, 0.82–1.05) per 100 000 (data courtesy of the GBD Study 2020).
- Between 1999 and 2019, there were a total of 279 154 reported deaths across the United States related to IE.¹⁶⁸
 - The overall AAMR from IE in the United States declined from 54.2 per 1 million in 1999 to 51.4 per 1 million in 2019.

- AAMR from IE in the United States during this time period among annual percentage change. 0.6% (NH White change, 0.8% from 2009–1.1%). American Indian individuals (annual percentage 2009–2019 [95% CI, 0.7%–in rural areas (annual from 2009–2019 [95% CI,
- Heart Valve Procedure Costs**
- Among 190 563 patients with in the Nationwide 2012 and 2016, the average inpatient costs starting with months were as follows: for went SAVR, \$59 743; TAVR, therapy, \$23 460. TAVR costs and were similar to SAVR 2016.¹⁶⁹

Table 23-1. Global Mortality and Prevalence of Nonrheumatic Calcific Aortic Valve Disease, by Sex, 2021

	Both sexes		Males		Females	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	0.14 (0.12 to 0.16)	13.32 (11.42 to 15.25)	0.06 (0.05 to 0.06)	7.30 (6.26 to 8.34)	0.08 (0.07 to 0.09)	6.02 (5.14 to 6.90)
Percent change (%) in total number, 1990–	145.47 (122.89 to 160.95)	184.21 (170.20 to 198.41)	135.81 (117.36 to 151.78)	192.90 (179.17 to 207.41)	152.95 (124.95 to 169.55)	174.35 (159.53 to 190.78)
Percent change (%) in total	36.06 (31.62 to 39.58)	35.87 (31.28 to 40.71)	39.76 (35.02 to 43.88)	37.90 (32.82 to 43.91)	33.51 (27.97 to)	33.49 (28.71 to 38.17)
Rate per 100 000, age standardized	1.83 (1.54 to 2.00)	158.35 (135.92 to 181.00)	1.89 (1.66 to 2.02)	193.24 (166.56 to 220.38)	1.73 (1.40 to 1.95)	128.88 (110.13 to 147.63)
Percent change (%) in rate, age	–5.03 (–12.20 to –0.20)	22.04 (16.30 to 28.85)	–2.68 (–9.33 to 2.58)	23.62 (17.67 to 29.94)	–5.98 (–14.07 to –0.84)	19.09 (13.09 to 26.84)
Percent change (%) in rate, age	–7.20 (–9.39 to –5.00)	–1.62 (–4.93 to 2.01)	–3.12 (–5.85 to –0.65)	–0.31 (–4.14 to 3.99)	–9.56 (–12.51 to –7.01)	–3.01 (–6.48 to 0.33)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁴

Table 23-2. Global Prevalence and Mortality of Nonrheumatic Degenerative Mitral Valve Disease, 2021

	Both sexes		Males		Females	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	0.04 (0.03 to 0.04)	15.49 (14.46 to 16.70)	0.01 (0.01 to 0.02)	9.83 (9.18 to 10.62)	0.02 (0.02 to 0.03)	5.67 (5.28 to 6.07)
Percent change (%) in total number, 1990–	53.81 (40.02 to 68.23)	117.87 (112.40 to 122.81)	65.55 (52.10 to 84.45)	127.29 (121.24 to 132.62)	47.28 (29.97 to 66.08)	103.26 (98.49 to 107.99)
Percent change (%) in total	27.15 (22.08 to 32.01)	31.57 (28.00 to 33.66)	33.61 (27.71 to 39.69)	33.72 (29.47 to 36.16)	23.43 (17.25 to 30.01)	28.00 (25.31 to 29.98)
Rate per 100 000, age stan-	0.46 (0.39 to 0.51)	182.13 (169.95 to 196.07)	0.41 (0.36 to 0.46)	257.92 (240.96 to 278.21)	0.49 (0.40 to 0.57)	121.11 (112.92 to 129.82)
Percent change (%) in rate, age	–36.05 (–40.73 to –30.59)	–5.65 (–7.74 to –3.71)	–30.37 (–35.19 to –23.57)	–5.30 (–7.51 to –3.21)	–38.59 (–44.64 to –31.28)	–9.97 (–11.98 to –7.93)
Percent change (%) in rate, age	–9.53 (–12.69 to –6.40)	–5.31 (–7.88 to –3.86)	–3.71 (–7.58 to 0.42)	–4.77 (–7.76 to –2.99)	–11.87 (–15.84 to –7.17)	–7.06 (–8.99 to –5.61)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full

time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

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Table 23-3. Rheumatic Fever/Rheumatic HD in the United States

Population group	Mortality, 2022: all ages*	Age-adjusted mortality rates per 100 000 (95%
Both sexes	4294	1.0 (1.0–1.1)
Males	1522 (35.4%)†	0.8 (0.8–0.9)
Females	2772 (64.6%)†	1.2 (1.1–1.2)
NH White males	1196	0.9 (0.9–1.0)
NH White females	2227	1.3 (1.2–1.3)
NH Black males	125	0.7 (0.6–0.8)
NH Black females	240	1.0 (0.8–1.1)
Hispanic males	112	0.6 (0.4–0.7)
Hispanic females	167	0.7 (0.6–0.8)
NH Asian males	55‡	0.6 (0.4–0.8)‡
NH Asian females	92‡	0.7 (0.6–0.9)‡
NH American Indian or Alaska Native	31	1.2 (0.8–1.8)
NH Hawaiian or Pacific Islander	15	Unreliable (1.4–4.2)

Ellipses (...) indicate data not available; HD, heart disease; and NH, non-Hispanic.

*Mortality for American Indian or Alaska Native people and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native decedents, Asian decedents, Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses. †These percentages represent the portion of total mortality that is for males vs females.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Mortality (for underlying cause of rheumatic fever/rheumatic HD): Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System¹; and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research²; data represent underlying cause of death only.

Table 23-4. Global Mortality and Prevalence of Rheumatic HD by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	0.37 (0.32 to 0.44)	54.79 (43.33 to 67.61)	0.16 (0.13 to 0.24)	24.71 (19.41 to 30.54)	0.21 (0.18 to 0.26)	30.08 (24.11 to 37.04)
Percent change (%) in total	–10.76 (–25.98 to 7.00)	69.43 (65.40 to 73.38)	–11.86 (–25.67 to 10.18)	67.36 (63.40 to 71.38)	–9.91 (–32.39 to 24.40)	71.16 (66.76 to 75.45)
Percent change (%) in total	–2.86 (–17.09 to 12.18)	17.88 (16.66 to 19.30)	–9.19 (–23.45 to 7.61)	16.83 (15.63 to 18.29)	2.54 (–16.58 to 29.14)	18.76 (17.27 to 20.49)
Rate per 100 000, age	4.47 (3.89 to 5.31)	684.20 (540.41 to 848.90)	4.22 (3.54 to 6.19)	614.20 (482.58 to 761.31)	4.72 (4.01 to 5.82)	754.77 (600.82 to 936.66)
Percent change (%) in rate, age	–56.22 (–63.78 to –47.51)	12.58 (10.34 to 14.39)	–56.53 (–63.31 to –45.71)	12.08 (10.42 to 13.66)	–56.21 (–67.27 to –40.07)	13.28 (10.51 to 15.63)
Percent change (%) in rate, age	–25.81 (–36.61 to –14.67)	5.26 (4.30 to 6.15)	–30.18 (–41.15 to –17.82)	4.39 (3.27 to 5.44)	–22.19 (–36.53 to –2.34)	6.11 (4.97 to 7.42)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; HD, heart disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁴

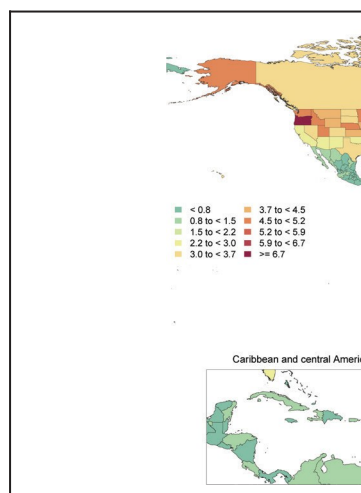


Chart 23-1. Age-standardized mortality rates of nonrheumatic calcific aortic valve disease per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

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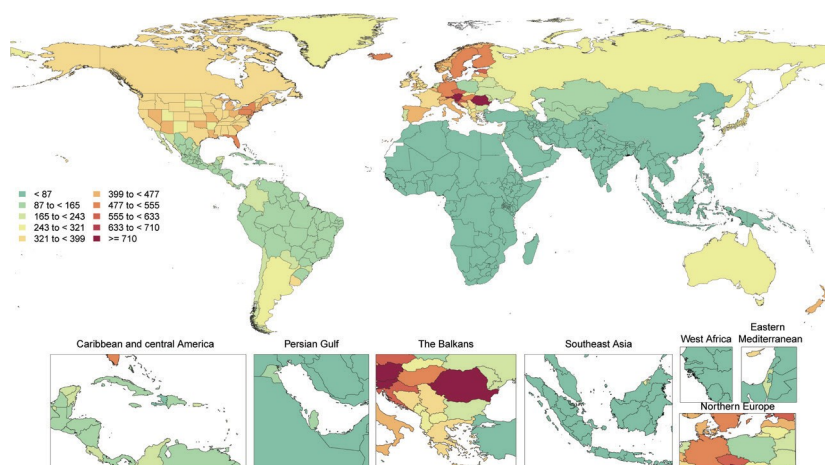


Chart 23-2. Age-standardized prevalence rates of nonrheumatic calcific aortic valve disease per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

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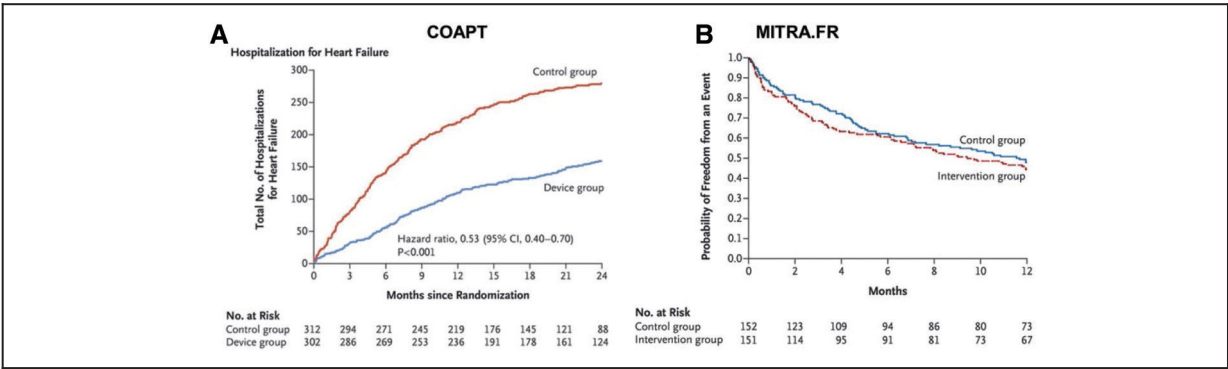


Chart 23-3. Comparison of primary outcomes after MitraClip implantation for secondary MR in the COAPT and MITRA-FR trials.

A, COAPT trial. **B**, MITRA-FR trial.
COAPT indicates Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional; MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; and MR, mitral regurgitation. Source: **A**, Reprinted from Stone et al.¹²⁰ Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. **B**, Reprinted from Obadia et al.¹²¹ Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

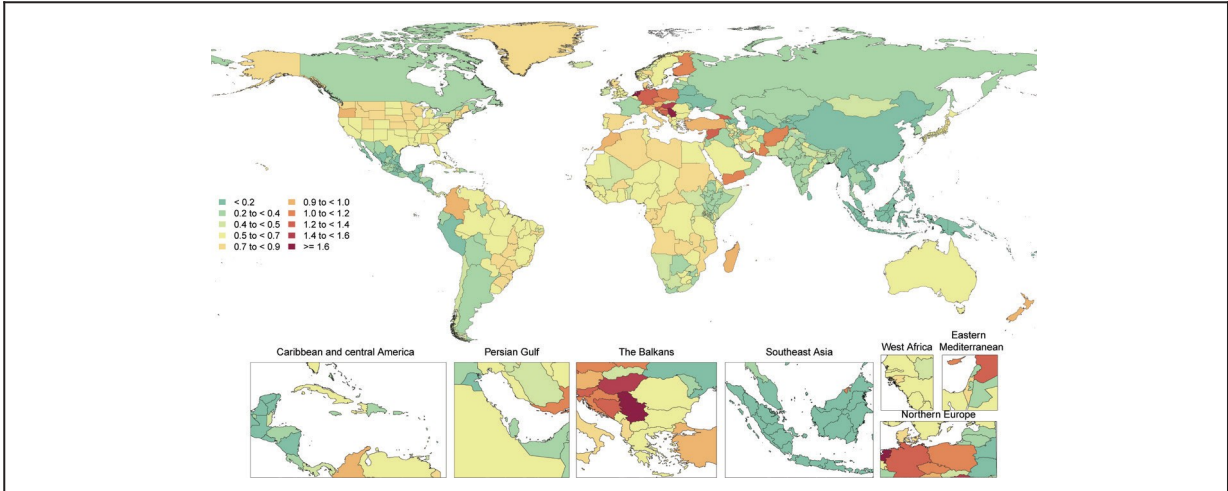


Chart 23-4. Age-standardized mortality rates of nonrheumatic degenerative mitral valve disease per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.
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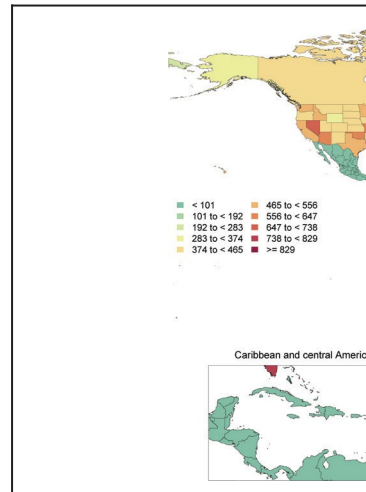


Chart 23-5. Age-standardized prevalence rates of nonrheumatic degenerative mitral valve disease per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors.

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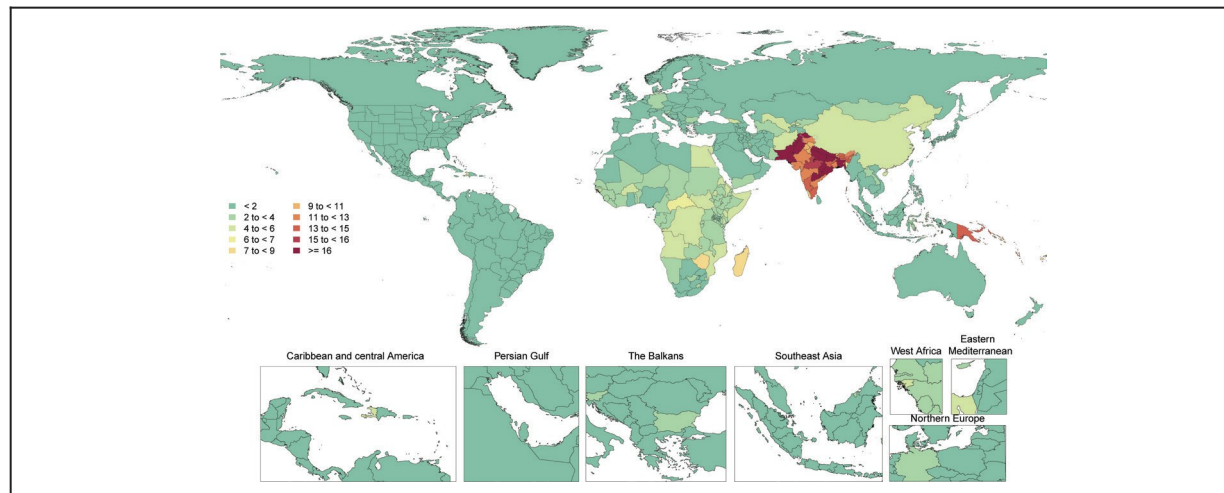


Chart 23-6. Age-standardized global mortality rates of rheumatic HD per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and HD, heart disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁴

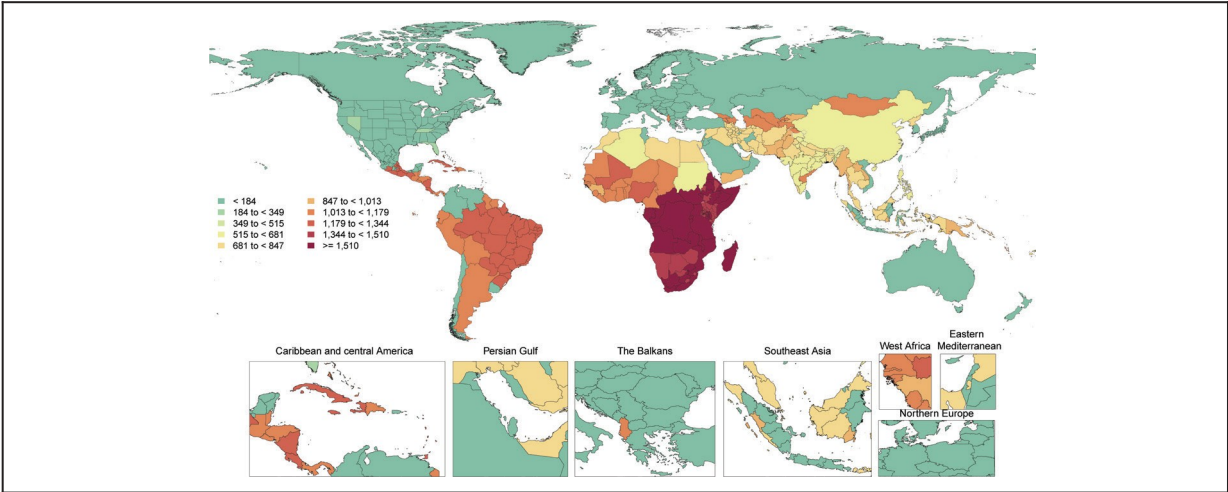


Chart 23-7. Age-standardized global prevalence rates of rheumatic HD per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and HD, heart disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁴

REFERENCES

1. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documenta-tion: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.

11. Sillesen A-S, Vøgg O, Pihl C, Raja AA, Sundberg K, Vedel C, Zingenberg H, Jørgensen FS, Vejlsstrup N, Iversen K, et al. Prevalence of bicuspid aortic valve and associated aortopathy in newborns in Copenhagen, Denmark. *JAMA*. 2021;325:561–567. doi: 10.1001/jama.2020.27205
12. Li P, Bačová M, Dalla-Pozza R, Haas NA, Oberhoffer FS. Prevalence of bicuspid aortic valve in Turner syndrome patients receiving cardiac MRI and CT: a meta-analysis. *Congenital Heart Dis*. 2022;17:129–140. doi: 10.32604/CHD.2022.018300
2. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Utilization Project (HCUP). Accessed April 1, 2024. <http://hcupn>
4. al Burden of Disease Study and Institute for Health Metrics and Evaluation. University of Washington. Accessed July 1, 2024. <http://ghdx>
3. Agency for Healthcare Research and Quality. Healthcare Cost and

13. Ahmed Y, van Bakel PAJ, Hou H, Sukul D, Likosky DS, van Herwaarden JA, Watkins DC, Ailawadi G, Patel HJ, Thompson MP, et al; Aortic Diseases Outcomes Research Workgroup Investigators. Racial and ethnic disparities in diagnosis, management and outcomes of aortic stenosis in the Medicare population. *PLoS One*. 2023;18:e0281811. doi: 10.1371/journal.pone.0281811
healthdata.org/
14. Kurasawa S, Okazaki M, Imaizumi T, Kondo T, Hishida M, Nishibori N,
5. Jaggett B, Dorbala P, Skali H, Solomon SD, Matsushita K, Konety S, Mosley TH, Shah AM. Stages of valvular heart disease among older adults in the community: the Atherosclerosis

- Takeda Y, Kasuga H, Maruyama S. Number of calcified aortic valve leaf-lets: natural history and prognostic value in patients undergoing haemodialysis. *Eur Heart J Cardiovasc Imaging*. 2023;24:909–920. doi: 10.1093/ehjci/jead020
- Risk in Communities study. *Circulation*. 2023;147:638–649. doi: 10.1161/CIRCULATIONAHA.122.061396
6. Rubin J, Aggarwal SR, Swett KR, Kirtane AJ, Kodali SK, Nazif TM, Pu M, Dadhania R, Kaplan RC, Rodriguez CJ. Burden of valvular heart diseases in hispanic/latino individuals in the united states: the Echocardiographic

15. Yang Y, Wang Z, Chen Z, Wang X, Zhang L, Li S, Zheng C, Kang Y, Jiang L, Zhu Z, et al. Current status and etiology of valvular heart disease in China: a population-based survey. *BMC Cardiovasc Disord.* 2021;21:339. doi: 10.1186/s12872-021-02154-8

Study of Latinos. *Mayo Clin Proc.* 2019;94:1488– doi: 16.

10.1016/j.mayocp.2018.12.035

7. Czarny MJ, Shah SJ, Whelton SP, Blaha MJ, Tsai MY, Denis R, Bertoni A, Post WS. Race/ethnicity and prevalence of aortic

stenosis by echocardiography in the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol.*

2021;78:195–197. doi: 10.1016/j.jacc.2021.04.078

incidence and predictors of acquired aortic stenosis in a large population of men followed for up to 43 years. *BMC Cardiovasc Disord.* 2022;22:43. doi: 10.1186/s12872-022-02487-y

17. Kaltoft M, Langsted A, Nordestgaard BG. Obesity as a causal risk factor for aortic valve stenosis. *J Am Coll Cardiol.* 2020;75:163–176. doi: 10.1016/j.jacc.2019.10.050
8. Deleted in proof.
9. Yu J, Wang Z, Bao Q, Lei S, You Y, Yin Z, Xie X. Global burden of calcific aortic valve disease and attributable risk factors from 1990 to 2019. *Front Cardiovasc Med.* 2022;9:1003233. doi: 10.3389/fcvm.2022.1003233

18. Huang N, Zhuang Z, Liu Z, Huang T. Observational and genetic associations of modifiable risk factors with aortic valve stenosis: a prospective cohort study of 0.5 million participants. *Nutrients*. 2022;14:2273. doi: 10.3390/nu14112273
- 9a. Shu S, Yang Y, Sun B, Su Z, Fu M, Xiong C, Zhang X, Hu S, Song J.

19. Kaltoft M, Langsted A, Afzal S, Kamstrup PR, Nordestgaard BG. Lipoprotein(a) and body mass compound the risk of calcific aortic valve disease. *J Am Coll Cardiol*. 2022;79:545–558. doi: 10.1093/ehjqtcc/qcad018
10. Kontogeorgos S, Thunstrom E, Basic C, Hansson PO, Zhong Y, Ergatoudes C, Morales D, Mandalenakis Z, Rosengren A, Caidahl K, et al. Prevalence and risk factors of aortic stenosis and aortic sclerosis: a 21-year follow-up of middle-aged men. *Scand Cardiovasc J*. 2020;54:115–123. doi: 10.1080/14017431.2019.1685126

20. Wodaje T, Littmann K, Häbel H, Bottai M, Bäck M, Parini P, Brinck J. Plasma Lipoprotein(a) measured in routine clinical care and the association with incident calcified aortic valve stenosis during a 14-year observational period. *Atherosclerosis*. 2022;349:175–182. doi: 10.1016/j.atherosclerosis.2022.02.016

21. Sasakawa Y, Okamoto N, Fujii M, Kato J. Factors associated with aortic valve with end-stage kidney disease. *BMC* 10.1186/s12882-022-02758-v
22. Glotzbach JP, Hanson HA, Tonna JE, Horns AP, Griffin CL, Zak M, Sharma V. Tristations of prevalence and cause-specific ease and bicuspid aortic valve in a large-2023;148:637–647. doi:
23. Galian-Gav L, Carro Hevia A, Teixido-Tura G, Gutierrez-Moreno L, Maldonado G, A. Galleo P, Calvo-Iglesias F, et al: clustering of bicuspid aortic valve and its tic dilation in first-degree relatives. *Heart*. 2019;105:603–608. doi: 10.1136/heartjnl-2018-313802
24. Padang R, Bagnall RD, Richmond DR, Bannon PG, Semsarian C. Rare non-synonymous variations in the transcriptional activation domains of GATA5 in bicuspid aortic valve disease. *J Mol Cell Cardiol*. 2012;53:277–281. doi: 10.1016/j.jmcc.2012.05.009
25. Yang B, Zhou W, Jiao J, Nielsen JB, Mathis MR, Heydarpour M, Lettre G, Folkersen L, Prakash S, Schurmann C, et al. Protein-altering and regulatory genetic variants near GATA4 implicated in bicuspid aortic valve. *Nat Commun*. 2017;8:15481. doi: 10.1038/ncomms15481
26. Xu YJ, Di RM, Qiao Q, Li XM, Huang RT, Xue S, Liu XY, Wang J, Yang YQ. GATA6 loss-of-function mutation contributes to congenital bicuspid aortic valve. *Gene*. 2018;663:115–120. doi: 10.1016/j.gene.2018.04.018
27. Luyckx I, MacCarrick G, Kempers M, Meester J, Geryl C, Rombouts O, Peeters N, Claes C, Boeckx N, Sakalihasan N, et al. Confirmation of the role of pathogenic SMAD6 variants in bicuspid aortic valve-related aortopathy. *Eur J Hum Genet*. 2019;27:1044–1053. doi: 10.1038/s41431-019-0363-z
28. Hanchard NA, Swaminathan S, Bucacas K, Furthner D, Fernbach S, Azamian MS, Wang X, Lewin M, Towbin JA, D'Alessandro LC, et al. A genome-wide association study of congenital cardiovascular left-sided lesions shows association with a locus on chromosome 20. *Hum Mol Genet*. 2016;25:2331–2341. doi: 10.1093/hmg/ddw071
29. Fulmer D, Toomer K, Guo L, Moore K, Glover J, Moore R, Stairley R, associations of genetically predicted hepatic LPA gene expression levels delian randomization and 2021;14:e003271. doi:
38. Theriault S, Dina C, Messika-Zeitoun D, Gaudreault N, Riade S, Li Z, Simonet Group. Genetic association analyses new susceptibility genes underlying *Precis Med*. 2019;12:e002617. doi:
39. Helgadóttir A, Thorleifsson G, Thorólfsson RB, Jónsdóttir I, et al. Genome-wide analysis yields stenosis. *Nat Commun*. 2018;9:987
- Lobo G, Zuo X, Dang Y, et al. Defects in the exocyst-cilia machinery cause bicuspid aortic valve disease and aortic stenosis. *Circulation*. 2019;140:1331–1341. doi: 10.1161/CIRCULATIONAHA.119.038376
30. Björnsson T, Thorólfsson RB, Sveinbjörnsson G, Sulem P, Norddahl GL, Helgadóttir A, Gretarsdóttir S, Magnúsdóttir A, Danielsen R, Sigurdsson EL, et al. A rare missense mutation in MYH6 associates with non-syndromic coarctation of the aorta. *Eur Heart J*. 2018;39:3243–3249. doi: 10.1093/eurheartj/ehy142
31. Gould RA, Aziz H, Woods CE, Seman-Senderos MA, Sparks E, Preuss C, Wunnemann F, Bedja D, Moats CR, McClymont SA, et al; Baylor-Hopkins Center for Mendelian Genomics, MIBAVA Leducq Consortium. *ROBO4* variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. *Nat Genet*. 2019;51:42–50. doi: 10.1038/s41588-018-0265-y
32. Martinsson A, Li X, Zoller B, Andell P, Andersson C, Sundquist K, Smith JG. Familial aggregation of aortic valvular stenosis: a nationwide study of sibling risk. *Circ Cardiovasc Genet*. 2017;10:e001742. doi: 10.1161/circgenetics.117.001742
33. Gehlen J, Stundl A, Debiec R, Fontana F, Krane M, Sharipova D, Nelson CP, Al-Kassou B, Giel AS, Sinning JM, et al. Elucidation of the genetic causes of bicuspid aortic valve disease. *Cardiovasc Res*. 2023;119:857–866. doi:

40. Theriault S, Gaudreault N, Lamontagne M, Rosa M, Boulanger MC, Messika-Zeitoun D, Clavel MA, Capoulade R, Dagenais F, Pibarot P, et al. A transcriptome-wide association study identifies *PALMD* as a susceptibility gene for calcific aortic valve stenosis. *Nat Commun*. 2018;9:988. doi: 10.1038/s41467-018-03260-6
41. Small AM, Peloso G, Linefsky J, Aragam J, Galloway A, Tanukonda V, Wang LC, Yu Z, Sunitha Selvaraj M, Farber-Eger EH, et al. Multiancestry genome-wide association study of aortic stenosis identifies multiple novel loci in the Million Veteran Program. *Circulation*. 2023;147:942–955. doi: 10.1161/CIRCULATIONAHA.122.061451
42. Theriault S, Li ZL, Abner E, Luan JA, Manikpurage HD, Houessou U, Zamani P, Briend M, Team EBR, Boudreau DK, et al. Integrative genomic analyses identify candidate causal genes for calcific aortic valve stenosis involving tissue-specific regulation. *Nat Commun*. 2024;15:2407. doi: 10.1038/s41467-024-46639-4
43. Smith JG, Luk K, Schulz CA, Engert JC, Do R, Hindy G, Rukh G, Dufresne L, Almgren P, Owens DS, et al. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. *JAMA*. 2014;312:1764–1771. doi: 10.1001/jama.2014.13959
44. Perrot N, Valerio V, Moschetta D, Boekholdt SM, Dina C, Chen HY, Abner E, Martinsson A, Manikpurage HD, Rigade S, et al. Genetic and in vitro inhibition of PCSK9 and calcific aortic valve stenosis. *JACC Basic Transl Sci*. 2020;5:649–661. doi: 10.1016/j.jacbts.2020.05.004
45. Nazarzadeh M, Pinho-Gomes AC, Smith Byrne K, Canoy D, Raimondi F, Ayala Solares JR, Otto CM, Rahimi K. Systolic blood pressure and risk of valvular heart disease: a mendelian randomization study. *JAMA Cardiol*. 2019;4:788–795. doi: 10.1001/jamacardio.2019.2202
46. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, Kotrc M, Glaveckaite S, Gasparovic H, Pavlovic N, et al. Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. *Circulation*. 2022;145:648–658. doi: 10.1161/circulationaha.121.057639
47. El-Hamamsy I, Toyoda N, Itagaki S, Stelzer P, Varghese R, Williams EE, Erogoval N, Adams DH. Propensity-matched comparison of the Ross procedure and prosthetic aortic valve replacement in adults. *J Am Coll Cardiol*. 2022;79:805–815. doi: 10.1016/j.jacc.2021.11.057
48. Yokoyama Y, Kuno T, Toyoda N, Fujisaki T, Takagi H, Itagaki S, Ibrahim M, Ouzounian M, El-Hamamsy I, Fukuhara S. Ross procedure versus mechanical versus bioprosthetic aortic valve replacement: a network meta-analysis. *J Am Heart Assoc*. 2023;12:e8066. doi: 10.1161/jaha.122.027715
49. Lansac E, Di Cetta I, Danial P, Bouchot O, Arnaud-Crozat E, Hacini R, Doguet F, Demaria R, Verhoye JP, Jouan J, et al. Aortic valve repair versus mechanical valve replacement for root aneurysm: the CAVIAAR multicentric study. *Eur J Cardiothorac Surg*. 2022;62:ezac283. doi: 10.1093/cvr/cvac099
34. Cordova-Palomera A, Tcheandjie C, Fries JA, Varma P, Chen VS, Fiterau M, Xiao K, Tejeda H, Keavney BD, Cordell HJ, et al. Cardiac imaging of aortic valve area from 34 287 UK Biobank participants reveals novel genetic associations and shared genetic comorbidity with multiple disease phenotypes. *Circ Genom Precis Med*. 2020;13:e003014. doi: 10.1161/CIRCGEN.120.003014
35. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, Kerr KF, Pechlivanis S, Budoff MJ, Harris TB, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368:503–512. doi: 10.1056/NEJMoa1109034
36. Perrot N, Theriault S, Dina C, Chen HY, Boekholdt SM, Rigade S, Despres AA, Poulin A, Capoulade R, Le Tourneau T, et al. Genetic variation in LPA, calcific aortic valve stenosis in patients undergoing cardiac surgery, and familial risk of aortic valve microcalcification. *JAMA Cardiol*. 2019;4:620–627. doi: 10.1001/jamacardio.2019.1581
37. Guertin J, Kaiser Y, Manikpurage H, Perrot N, Bourgeois R, Couture C, Wareham NJ, Bossé Y, Pibarot P, Stroes ESG, et al. Sex-specific

50. Russo MJ, Thourani VH, Cohen DJ, Malaisrie SC, Szeto WY, George I, Kodali SK, Makkar R, Lu M, Williams M, et al. Minimally invasive versus full sternotomy for isolated aortic valve replacement in low-risk patients. *Ann Thorac Surg.* 2022;114:2124–2130. doi: 10.1016/j.athoracsur.2021.11.048 51. Telyuk P, Hancock H, Maier R, Batty JA, Goodwin A, Owens WA, Ogundimu E, Akowuah E. Long-term outcomes of mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised controlled trial. *Eur J Cardiothorac Surg.* 2022;63:ezac540. doi: 10.1093/ejcts/ezac540 52. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol.* 2020;76:2492–2516. doi: 10.1016/j.jacc.2020.09.595 53. Toff WD, Hildick-Smith D, Kovac J, Mullen MJ, Wendler O, Mansouri A, Rombach I, Abrams KR, Conroy SP, Flather MD, et al; UK TAVI Trial Investigators. Effect of transcatheter aortic valve implantation vs surgical aortic valve replacement on all-cause mortality in patients with aortic

- stenosis: a randomized clinical trial. *JAMA*. 2022;327:1875–1887. doi: 10.1001/jama.2022.5776
54. Alkhouli M, Holmes DR Jr, Carroll JD, Li Z, Inohara T, Kosinski AS, Szerlip M, Thourani VH, Mack MJ, Vemulapalli S. Racial disparities in the utilization and outcomes of TAVR: TVT Registry report. *JACC Cardiovasc Interv*. 2019;12:936–948. doi: 10.1016/j.jcin.2019.03.007
55. Beyersdorf F, Bauer T, Freemantle N, Walther T, Frerker C, Herrmann E, Bleiziffer S, Möllmann H, Landwehr S, Ensminger S, et al. Five-year outcome in 18 010 patients from the German Aortic Valve Registry. *Eur J Cardiothorac Surg*. 2021;60:1139–1146. doi: 10.1093/ejcts/ezab216
56. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN. Placement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484. doi: 10.1016/s0140-6736(15)60308-7
57. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, Kleiman NS, Chetcuti S, Hermiller JB Jr, Heiser J, et al; CoreValve USPHRTCI. 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol*. 2018;72:2687–2696. doi: 10.1016/j.jacc.2018.08.2146
58. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321–1331. doi: 10.1056/NEJMoa1700456
59. Van Mieghem NM, Deeb GM, Søndergaard L, Grube E, Windecker S, lower surgical risk patients. *Circulation*. 2019;139:2714–2723. doi: 10.1161/CIRCULATIONAHA.118.036606
70. Fu J, Popal MS, Li Y, Li G, Qi Y, Fang F, Kwong JSW, You B, Meng X, Du J. Transcatheter versus surgical aortic valve replacement in low and intermediate risk patients with severe aortic stenosis: systematic review and meta-analysis of randomized controlled trials and propensity score matching observational studies. *J Thorac Dis*. 2019;11:1945–1962. doi: 10.21037/jtd.2019.04.97
71. Vemulapalli S, Carroll JD, Mack MJ, Li Z, Dai D, Kosinski AS, Kumbhani DJ, Ruiz CE, Thourani VH, Hanzel G, et al. Procedural volume and outcomes for transcatheter aortic-valve replacement. *N Engl J Med*. 2019;380:2541–2550. doi: 10.1056/NEJMoa1905555
- Gada H, Mumtaz M, Olsen PS, Heiser JC, Merhi W, et al. Self-expanding transcatheter vs surgical aortic valve replacement in intermediate-risk patients: 5-year outcomes of the SURTAVI randomized clinical trial. *JAMA Cardiol*. 2022;7:1000–1008. doi: 10.1001/jamacardio.2022.2695
60. Mahoney P, Newton J, Gada H, Mumtaz M, Williams M, Waksman R, Bafi A, Fail P, Netherland D, Davis T, et al. CRT-700.03 TAVR in intermediate-risk patients: 5-year outcomes from the SURTAVI Continued Access Study. *JACC Cardiovasc Interv*. 2023;16:S83–S84. doi: 10.1016/j.jcin.2023.01.268
61. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, Yoon SH, Trento A, Svensson LG, Herrmann HC, et al; PARTNER 2 Investigators. Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2020;382:799–809. doi: 10.1056/NEJMoa1910555
62. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK,

- S, Sondergaard L, De Backer O, Dalsgaard M, D'Ascenzo F, et al. Outcomes of transcatheter aortic valve replacement in patients with Low Systolic Function and Transcatheter Aortic Valve Implantation (LOSTAVI) registry. *Am J Cardiol.* 2023;201:349–358. doi: 10.1016/j.amjcard.2023.06.025
73. Abraham B, Sous M, Sedhom R, Megaly M, Roman S, Sweeney J, Alkhouli M, Pollak P, El Sabbagh A, Garcia S, et al. Meta-analysis on transcatheter aortic valve implantation: transcatheter versus transfemoral and other alternate accesses for transcatheter aortic valve implantation. *Am J Cardiol.* 2023;192:196–205. doi: 10.1016/j.amjcard.2023.01.023
74. Kirmani BH, Jones SG, Muir A, Malaisrie SC, Chung DA, Williams RJ, Akowuah E. Limited versus full sternotomy for aortic valve replacement. *Cochrane Database Syst Rev.* 2023;12:CD011793. doi: 10.1002/14651858.CD011793.pub3
75. Alboom M, Belley-Cote E, Whitlock R. LAAOS III substudy: addition of left atrial appendage occlusion in aortic valve clinic discussions to aid in decisions between SAVR and TAVR in patients with aortic stenosis. *Can J Cardiol.* 2023;39:S213–S213. doi: 10.1016/j.cjca.2023.06.326
76. Kapadia SR, Krishnaswamy A, Whisenant B, Potluri S, Iyer V, Aragon J, Gideon P, Strote J, Leonardi R, Agarwal H, et al. Concomitant left atrial appendage occlusion and transcatheter aortic valve replacement among patients with atrial fibrillation. *Circulation.* 2024;149:734–743. doi: 10.1161/CIRCULATIONAHA.123.067312
77. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, Yun SC, Hong GR, Song JM, Chung CH, et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med.* 2020;382:111–119. doi: 10.1056/NEJMoa1912846
- Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med.* 2016;374:1609–1620. doi: 10.1056/NEJMoa1514616
63. Madhavan MV, Kodali SK, Thourani VH, Makkar R, Mack MJ, Kapadia S, Webb JG, Cohen DJ, Herrmann HC, Williams M, et al. Outcomes of SAPIEN 3 transcatheter aortic valve replacement compared with surgical valve replacement in intermediate-risk patients. *J Am Coll Cardiol.* 2023;82:109–123. doi: 10.1016/j.jacc.2023.04.049
64. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia

78. Tribouilloy C, Bohbot Y, Rusinaru D, Belkhir K, Diouf M, Altes A, Delpierre Q, Serbout S, Kubala M, Levy F, et al. Excess mortality and undertreatment of women with severe aortic stenosis. *J Am Heart Assoc.* 2021;10:e018816. doi: 10.1161/JAHA.120.018816
79. Alcón B, Martínez-Legazpi P, Stewart S, Gonzalez-Mansilla A, Cuadrado V, Strange G, Yotti R, Cascos E, Delgado-Montero A, Prieto-Arévalo R, et al. Transvalvular jet velocity, aortic valve area, mortality, and cardiovascular outcomes. *Eur Heart J Cardiovasc Imaging.* 2022;23:601–612. doi: 10.1093/ehjci/jeac003
- SR, Malaisrie SC, Cohen DJ, Pibarot P, et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* 2019;380:1695–1705. doi: 10.1056/NEJMoa1814052
65. Mack MJ, Leon MB, Thourani VH, Pibarot P, Hahn RT, Genereux P, Kodali SK, Kapadia SR, Cohen DJ, Pocock SJ, et al. Transcatheter aortic-valve replacement in low-risk patients at five years. *N Engl J Med.* 2023;389:1949–1960. doi: 10.1056/NEJMoa2307447
66. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* 2019;380:1706–1715. doi: 10.1056/NEJMoa1816885
67. Forrest JK, Deeb GM, Yakubov SJ, Rovin JD, Mumtaz M, Gada H, O'Hair D, Bajwa T, Sorajja P, Heiser JC, et al. 2-Year outcomes after transcatheter versus surgical aortic valve replacement in low-risk patients. *J Am Coll*

80. Stewart S, Afoakwah C, Chan YK, Strom JB, Playford D, Strange GA. Counting the cost of premature mortality with progressively worse aortic stenosis in Australia: a clinical cohort study. *Lancet Healthy Longev.* 2022;3:e599–e606. doi: 10.1016/s2666-7568(22)00168-4
81. Strom JB, Playford D, Stewart S, Li S, Shen C, Xu J, Strange G. Increasing risk of mortality across the spectrum of aortic stenosis is independent of comorbidity & treatment: an international, parallel cohort study of 248,464 patients. *PLoS One.* 2022;17:e0268580. doi: 10.1371/journal.pone.0268580
82. Strange G, Stewart S, Playford D, Strom JB. Risk for mortality with increasingly severe aortic stenosis: an international cohort study. *J Am Soc Echocardiogr.* 2023;36:60–68.e2. doi: 10.1016/j.echo.2022.09.020
83. Li Y, Chen X, Qi Y, Qu Y, Kumar A, Dong S, Yang Y, Zhao Q. Gender differences in bicuspid aortic valve Sievers types, valvulopathy, aortopathy, and outcome of aortic valve replacement. *Echocardiography.* 2022;39:1064–1073. doi: 10.1016/j.jacc.2021.11.062
68. Awad AK, Ahmed A, Mathew DM, Varghese KS, Mathew SM, Khaja S, Newell PC, Okoh AK, Hirji S. Minimally invasive, surgical, and transcatheter aortic valve replacement: a network meta-analysis. *J Cardiol.* 2024;83:177–183. doi: 10.1016/j.jjcc.2023.08.010
69. Thyregod HGH, Ihlemann N, Jorgensen TH, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, et al. Five-year clinical and echocardiographic outcomes from the

84. Pereira SC, Abrantes AL, António PS, Morais P, Sousa C, David C, Pinto FJ, Almeida AG, Caldeira D. Infective endocarditis risk in patients with bicuspid aortic valve: systematic review and meta-analysis. *Int J Cardiol Heart Vasc.* 2023;47:101249. doi: 10.1016/j.ijcha.2023.101249
 85. Silversides CK, G J, Mason J, Sermer M, Kiess M, Rychel V, Wald RM, Colman JM, Siu SC. Pregnancy outcomes in women with heart disease: the CARPREG II study. *J Am Coll Cardiol.* 2018;71:2419–2430.
- Nordic Aortic Valve Intervention (NOTION) randomized clinical trial in

86. Al-Abdoun A, Upadhrasta S, Fashanu O, Michos ED. Transcatheter aortic valve a meta-analysis of randomized controlled 2020;21:461–466. doi: 10.1016/j.amjcard.2021.07.027
87. Mvat A, Buckner L, Mouv F, Cockburn J, Blackman DJ, Curzen N, MacCarthy P. after transcatheter aortic valve hort analysis. *Catheter Cardiovasc Interv*. 10.1002/ccd.29157
88. Bansal A, Kalra A, Puri R, Saliba W, GW. Incidence and outcomes of pericardial ponade following permanent pacemaker eter aortic valve implantation. *Am J Cardiol* 2021;127:1000–1006. doi: 10.1016/j.amjcard.2021.07.027
89. Bruno F, Munoz Pousa I, Saia F, Vaira MP, Baldi E, Leone PP, Cabanas-Grandio P, Corcione N, Spinoni EG, Annibali G, et al. Impact of right ventricular pacing in patients with TAVR undergoing
103. Yu M, Kyryachenko S, Debette S, Dina C, Norris RA, Haneke AA. sociation meta-analysis supports velonment to associate with mitral 2021;14:e003148. doi: 10.1161/STROKEAHA.121.03148
104. Brady AF, Demirdas S, Fournel-Kanferer-Seebacher I, Kosho T, M. et al. The Ehlers-Danlos *Semin Med Genet*. 2017;175:70–115.
105. Mominostar JE, Nieman A, Wang C. valve prolapse and its motley crew: oav. and progression of a common 2021;10:e020919. doi: 10.1161/JAHA.121.020919
- permanent pace- maker implantation. *JACC Cardiovasc Interv*. 2023;16:1081–1091. doi: 10.1016/j.jcin.2023.03.001

106. Chahal A, Bouatia-Naji N. Genetics of mitral valve prolapse and its clinical impact. *J Cardiol Pract.* 2019;16:35.

107. Nesta F, Leyne M, Yosefy C, Simpson C, Dai D, Marshall JE, Hung J, Slaughter SA, Levine RA. New locus for autosomal dominant mitral valve prolapse on chromosome 13: clinical insights from genetic studies. *Circulation.* 2005;112:2022–doi:10.1016/

90. Gorla R, Tua L, D'Errigo P, Barbanti M, Biancari F, Tarantini G, Badoni G, Ussia GP, Ranucci M, Bedogni F, et al. Incidence and predictors of 30-day and 6-month stroke after TAVR: insights from the multicenter OBSERVANT II study. *Catheter Cardiovasc Interv.* 2023;102:1122–1131.

- 10.1161/circulationaha.104.516930
108. Disse S, Abergel E, Berrebi A, Houot AM, Le Heuzey JY, Diebold B, Guize L, et al. Prevalence of isolated mitral dominant myxomatous mitral-valve prolapse to chromosome 16p11.2. *Am J Hum Genet.* 2012;92:114–120. doi: 10.1002/ccd.30848
91. Matta A, Regueiro A, Urena M, Nombela-Franco L, Riche M, Rodriguez-Gabella T, Amat-Santos I, Chamandi C, Akiki T, Gabani R, et al. Comparison of paravalvular leak in SAPIEN 3 and EVOLUT PRO valves in transcatheter aortic valve replacement: a multicenter registry. *Am J Cardiol.* 2023;207:114–120. doi: 10.1016/j.amjcard.2023.08.098
92. Goodall G, Lamotte M, Ramos M, Maunoury F, Pejchalova B, de Pourville G. Cost-effectiveness analysis of the SAPIEN 3 TAVI valve compared with surgery in intermediate-risk patients. *J Med Econ.* 2019;22:289–296. doi: 10.1080/13696998.2018.1559600
93. Geisler BP, Jorgensen TH, Thyregod HGH, Pietzsch JB, Sondergaard L. Cost-effectiveness of transcatheter versus surgical aortic valve replacement in patients at lower surgical risk: results from the NOTION trial. *EuroIntervention.* 2019;15:e959–e967. doi: 10.4244/EIJ-D-18-00847
94. Galper BZ, Chinnakondepalli KM, Wang K, Magnuson EA, Lu M, Thourani VH, Kodali S, Makkar R, Herrmann HC, Kapadia S, et al. Economic outcomes of transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis and low surgical risk: results from the PARTNER 3 trial. *Circulation.* 2023;147:1594–1605. doi: 10.1161/circulationaha.122.062481
- Carpentier A, Corvol P, Jeunemaitre X. Mapping of a first locus for autosomal dominant mitral valve prolapse to chromosome 16p11.2. *Am J Hum Genet.* 1999;65:1242–1251. doi: 10.1086/302624
95. Wei S, Miranda JJ, Mamas MA, Zuhlke LJ, Kontopantelis E, Thabane L, Van Spall HGC. Sex differences in the etiology and burden of heart failure across country income level: analysis of 204 countries and territories 1990–2019. *Eur Heart J Qual Care Clin Outcomes.* 2022;9:662–672. doi: 10.1093/ehjqcco/qcac088
96. Delling FN, Gona P, Larson MG, Lehman B, Manning WJ, Levine RA, Benjamin EJ, Vasan RS. Mild expression of mitral valve prolapse in the Framingham offspring: expanding the phenotypic spectrum. *J Am Soc Echocardiogr.* 2014;27:17–23. doi: 10.1016/j.echo.2013.09.015
97. Delling FN, Rong J, Larson MG, Lehman B, Fuller D, Osypiuk E, Stantchev P, Hackman B, Manning WJ, Benjamin EJ, et al. Evolution of mitral valve prolapse: insights from the Framingham Heart Study. *Circulation.* 2016;133:1688–1695. doi: 10.1161/circulationaha.115.020621
98. Durst R, Sauls K, Peal DS, deVlaming A, Toomer K, Leyne M, Salani M, Talkowski ME, Brand H, Perrocheau M, et al. Mutations in *DCHS1*

109. Le Tourneau T, Le Scouarnec S, Cueff C, Bernstein D, Aalberts JJJ, Lecointe S, Merot J, Bernstein JA, Oomen T, Dina C, et al. New insights into mitral valve dystrophy: a Filamin-A genotype-phenotype and outcome study. *Eur Heart J*. 2018;39:1269–1277. doi: 10.1093/eurheartj/ehx505

110. Delling FN, Li X, Li S, Yang Q, Xanthakis V, Martinsson A, Andell P, Lehman BT, Osypiuk EW, Stantchev P, et al. Heritability of mitral regurgitation: observations from the Framingham Heart Study and Swedish population. *Circ Cardiovasc Genet*. 2017;10:e001736. doi: 10.1161/circgenetics.117.001736

111. Delling FN, Rong J, Larson MG, Lehman B, Osypiuk E, Stantchev P, Slaughter SA, Benjamin EJ, Levine RA, Vasani RS. Familial clustering of mitral valve prolapse in the community. *Circulation*. 2015;131:263–268. doi: 10.1161/circulationaha.114.012594

112. van Wijngaarden AL, Hiemstra YL, Koopmann TT, Ruivenkamp CAL, Aten E, Schali J MJ, Bax JJ, Delgado V, Barge-Schaapveld D, Ajmone Marsan N. Identification of known and unknown genes associated with mitral valve prolapse using an exome slice methodology. *J Med Genet*. 2020;57:843–850. doi: 10.1136/jmedgenet-2019-106715

113. Roselli C, Yu MY, Nauffal V, Georges A, Yang Q, Love K, Weng LC, Delling FN, Maurya SR, Schrölkamp M, et al. Genome-wide association study reveals novel genetic loci: a new polygenic risk score for mitral valve prolapse. *Eur Heart J*. 2022;43:1668–1680. doi: 10.1093/eurheartj/ehac049

114. Yu MY, Tcheandjieu C, Georges A, Xiao K, Tejeda H, Dina C, Le Tourneau T, Fitterau M, Judy R, Tsao NL, et al. Computational estimates of annular diameter reveal genetic determinants of mitral valve function and disease. *Jci Insight*. 2022;7:e146580. doi: 10.1172/jci.insight.146580

115. Mack M, Carroll JD, Thourani V, Vemulapalli S, Squiers J, Manandhar P, Deeb GM, Batchelor W, Herrmann HC, Cohen DJ, et al. Transcatheter mitral valve therapy in the United States: a report from the STS-ACC TVT Registry. *J Am Coll Cardiol*. 2021;78:2326–2353. doi: 10.1016/j.jacc.2021.07.058

116. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engoron E, et al; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1025–1035. doi: 10.1056/NEJMoa1011484

99. Toomer KA, Yu M, Fulmer D, Guo L, Moore KS, Moore R, Drayton KD, Glover J, Peterson N, Ramos-Ortiz S, et al. Primary cilia defects causing mitral valve prolapse. *Sci Transl Med*. 2019;11:eaax0290. doi: 10.1126/scitranslmed.aax0290

100. Yu M, Georges A, Tucker NR, Kyryachenko S, Toomer K, Schott JJ, Delling FN, Fernandez-Friera L, Solis J, Ellinor PT, et al. Genome-wide association study-driven gene-set analyses, genetic, and functional follow-up suggest *GLIS1* as a susceptibility gene for mitral valve prolapse. *Circ Genom Precis Med*. 2019;12:e002497. doi: 10.1161/CIRCGEN.119.002497

101. Le Tourneau T, Merot J, Rimbert A, Le Scouarnec S, Probst V, Le Marec H, Levine RA, Schott JJ. Genetics of syndromic and non-syndromic mitral valve prolapse. *Heart*. 2018;104:978–984. doi: 10.1136/heartjnl-2017-312420

102. Trenkwalder T, Krane M. Mitral valve prolapse: will genetics finally solve the puzzle? *Eur Heart J*. 2022;43:1681–1683. doi: 10.1093/eurheartj/ehac048

- Gillinov M, Moskowitz A, Gelijns A. Trends in MitraClip, mitral valve repair, and mitral valve replacement from 2000 to 2016. *J Thorac Cardiovasc Surg*. 2021;162:551–562.e4. doi: 10.1016/j.jtcvs.2019.12.097
118. Wong N, Yeo KK. MitraClip in Asia: current adoption and regional data. *Circ Rep*. 2019;1:397–400. doi: 10.1253/circrep.CR-19-0074
119. Wojakowski W, Baumgartner H. The year in cardiology 2018: valvular heart disease. *Eur Heart J*. 2019;40:414–421. doi: 10.1093/eurheartj/ehy893 120.
- Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318. doi: 10.1056/NEJMoa1806640
121. Obadia JF, Messika-Zeitoun D, Leurent G, lung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297–2306. doi: 10.1056/NEJMoa1805374

- 121a. Stone GW, Abraham WT, Lindenfeld J, Kar S, Grayburn PA, Lim DS, Mishell JM, Whisenant B, Rinaldi M, Kapadia SR, et al. Five-year follow-up after transcatheter repair of secondary mitral regurgitation. *N Engl J Med*. 2023;388:2037–48. doi: 10.1056/NEJMoa2300213
122. Ludwig S, Conradi L, Cohen DJ, Coisne A, Scotti A, Abraham WT, Ben Ali W, Zhou Z, Li Y, Kar S, et al. Transcatheter mitral valve replacement versus medical therapy for secondary mitral regurgitation: a propensity score-matched comparison. *Circ Cardiovasc Interv*. 2023;16:e013045. doi: 10.1161/circinterventions.123.013045
123. Ahmed A, Awad AK, Varghese KS, Sehgal VS, Hisham K, George J, Pandey R, Vega E, Polizzi M, Mathew DM. Bioprosthetic versus mechanical valves for mitral valve replacement in patients < 70 years: an updated pairwise meta-analysis. *Gen Thorac Cardiovasc Surg*. 2024;72:95–103. doi: 10.1007/s11748-023-01956-1
- TH, Pahwa S, Dixon LK, Slaughter MS, Gerosa G. Surgical ablation for atrial fibrillation during mitral valve surgery: a systematic review and meta-analysis of randomized controlled trials. *Am J Cardiol*. 2023;209:104–113.
- transcatheter heart valve system. *EuroIntervention*. 2019;14:1378–1385. doi: 10.4244/EIJ-D-18-01035
138. Chatterjee A, Bajaj NS, McMahon WS, Cribbs MG, White JS, Mukherjee A, Law MA. Transcatheter pulmonary valve implantation: a comprehensive systematic review and meta-analyses of observational studies. *J Am Heart Assoc*. 2017;6:e006432. doi: 10.1161/JAHA.117.006432
139. Haas NA, Carere RG, Kretschmar O, Horlick E, Rodes-Cabau J, de Wolf D, Gewillig M, Mullen M, Lehner A, Deutsch C, et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN XT transcatheter heart valve system. *Int J Cardiol*. 2018;250:86–91. doi: 10.1016/j.ijcard.2017.10.015
140. Patel A, Patel A, Bhatt P, Savani C, Thakkar B, Sonani R, Patel doi: 10.1016/j.amjcard.2023.09.088
125. Dziadzko V, Clavel MA, Dziadzko M, Medina-Inojosa JR, Michelena H,

141. Lee C, Kim YM, Lee CH, Kwak JG, Park CS, Song JY, Shim WS, Choi EY, Lee SY, Baek JS. Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ven-tricular outflow tract obstruction: implications for optimal timing of pulmonary valve replacement. *J Am Coll Cardiol*. 2012;60:1005–1014. doi: 10.1016/j.jacc.2012.03.077
- Maalouf J, Nkomo V, Thapa P, Enriquez-Sarano M. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet*. 2018;391:960–969. doi: 10.1016/s0140-6736(18)30473-2
126. Giustino G, Overbey J, Taylor D, Ailawadi G, Kirkwood K, DeRose J, Gillinov MA, Dagenais F, Mayer ML, Moskowitz A, et al. Sex-based differences in outcomes after mitral valve surgery for severe ischemic mitral regurgitation: from the Cardiothoracic Surgical Trials Network. *JACC Heart Fail*.

142. Zhou Y, Xiong T, Bai P, Chu C, Dong N. Clinical outcomes of transcatheter versus surgical pulmonary valve replacement: a meta-analysis. *J Thorac Dis.* 2019;11:5343–5351. doi: 10.21037/jtd.2019.11.64
143. Kolte D, Kennedy KF, Passeri JJ, Inglessis I, Elmariah S. Temporal trends in prevalence of tricuspid valve disease in hospitalized patients in the United States. *Am J Cardiol.* 2020;125:1879–1883. doi: 10.1016/j.jchf.2019.03.001
127. Amabile A, Muncan B, Geirsson A, Kalogeropoulos AP, Krane M. Surgical versus interventional mitral valve repair: analysis of 1,100 propensity score-matched patients. *J Card Surg.* 2023;2023:1–7. doi: 10.1155/2023/8838005
128. Yadgir S, Johnson CO, Aboyans V, Adebayo OM, Adedoyin RA, Afarideh M, Alahdab F, Alashi A, Alipour V, Arabloo J, et al; Global Burden of Disease Study Nonrheumatic Valve Disease Collaborators. Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990-2017. *Circulation.* 2020;141:1670–1680. doi: 10.1161/CIRCULATIONAHA.119.043391

144. Adamo M, Chioncel O, Benson L, Shahim B, Crespo-Leiro MG, Anker SD, Coats AJS, Filippatos G, Lainscak M, McDonagh T, et al. Prevalence, clinical characteristics and outcomes of heart failure patients with or without isolated or combined mitral and tricuspid regurgitation: an analysis from the ESC-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2023;25:1061–1071. doi: 10.1002/ehf.2929
145. Alnaimat S, Doyle M, Krishnan K, Biederman RWW. Worsening tricuspid regurgitation associated with permanent pacemaker and implantable cardioverter-defibrillator implantation: a systematic review and meta-analysis of more than 66,000 subjects. *Heart Rhythm*. 2023;20:1491–1501. doi: 10.1016/j.hrthm.2023.07.064
129. Grigioni F, Benfari G, Vanoverschelde JL, Tribouilloy C, Avierinos JF, Bursi F, Suri RM, Guerra F, Pasquet A, Rusinaru D, et al; MIDA Investigators. Long-term implications of atrial fibrillation in patients with degenerative mitral regurgitation. *J Am Coll Cardiol*. 2019;73:264–274. doi: 10.1016/j.jacc.2018.10.067
130. Nazir S, Gupta T, Ahuja KR, Minhas AMK, Ariss RW, Gupta R, Goel SS, Kleiman NS. Association of peri-procedural major bleeding with outcomes in patients undergoing transcatheter mitral edge-to-edge repair. *Am J Cardiol*. 2021;152:172–174. doi: 10.1016/j.amjcard.2021.04.025
131. Ailawadi G, Lim DS, Mack MJ, Trento A, Kar S, Grayburn PA, Glower DD, Wang A, Foster E, Qasim A, et al. One-year outcomes after mitra-clip for functional mitral regurgitation. *Circulation*. 2019;139:37–47. doi: 10.1161/circulationaha.117.031733
132. Chikwe J, O'Gara P, Fremes S, Sundt TM 3rd, Habib RH, Gammie J, Gaudino M, Badhwar V, Gillinov M, Acker M, et al. Mitral surgery after trans-catheter edge-to-edge repair: Society of Thoracic Surgeons database analysis. *J Am Coll Cardiol*. 2021;78:1–9. doi: 10.1016/j.jacc.2021.04.062
133. Kaneko T, Newell PC, Nisivaco S, Yoo SGK, Hirji SA, Hou H, Romano M,

146. Safiriyu I, Mehta A, Adefuye M, Nagraj S, Kharawala A, Hajra A, Shamaki GR, Kokkinidis DG, Bob-Manuel T. Incidence and prognostic implications of cardiac-implantable device-associated tricuspid regurgitation: a meta-analysis and meta-regression analysis. *Am J Cardiol.* 2023;209:203–211. doi: 10.1016/j.amjcard.2023.09.064
147. Taramasso M, Alessandrini H, Latib A, Asami M, Attinger-Toller A, Biasco L, Braun D, Brochet E, Connelly KA, Denti P, et al. Outcomes after current transcatheter tricuspid valve intervention: mid-term results from the International TriValve Registry. *JACC Cardiovasc Interv.* 2019;12:155–165. doi: 10.1016/j.jcin.2018.10.022
148. Gammie JS, Chu MWA, Falk V, Overbey JR, Moskowitz AJ, Gillinov M, Mack MJ, Voisine P, Krane M, Yerokun B, et al. Concomitant tricuspid repair in patients with degenerative mitral regurgitation. *N Engl J Med.* 2022;386:327–339. doi: 10.1056/NEJMoa2115961
149. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P, Price MJ, Singh G, Fam N, Kar S, et al. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med.* 2023;388:1833–1842. doi: 10.1056/NEJMoa2300525
- Lim DS, Chetcuti S, Shah P, et al. Incidence, characteristics, and outcomes of reintervention after mitral transcatheter edge-to-edge repair. *J Thorac Cardiovasc Surg.* 2024;167:143–154.e6. doi: 10.1016/j.jtcvs.2022.02.060
134. Baron SJ, Wang K, Arnold SV, Magnuson EA, Whisenant B, Brieke A, Rinaldi M, Asgar AW, Lindenfeld J, Abraham WT, et al; COAPT

150. Arnold SV, Goates S, Sorajja P, Adams DH, Stephan von Bardeleben R, Kapadia SR, Cohen DJ. Health status after transcatheter tricuspid-valve repair in patients with severe tricuspid regurgitation: results from the TRILUMINATE pivotal trial. *J Am Coll Cardiol.* 2024;83:1–13. doi: 10.1016/j.jacc.2023.10.008
- Investigators. Cost-effectiveness of transcatheter mitral valve repair versus medical therapy in patients with heart failure and secondary mitral regurgitation: results from the COAPT trial. *Circulation.* 2019;140:1881–1891. doi: 10.1161/CIRCULATIONAHA.119.043275
135. Allen H, Shaddy R, Penny D, Feltes T, Cetta F. *Moss & Adams' Heart Disease In Infants, Children, and Adolescents*. 9th ed. Wolters Kluwer; 2016.
136. Aggarwal V, Mulukutla V, Maskatia S, Justino H, Mullins CE, Qureshi AM. Outcomes after balloon pulmonary valvuloplasty for critical pulmonary stenosis and incidence of coronary artery fistulas. *Am J Cardiol.* 2018;121:1617–1623. doi: 10.1016/j.amjcard.2018.02.049
137. Hascoet S, Dalla Pozza R, Bentham J, Carere RG, Kanaan M, Ewert P, Biernacka EK, Kretschmar O, Deutsch C, Lecerf F, et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN 3

151. Fareed A, Saleh O, Maklady F. Screening for the prevalence of rheumatic heart disease among school children in Egypt. *Echocardiography*. 2023;40:494–499. doi: 10.1111/echo.15580
152. Scheel A, Ssinabulya I, Aliku T, Bradley-Hewitt T, Clauss A, Clauss S, Crawford L, DeWyer A, Donofrio MT, Jacobs M, et al. Community study to uncover the full spectrum of rheumatic heart disease in Uganda. *Heart*. 2019;105:60–66. doi: 10.1136/heartjnl-2018-313171
153. Hovis IW, Namuyonga J, Kisitu GP, Ndagire E, Okello E, Longenecker CT, Sanyahumbi A, Sable CA, Penny DJ, Lwabi P, et al. Decreased prevalence of rheumatic heart disease confirmed among HIV-positive youth. *Pediatr Infect Dis J*. 2019;38:406–409. doi: 10.1097/INF.0000000000002161

154. Liao YB, Wang TKM, Wang MTM, analysis of mitral valve repair versus ic mitral valve disease. *Heart Lung Circ.* 10.1016/j.hlc.2021.11.011
155. Elzeneini M, Ashraf H, Mahmoud A, Anderson RD, Jneid H. Outcomes of mitral nair in patients with rheumatic heart 173. doi: 10.1016/j.amicard.2023.01.034
156. Jaiteh LES, Drammeh L, Anderson ST, U. Caranetis J, Mirabel M, Erhart A. Gambia: clinical and valvular aspects at der penicillin prophylaxis. *BMC Cardiovasc* 10.1186/s12872-021-02308-8
157. Wong CY, Zhu W, Aurigemma GP, Furukawa N, Teshale EH, Huang YA, Peters PJ, Hoover KW. Infective endocarditis among persons aged 18-64 years living with human immunodeficiency virus, hepatitis C infec-tion, or opioid use disorder, United States, 2007-2017. *Clin Infect Dis.* 2021;72:1767–1781. doi: 10.1093/cid/ciaa372
158. Yang X, Chen H, Zhang D, Shen L, An G, Zhao S. Global magnitude and temporal trend of infective endocarditis, 1990-2019: results from the
162. Del Val D, Abdel-Wahab M, Linke A, Pellenrini C, Giannini F, Landt M. acteristics. and outcomes of infective aortic valve replacement. *Clin Infect* 10.1093/cid/ciaa1941
163. Storteckv S, Hen D, Tueller D, Pilarim Tondweiler S, Ferrari E, Taramasso transcatheter aortic valve 3030. doi: 10.1016/j.iacc.2020.04.044
164. Iversen K, Ihlemann N, Gill SU, Hofsten DE, Fursted K, Christensen nous antibiotic treatment of 424. doi: 10.1056/NEJMoa1808312 Global Burden of Disease Study. *Eur J Prev Cardiol.* 2022;29:1277–1286. doi: 10.1093/eurjpc/zwab184
159. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in drug use- associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med.* 2019;170:31–40. doi:

165. Bundgaard H, Ihlemann N, Gill SU, Bruun NE, Elming H, Madsen T, Jensen KT, Fursted K, Christensen JJ, Schultz M, et al. Long-term outcomes of par-tial oral treatment of endocarditis. *N Engl J Med*. 2019;380:1373–1374. doi: 10.1056/NEJMc1902096
166. Friedrich C, Salem M, Puehler T, Panholzer B, Herbers L, Reimers J, Hummitzsch L, Cremer J, Haneya A. Sex-specific risk factors for short-and long-term outcomes after surgery in patients with infective endocarditis. *J Clin Med*. 2022;11:1875. doi: 10.3390/jcm11071875
167. Sambola A, Lozano-Torres J, Boersma E, Olmos C, Ternacle J, Calvo F, Tribouilloy C, Reskovic-Luksic V, Separovic-Hanzevacki J, Park SW, et al. Predictors of embolism and death in left-sided infective endocarditis: the European Society of Cardiology EURObservational Research Programme European Infective Endocarditis Registry. *Eur Heart J*. 2023;44:4566–10.7326/M18-2124
160. Katan O, Michelena HI, Avierinos JF, Mahoney DW, DeSimone DC, Baddour LM, Suri RM, Enriquez-Sarano M. Incidence and predictors of infective endocarditis in mitral valve prolapse: a population-based study. *Mayo Clin Proc*. 2016;91:336–342. doi: 10.1016/j.mayocp.2015.12.006
161. Snygg-Martin U, Giang KW, Dellborg M, Robertson J, Mandalenakis Z. Cumulative incidence of infective endocarditis in patients with congenital heart disease: a nationwide, case-control study over nine decades. *Clin Infect Dis*. 2021;73:1469–1475. doi: 10.1093/cid/ciab478

4575. doi: 10.1093/eurheartj/ehad507
168. Agha A, Nazir S, Minhas AMK, Kayani W, Issa R, Moukarbel GV, DeAnda A, tis-related mortality in the United States, 1999 to 2019. *Curr Probl Cardiol.* 2023;48:101397. doi: 10.1016/j.cpcardiol.2022.101397
169. Goldsweig AM, Tak HJ, Chen LW, Aronow HD, Shah B, Kolte D, Desai NR, eter aortic valve replacement and medical therapy. *Circ Cardiovasc Interv.* 2020;13:e008681. doi: 10.1161/CIRCINTERVENTIONS.119.008681

Cram P, Jneid H. Demographic and regional trends of infective endocardi-

Szerlip M, Velagapudi P, Abbott JD. Relative costs of surgical and transcath-

24. VENOUS THROMBOEMBOLISM
(DEEP VEIN THROMBOSIS
AND PULMONARY EMBOLISM),
CHRONIC VENOUS
INSUFFICIENCY, PULMONARY
HYPERTENSION

See Table 24-1 and Charts 24-1 through 24-4

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In this chapter, 2022 mortality data come from unpublished NHLBI tabulations using NVSS¹ and CDC WON-DER.² Hospital discharge data, from 2021, come from unpublished NHLBI tabulations using HCUP.³

Pulmonary Embolism

ICD-9 415.1; ICD-10 I26.

2022, United States: Underlying cause mortality—9114. Any-mention mortality—50 620.

2021, United States: Hospital discharges—197 080 (principal diagnosis), 523 994 (all-listed diagnoses).

Deep Vein Thrombosis

ICD-9 451.1, 451.2, 451.81, 451.9, 453.0, 453.1, 453.2, 453.3, 453.4, 453.5, 453.9; ICD-10 I80.1, I80.2, I80.3, I80.9, I82.0, I82.1, I82.2, I82.3, I82.4, I82.5, I82.9.

≈1 280 508 total VTE cases in the United States in inpatient settings. An analysis of health care claims data between 2011 and 2018 that included ≈200 000 individuals with VTE diagnosis observed that 37.6% of all patients were treated as out-patients. Moreover, a study with NHAMCS data from 2012 to

charged from the ED. The discharge rate from the ED

2022, United States: Underlying cause mortality—3473. Any-mention mortality—23 731.

2021, United States: Hospital discharges—70 450 (principal diagnosis), 756 514 (all-listed diagnoses).

Venous Thromboembolism

Incidence

(See Charts 24-1 and 24-2)

- VTE includes both PE and DVT. In 2021, there were an estimated ≈523 994 cases of PE₃ (Chart 24-1), ≈756 514 cases of DVT₃ (Chart 24-2), and

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- A study in individuals in Oklahoma (whose ethnic profile is similar to that of the US population) observed an age-standardized incidence of 2.47 (95% CI, 2.39–2.55), 1.47 (95% CI, 1.41–1.54), and 0.99 (95% CI, 0.93–1.04) per 1000 PY for VTE, DVT, and PE, respectively.⁵
 - In this analysis, the incidence in the Black population for VTE, DVT, and PE was 3.25 (95% CI, 3.02–3.49), 1.97 (95% CI, 1.80–2.16), and 1.27 (95% CI, 1.13–1.43) per 1000 PY, respectively, much higher than in NH White individuals (2.71 [95% CI, 2.61–2.63], 1.59 [95% CI, 1.50–1.67], and 1.12 [95% CI, 1.06–1.20] per 1000 PY), who have a higher incidence than Hispanic individuals (0.67 [95% CI, 0.54–0.82], 0.39 [95% CI, 0.30–0.51], and 0.27 [95% CI, 0.19–0.37] per 1000 PY) and Asian/Pacific Islander individuals (0.63 [95% CI, 0.43–0.91], 0.41 [95% CI, 0.26–0.65], and 0.22 [95% CI, 0.11–0.41] per 1000 PY).
- The MESA cohort yielded similar findings, with Black participants having an incidence rate of VTE of 4.02 per 1000 PY, which was higher compared with White participants (2.98 per 1000 PY) and Hispanic participants (2.08 per 1000 PY). These 3 ethnic groups had a higher incidence rate than Chinese participants (0.79 per 1000 PY).⁶
- Data from Medicare that involved ≈4 115 000 beneficiaries who underwent major surgeries revealed an overall 90-day rate of VTE of 2.8%.⁷ Among the major procedures, the highest rate of VTE was found in patients who underwent pancreatectomy (VTE event rate, 4.68% [95% CI, 4.32%–5.04%]) whereas the lowest event rate was found in AAA repair (VTE event rate, 2.16% [95% CI, 2.03%–2.29%]). In patients who underwent orthopedic surgery, a study of a claims database with ≈132 000 individuals showed that the 30- and 90-day cumulative incidence of VTE was 1.19% (95% CI, 1.06%–1.32%) and 1.86% (95% CI, 1.70%–2.02%), respectively.⁸
- A study using data from 73 million childbirths in the United States found a VTE incidence of 6.6 per 10 000 deliveries.⁹
- Cancer-associated thrombosis is a prevalent condition among patients with active malignancy:

- A 16-year cohort study from the Veterans Affairs the treatment of cancer incidence of 4.5%.¹⁰
- The highest incidence of noted in patients with acute leukemia (18.6%), pancreatic cancer (11.1%), aggressive phoma (11%), and gastric cer (10%). The lowest thyroid cancer (1.5%), prostate cancer (1.6%), and melanoma (1.7%).
- Several studies since 2020 COVID-19 pandemic have and prevalence of VTE in
 - Among ≈400 000 US 19 diagnosis in Northern the overall incidence of 0.24–0.30) per 100 PY.¹⁶
 - In an analysis of a health ≈546 000 hospitalized States with a COVID-19
 - VTE is a prevalent disease in the hospitalized patient

events were found in 10.0% of all hospitalized patients. The rate of DVT was 20.8% in those admitted to the ICU.¹⁷

setting:

– It is important to note that most COVID-19

stud-

- In an analysis of administrative data from 204 hospitals in Illinois involving 22 244 hospitalizations with a principal diagnosis of PE, ≈50% of patients hospitalized were <65 years of age.¹¹ In all age groups, NH Black males and females had higher rates of PE hospitalization (14.5 [95% CI, 2.0–103.2] and 16.5 [95% CI, 2.3–117.5] per 10 000 population, respectively) compared with NH White males and females (8.8 [95% CI, 1.2–62.8] and 9.3 [95% CI, 1.3–66.0] per 10 000 population, respectively). Overall, NH Black individuals were almost twice as likely to be hospital-ized for PE as NH White individuals (rate ratio, 1.9 [95% CI, 1.5–2.3]) after adjustment for age and sex.

- A study with ≈5000 patients in a Level 1 trauma center found that those who underwent screening duplex ultrasonography of the legs had an early DVT incidence of 3.3%. Furthermore, during hospitalization, 3.9% of the total sample were diagnosed with VTE.¹²
- An analysis of the National Surgical Quality Improvement Program observed a high incidence of VTE of 2.5% in 5003 patients undergoing colorectal surgery for inflammatory bowel

ies have issues related to selection bias attributable to the severity of the condition of the population admitted in most high-volume tertiary care centers and to the VTE diagnostic protocol; a routine screening showed a much higher VTE incidence compared with centers without a routine screening approach (pooled incidence, 47.5% [95% CI, 25.3%–69.7%] versus 15.1% [95% CI, 8.35%–21.9%]; $P<0.001$).¹⁸

– Data from the 2020 National Readmission Database revealed that VTE was the principal diagnosis in 22.5% among ≈645 000 readmissions of patients with COVID-19.¹⁹

– An analysis involving ≈855 000 veterans >45 years of age observed a VTE rate in those vaccinated for COVID-19 of 1.3755 events per 1000 individuals (95% CI, 1.3752–1.3758) compared with 1.3741 per 1000 individuals (95% CI, 1.3738–1.3744) in nonvaccinated control subjects.²⁰ This translates to a marginal excess of 1.4 VTE events per 1 000 000 individuals, an incidence of significantly lower magnitude compared with the COVID-19–associated VTE data.

■ Furthermore, the incidence of VTE in the population with the COVID-19 vaccine did not differ from that in individuals who received the influenza disease.¹³

- Invasive devices, particularly the size of peripherally inserted central catheters, were the focus of a 2023 meta-analysis comprising >45 000 procedures involving mostly US patients. The analysis found a pooled incidence for symptomatic DVT of 0.89% (95% CI, 0.18%–4.31%) for 3F catheters, 3.26% (95% CI, 2.12%–4.98%) for 4F catheters, 5.46% (95% CI, 3.56%–8.29%) for 5F catheters, and 10.66% (95% CI, 4.69%–22.46%) for 6F

catheters.¹⁴

- In patients with systemic lupus erythematosus, a 2023 meta-analysis observed a pooled incidence ratio of 8.04 per 1000 PY (95% CI, 4.58–11.08; 12 studies) for VTE, 3.11 per 1000 PY (95% CI, 1.73–4.86; 7 studies) for DVT, and 1.40 per 1000 PY (95% CI, 0.15–3.60; 7 studies) for PE.¹⁵

enza vaccine before the SARS-CoV-2 pan-demic (aHR, 0.95 [95% CI, 0.85–1.05]).²¹

Lifetime Risk

- The lifetime risk of VTE at 45 years of age was 8.1% (95% CI, 7.1%–8.7%) overall, 11.5% in Black individuals, 10.9% in those with obesity, 17.1% in individuals with the FVL genetic variant, and 18.2% in people with sickle cell trait or disease according to data derived from nearly 20 000 participants of 2 US cohorts who were 45 to 99 years of age.²²

Secular Trends
(See Charts 24-1 and 24-2)

- The HCUP NIS (Chart 24-1) shows increasing numbers of hospitalized cases for all-listed diagnoses of PE from 1996 to 2021, accompanied by a

progressive increase in the in-hospital death rate.

Although the all-listed diagnoses (Chart 24-2) show that the number of hospitalized DVT cases also increased from 2005 to 2021, discharges with DVT as a principal diagnosis have fallen in the past 5 years.³

- An analysis of 20-year data from CDC WONDER found an increasing mortality rate in the young adult US population.²³ Among from 2.27 (95% CI, 2.17–2.37) in 1999 to 3.20 (95% CI, 3.13–3.31) in 2019, with an annual percentage change of 1.4% (95% CI, 1.1%–1.7%).
- From 1999 to 2017, NIS data showed a consistent trend of reduced mortality rates among patients with high-risk PE, whether treated with anticoagulants alone or with thrombolytic therapy. The

on 2 distinct dates in the year before the index VTE admission.

- Hospitalized patients are at particularly high risk of VTE:
 - One study demonstrated that asymptomatic DVT was associated with a greater risk of death among acutely ill hospitalized patients (HR, 2.31 [95% CI, 1.52–3.51]).²⁹

mortality rate decreased from 72.7% in 1999 to 49.8% in 2017 ($P<0.001$), despite a clear increase in both the absolute number (104 procedures in 1999 versus 955 in 2017; $P<0.001$) and relative rate of high-risk patients treated (6.3% in 1999 versus 19.3% in 2017; $P<0.001$) with thrombolytic

associated VTE, even after adjustment: active cancer (OR, 1.96 [95% CI, 1.85–2.08]), previous VTE (OR, 1.71 [95% CI, 1.63–1.79]), central line (OR, 1.63 [95% CI, 1.53–1.73]), recent surgery or trauma (OR, 1.50 [95% CI, 1.39–1.61]), known thrombophilia (OR, 1.22 [95% CI, 1.06–1.40]), obesity (OR, 1.12 [95% CI, 1.07–1.16] for BMI >30 kg/m²), infection as cause of admission (OR, 1.07 [95% CI, 1.04–1.11]), and male sex (OR, 1.07 [95% CI, 1.03–1.10]).³⁰

- Independent VTE risk factors beyond the provoking factors noted previously:

- An individual-level study by the Emerging Risk therapy.²⁴

- Another NIS analysis from 2000 to 2018 showed a progressive increase in incidence of DVT in vaginal deliveries (average annual percent

Factors Collaboration found an association change, 2.5% [95% CI, 1.5%–3.5%]) and in incidence of PE in

between VTE incidence and age (HR per decade, 2.67 [95% CI, 2.45–2.91]), diabetes (HR, 1.69 [95% CI, 1.33–2.16]), WC (HR, 1.54 [95% CI, 1.37–1.73]), and smoking (HR, 1.38 [95% CI, 1.20–1.58]).³¹

both vaginal and cesarean deliveries (average annual percent change, 8.7% [95% CI, 6.0%–11.5%] and 4.9% [95% CI, 3.6%–6.2%], respectively).⁹

- In the maternal PE setting, mortality has remained stable between 2003 and 2020 (overall inci-

- Presence of HF was associated with a 3-fold greater VTE risk (HR, 3.13 [95% CI, 2.58–3.80]) in a 2019 publication from the ARIC study. The association was present for both HFpEF and HFrEF.³²
 dence rate per 100 000 live births, 1.02 [95% CI, 0.95–1.10]).^{10,25}
 $P < 0.001$).²⁶
- Despite increasing trends in VTE diagnosis, an 18-year study of >6 million cardiac surgeries in the United States showed a consistent reduction in inpatient deaths after VTE complications (percent-age change per year, –6.4%;
 • In the orthopedic leg surgery setting, a study using Medicare data between 2010 and 2017 found a decrease in VTE incidence after total knee arthroplasty (in-hospital incidence rate, 0.3% in 2010 and 0.1% in 2017; $P_{\text{trend}} = 0.035$).²⁷

– Autoimmune diseases such as giant-cell arthritis and polymyalgia rheumatica are risk factors for DVT (IRR, 4.12 [95% CI, 3.13–5.35] and 1.44 [95% CI, 1.20–1.72], respectively) and PE (IRR, 3.99 [95% CI, 2.63–5.81] and 1.79 [95% CI, 1.39–2.28], respectively).³³ A 2023 meta-analysis found similar risk in patients with systemic lupus erythematosus for VTE (pooled RR, 4.38 [95% CI, 2.63–7.29]; 5 studies), DVT (pooled RR, 6.35 [95% CI, 2.70–14.94]), and PE (pooled RR, 4.94 [95% CI, 1.90–12.86]).¹⁵

– An analysis of a 15-year US claims database

Risk Factors

- In a study involving 2 large databases, 32.4% of the ≈203 000 patients diagnosed with VTE among Medicare beneficiaries were considered provoked; this rate was 19.4% among ≈95 000 commercially insured individuals.²⁸ Provoked

identified an elevated risk of VTE in patients with VTE was determined if patients had a major trauma, fracture, or major surgery; if they were hospitalized for ≥3 days in the 90 days preceding the index VTE admission; or if there was a presence of a cancer diagnosis code

amyotrophic lateral sclerosis (HR, 3.30 [95% CI, 2.60–4.00]) in the occurrence of both DVT (HR, 3.20 [95% CI, 2.50–4.10]) and PE (HR, 3.60 [95% CI, 2.50–5.10]).³⁴

– Use of testosterone therapy was also associated with doubling of VTE risk in males with and without evidence of hypogonadism (aOR for VTE after 6 months, 2.02 [95% CI, 1.47–2.77] in those without hypogonadism and 2.32 [95%

Social Determinants of Health/Health Equity

- In 2020, patients from rural areas accounted for 13.7% of all DVT (95% CI, 13.0%–14.4%) hospital discharges.³
 - Although the rate of admissions for PE was higher in rural areas than in urban areas (discharges for 100 000 population, 65.6 [95% CI, 62.3–68.9] versus 47.0 [95% CI, 43.9–50.1] for patients living in large metro areas), the individual spendings were lower for rural inhabitants than for urban inhabitants who were admitted (average hospital charges per stay, \$43 153 [95% CI, \$41 152–\$45 154] versus \$68 782 [95% CI, \$65 521–\$72 043] for those living in large metro areas).
 - There is a similar scenario in those with DVT diagnosis (average hospital charges per stay, \$49 085 [95% CI, \$46 410–\$51 760] for patients living in rural areas versus \$68 175 [95% CI, \$64 692–\$71 658] for patients living in large metro areas).
- A 16-year cohort study involving ≈434 000 patients with cancer-associated thrombosis from the Veterans Affairs Health Care System observed that 35% of the individuals were from rural areas.¹⁰
 - In this same cohort, more than 289 000 individuals (61.9%) lived in areas of greater socioeconomic disadvantage. The prevalence of patients living in an Area Deprivation Index percentile of 51 to 75 and 76 to 100 was 29.6% and 32.3%, respectively. This was associated with a higher risk of mortality, with an HR of 1.06 (95% CI, 1.04–1.07) and 1.15 (95% CI, 1.13–1.16) for the respective percentiles.
- Data from ≈512 000 bariatric surgeries in the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Project revealed that VTE-associated mortality was more prevalent in Black patients and Hispanic patients (27.8% and 25% of all deaths, respectively) compared with White patients (13.3%; *P*<0.001).⁴²
- In a US cohort of 14 140 patients with diagnosed VTE, Black individuals were less likely to

be prescribed DOACs than White individuals (OR, 0.86 [95% CI, 0.77–0.97]). However, Hispanic individuals and Asian individuals had no difference in DOAC prescription compared with White individuals ($P=0.66$ and $P=0.74$, respectively).⁴³

- In a 2021 analysis of 65 000 elderly Medicare patients, Black individuals who used both apixaban and warfarin had a higher risk of adverse events after experiencing a VTE individuals: recurrent VTE, 2.0 versus 1.4 [apixaban] and 3.3 versus 2.2 [warfarin]; major bleeding, 7.4 versus 3.5 [apixaban] and 10.1 versus 5.3 [warfarin]).⁴⁴ Patients with lower SES also had worse outcomes (incidence rates per 100 PY versus high SES: recurrent VTE, 3.6 versus 2.6 [apixaban] and 3.3 versus 2.7 [warfarin]; major bleeding, 5.7 versus 3.2 [apixaban] and 7.0 versus 5.1 [warfarin]).

Family History and Genetics

- VTE is highly heritable, estimated to be 47% for

- Exome-wide analysis of rare variants in >24 000 individuals of European ancestry and 1858 individuals of African ancestry confirmed previously implicated loci but did not uncover rare novel variants associated with VTE. Similarly, targeted sequencing efforts did not uncover rare novel variants for DVT. However, multiancestry genome-wide GWAS

males and 40% for females from an analysis of 881 206 full-sibling pairs and 95 198 half-sibling pairs in the Swedish Multi-Generation Register.⁴⁵ is the most common inherited thrombophilia populations of European descent (prevalence, but is rare in African populations (1.2%) populations (0.45%).⁴⁶ In ARIC, ≈5% of and <1% of Black people were heterozygous carriers of FVL, and lifetime risk of VTE individuals with the FVL genetic variant data from 36 epidemiological studies that risk of VTE was increased 4-fold

- FVL in (5.2%) and Asian White people heterozygous was 17.1% in ant.²² Pooling studies showed

with higher odds of incident VTE event (OR, 51% per 1-SD increase in GRS).⁵⁴ The risk of VTE in the higher tail end of this GRS was similar to that attributed to monogenic VTE variants. This GRS may guide decision-making on which individuals may benefit from anticoagulant therapy.

Prevention

- Pharmacological prophylaxis has shown benefit with the use of low-molecular-weight heparin in critically ill patients (OR for DVT, 0.59 [95% CI, 0.33–0.90]).⁵⁵
 - In an analysis involving ≈5000 high-risk patients for VTE who underwent general surgery, the correct prescription of chemoprophylaxis was associated with lower rates of VTE (OR, 0.58 [95% CI, 0.34–0.95]) and lower mortality (OR, 0.57 [95% CI, 0.34–0.93]).⁵⁶
 - Furthermore, 2 meta-analyses showed benefit of low-molecular-weight heparin over unfractionated heparin in preventing DVT in patients in critical care (OR, 0.72 [95% CI, 0.46–0.98])⁵⁵ and patients with trauma (OR for DVT, 0.67 [95% CI, 0.50–0.88]).⁵⁷
- in people with heterozygous FVL (OR, 4.2 [95% CI, 3.4–5.3]) and 11-fold in those with homozygous FVL (OR, 11.4 [95% CI, 6.8–19.3]) compared with

- In patients with cancer, thromboprophylaxis reduces both VTE and DVT by half (RR, 0.51 noncarriers.⁴⁷ [95% CI, 0.32–0.81] and 0.53 [95% CI, 0.33–0.81]).⁴⁸ A Bayesian meta-analysis found that for childbearing females with this variant, VTE risk was 7% in the antepartum period and 11% in the postpartum period.
- Antithrombin deficiency is a rare disease (prevalence, 0.02%–0.2%) that is associated with greatly increased risk of incident VTE (OR, 14.0 [95% CI, 1.5–130.0]).⁴⁹

- 0.87], respectively) with no increase in major bleeding incidence ($P=0.15$).⁵⁸
- In pregnant females with a history of VTE, there was no superiority of weight-adjusted over fixed- low-dose low-molecular-weight heparin (rate of VTE events up to 6 weeks postpartum, 2% versus 3%; $P=0.33$).⁵⁹ For those with VTE risk in the a probable disease-causing genetic variant or variant of unknown significance in 39 of 64 individuals
 - Whole-exome sequencing of a panel of 55 thrombophilia genes in 64 patients with VTE identified

prepartum, peripartum, or postpartum period, it brings benefit to this population.⁶⁰

– DOACs are noninferior to low-molecular-weight (60.9%).⁵⁰

- GWASs have identified additional common genetic variants associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPM2*.⁵¹ These common variants individually

is unclear whether pharmacological prophylaxis

heparin in hip fracture scenarios (pooled OR for increase the risk of VTE to a small extent, but a GRS composed of a combination of 5 common variants yielded an OR for VTE risk of 7.5.⁵²

VTE, 0.52 [95% CI, 0.25–1.11])⁶¹ and are effective in outpatients with cancer (pooled RR for VTE incidence, 0.53 [95% CI, 0.36–0.78]; pooled RR for PE incidence, 0.50 [95% CI, 0.28–0.89]).⁶² In patients admitted with COVID-19, a 2022 Cochrane meta-analysis found that a higher dose of anticoagulants resulted in lower risk of PE

(pooled RR, 0.46 [95% CI, 0.31–0.70]; 4 studies) at the cost of increased risk of major bleeding (pooled RR, 1.78 [95% CI, 1.13–2.80]; 4 studies).⁶³

- The use of antiplatelet therapy is not associated with the prevention of cancer-associated thrombosis (*P*=not significant)¹⁰ or postoperative VTE in major orthopedic surgery (pooled RR of VTE compared with other anticoagulants, 1.45 [95% CI, 1.18–1.77]; 17 studies).⁶⁴

- Furthermore, beyond the pharmacologic prophylaxis:

- Elastic stockings play an important role in VTE prevention in individuals on long (>4 hours) airplane flights (OR for DVT, 0.10 [95% CI, 0.04–0.25]).⁶⁵ In addition, after a VTE, elastic stockings may prevent PTS (pooled RR, 0.73

person-difference analysis with those 0.69 [95% reported incidence ≈18 with any 2.29–100 PY, in DOAC compared with [95% CI, 0.53–1.00]), but there is no association with reduced risk of severe PTS, recurrent VTE, or

risk of hospitalization for bleeding and mortality.– An on-treatment analysis with GARFIELD-VTE data showed a lower all-cause mortality in the DOAC group (eg, rivaroxaban, apixaban, edoxa-ban, and dabigatran) compared with the vitamin K antagonists group (eg, warfarin; HR, 0.57 [95% CI, 0.42–0.79] in a mean follow-up of 12 months).⁶⁶

– A 2022 Cochrane meta-analysis found that incorporating intermittent pneumatic leg compression into standard VTE drug

prevention resulted in a reduction in the incidence of both PE (pooled OR,

- A retrospective analysis with Medicare patients who presented with cancer-associated thrombo-sis observed that the use of DOACs was asso-ciated with lower mortality (HR, 0.85 [95% CI, 0.46 [95% CI, 0.30–0.71]; 15 studies) and DVT (pooled OR, 0.38 [95% CI, 0.21–0.70]; 17 studies). There was no increased risk for orthopedic patients for PE and DVT incidence ($P=0.82$ and $P=0.69$, respectively).^{.67}
- An early strategy of prophylactic placement of a vena cava filter after major trauma did not result in lower incidence of symptomatic PE or death at 90 days after filter placement ($P=0.98$).^{.56,68} Even in patients at high risk for VTE, there is no net ben-efit in extended thromboprophylaxis compared with an inpatient-only strategy ($P=0.18$ for VTE and $P=0.43$ for bleeding).^{.69,70}

Awareness, Treatment, and Control

- Anticoagulation with oral or parenteral drugs is the mainstay of VTE treatment.
 - After DVT diagnosis, anticoagulants consistently reduced both VTE and DVT

0.78–0.91]).^{.75}

recurrence by 66% and 75%, respectively.^{.71}

– An analysis of 2 large databases involving >203 000 Medicare beneficiaries and >95 000 commercially insured patients revealed that the initial prescription of DOAC after a VTE episode increased from 0% in 2010 to 86.8% in Medicare patients and 92.1% in commercially insured individuals in 2020.^{.28}

– A study on anticoagulant strategy in ≈64 000 discharges showed an incidence of VTE recurrence with apixaban, rivaroxaban, and warfarin of 9.8 (95% CI, 6.8–13.6), 11.6 (95% CI, 8.5–

– Retrospective analyses of 5 US claims databases use of apixaban compared with warfarin was associated with the following:

- Lower recurrent VTE (HR, 0.78 [95% CI, 0.67–0.83]), and intracranial bleeding (HR, 0.56 [95% CI, 0.42–0.76]) in those with high risk of bleeding⁷⁶;
- Lower VTE recurrence (HR, 0.78 [95% CI, 0.65–0.88]) in patients with VTE diagnosis and prior CKD⁷⁷; and
- Lower VTE recurrence (HR, 0.58 [95% CI, 0.43–0.77]) and major bleeding (HR, 0.78 [95% CI, 0.62–0.98]) in patients on dialysis.⁷⁸

• In a cohort of >220 000 veterans, the use of anti-inflammatories in the treatment of COVID-19, when indicated, was associated with a lower risk of VTE compared with no medication.⁷⁹ Among those who received nirmatrelvir, the HR was 0.72 (95% CI, 0.53–0.96) for DVT and 0.61 (95% CI, 0.51–0.74) for PE.

Similar findings were issued among patients receiving molnupiravir (HR for DVT, 0.72 [95% CI, 0.53–0.99] and HR for PE, 0.65 [95% CI, 0.47–0.91]).⁸⁰ • A 2021 meta-analysis observed that inferior vena cava filters reduced early (within 3 months) new PE occurrence (pooled RR, 0.17 [95% CI, 0.04–0.65]) but not recurrent PE ($P=0.33$). Inferior vena cava filter did not provide a reduction in mortality (15.4), and 13.6 (95% CI, 10.2–17.6) per 100 000 ($P=0.61$).⁸¹

- Data from the National Readmission Database, which involved >58 000 patients hospitalized with a proximal VTE, revealed that inferior vena cava filter was associated with a higher risk of 30-day unplanned rehospitalization (HR, 1.47 [95% CI, 1.38–1.56]).⁸²
- In patients who had cancer-associated thrombosis, a US cohort analysis found a significant improvement in PE-free with (HR, 0.69 [95% CI, 0.64–0.75]) regardless of the underlying neoplasm.⁸³
- Systemic thrombolysis did not result in a reduction in all-cause mortality ($P=0.56$), lowering the risk

Mortality

- Data from Pulmonary Embolism Response Team Consortium Registry revealed a mortality of 20.6% in high-risk patients and 3.7% in intermediate-risk patients.⁸⁸ Among the high-risk individuals, in-hospital mortality was 42.1% for those admitted with a catastrophic PE; this of PTS after 6 months (pooled RR, 0.78 [95% CI, 0.66–0.93]) and 5 years (pooled RR, 0.56 [95% CI, 0.43–0.73]) at the cost of a higher bleeding rate (RR, 2.45 [95% CI, 1.58–3.78]).⁸⁴

related to PE during the COVID-19 pandemic compared with the preceding years.⁹¹ The AAMR per 100 000 people was 12.2 (95% CI, 12.1–12.3) in 2020 compared with 9.6 (95% CI, 9.5–9.7) in 2019 and 9.4 (95% CI, 9.3–9.5) in 2018.

- The GARFIELD-VTE study observed a 3-year mortality of 10.9% after a VTE. The incidence of death decreases gradually from the first month (incidence per 100 PY, 10.69
- Moreover, percutaneous pharmacomechanical catheter-directed thrombolysis for DVT may

reduce the risk of PTS (pooled RR, 0.84 [95% CI, 0.74–0.95]; 3 studies) but is associated with an increased risk of major bleeding (pooled RR, 2.03 [95% CI, 1.08–3.82]).⁸⁵

– A 2021 meta-analysis found no mortality benefit associated with systemic thrombolysis procedure ($P=0.83$).⁸⁶

- In patients with PE, ~5000 patients were treated with percutaneous pulmonary artery thrombectomy in the United States from 2016 to 2018, which was 0.5% of all PE diagnoses.⁸⁷

– In this scenario, females exhibited a higher rate of bleeding during the procedure (16.9% versus 11.2%), received more red blood transfusions (11.9% versus 5.7%), experienced more vascular complications (5.0% versus 1.5%; all $P<0.05$), and had higher in-hospital

mortality (OR, 1.90 [95% CI, 1.20–3.00]) than males.

- An analysis using the Pulmonary Embolism Response Team Consortium Registry of patients admitted with a high-risk PE diagnosis found that 41.9% received advanced therapies such as systemic thrombolytics, catheter-directed thrombolysis, catheter-based embolectomy, surgical embolectomy, or mechanical circulatory support.⁸⁸

• Although malignancy is a relevant risk factor with an incidence of 2.4% within 6 months after VTE diagnosis,⁸⁹ a Cochrane meta-analysis found no evidence for additional positron emission tomography/CT testing after a first unprovoked VTE because there was no benefit in any outcomes: cancer and all-cause mortality ($P=0.25$ and $P=0.66$, respectively), VTE-related morbidity ($P=0.96$), time to cancer diagnosis ($P=0.88$), and malignancy diagnosis in the early or advanced stage ($P=0.36$ and $P=1.00$, respectively).⁹⁰

pared with months 2 to 12 (6.54 [95% CI, 6.05–7.07]), the second year (3.1 [95% CI, 2.75–3.50]), and the third year (2.0 [95% CI, 1.72–2.34]).⁹²

- In patients with cancer diagnosis:

- Compared with prostate malignancy, the cancer sites with the highest risk of death attributable to cancer-associated thrombosis were pancreas (HR, 10.05 [95% CI, 9.79–10.31]), brain (HR, 8.09 [95% CI, 7.73–8.48]), and liver (HR, 7.08 [95% CI, 6.92–7.23]), whereas the cancers with the lowest risk of cancer-associated thrombosis were chronic myeloid leukemia (HR, 0.50 [95% CI, 0.48–0.53]), chronic lymphoid leukemia (HR, 0.50 [95% CI, 0.48–0.52]), and thyroid cancer (HR, 0.87 [95% CI, 0.82–0.92]).¹⁰

- Mortality caused by cancer-associated thrombosis increased with the stage of the disease. The HR for death was 1.58 for stage II (95% CI, 1.56–1.61), 2.18 for stage III (95% CI, 2.15–2.21), and 5.03 for stage IV (95% CI, 4.97–5.10) compared with stage I.

- Despite high heterogeneity among cancer sites, age (HR per 10-year increase, 1.47 [95% CI, 1.47–1.48]), hospitalization in the past 90 days (HR, 1.45 [95% CI, 1.43–1.46]), anemia (HR for hemoglobin <10 g/dL, 1.37 [95% CI, 1.35–1.39]), platelet count >350×10⁹/L (HR, 1.29 [95% CI, 1.27–1.31]), white blood cell count >10×10⁹/L (HR, 1.28 [95% CI, 1.27–1.30]), male sex (HR, 1.24 [95% CI, 1.21–1.28]), prior VTE (HR, 1.11 [95% CI, 1.09–1.13]), and immobility (HR, 1.09 [95% CI, 1.05–1.14]) emerged as additional epidemiological and laboratory risk factors for cancer-associated thrombosis mortality.

- In the hospitalized population with VTE diagnosis, patients with COVID-19 had at least a 3-fold risk of death compared with those admitted for influenza

infection (HR for 30-day all- [95% CI, 1.84–4.76] in the and 3.80 [95% CI, 2.41–6.00] vaccine availability).³⁷ When severity, the OR for mortality (95% CI, 1.49–4.67) and for cal ventilation was 3.14 (95%

Complications

- VTE is a chronic disease with
 - An analysis of a US health between January 2010 and (with ≈14 000 patients with VTE) observed a 6-month of 6.1%, with higher arrhythmia (HR, 1.46 [95% gestive HF (HR, 1.33 [95% CKD (HR, 1.24 [95% CI,
 - Data from GARFIELD-VTE incidence of recurrent VTE 100 PY [95% CI, 3.24– of follow-up (incidence per CI, 4.89–5.82)].⁹²
 - Although studies have of VTE in females using contraceptives, a 2022 found no association with whether in a follow-up of The meta-analysis reported (incidence per 100 patient- 1.10–2.23)].⁹⁵
- Major bleeding is a potentially adverse event that can occur
 - According to the site of major bleeding is the (31.6% of all events) (13%). Hemorrhagic stroke of the total major bleeding
 - Data from NIS with >138 proximal DVT indicated an rate of 0.2% in patients 0.7% in those receiving bolysis.⁹⁶ In this population, bleeding risk were a history [95% CI, 8.76–42.77]), age [95% CI, 1.17–4.28]), and CI, 1.06–4.68]). Centers dictors for fewer CI, 0.21–0.84]).
 - Patients from the

Team Consortium Registry with high- and inter- mediate-risk PE had a major bleeding rate of 10.5% and 3.5%, respectively.⁸⁸

- A study of ≈64 000 US patients followed up for 90 days after a VTE hospitalization showed no

- Heparin-induced as a complication in 0.6% of with VTE in an analysis of the involved ≈790 000
- Superior vena cava syndrome thoracic vein thrombosis. visits to 950 US EDs between showed a superior vena cava of 3.5 per 100 000 emergency most common causes were implantable electronic devices cular catheters (4.5%).
- PTS/venous stasis syndrome ulcers are important lower-extremity DVT, which depth in the Chronic Venous this chapter. Even under analyses found incidences for CI, 16.6%–31.7%⁹⁹; 17 (median follow-up, 21 the long term (follow-up >5 text, the PTS incidence was with DOAC drugs (11.8% than low-molecular-weight 36.2%) and vitamin K CI, 17.6%–33.1%)).⁹⁹

Health Care Use: Hospital Care Visits

- In 2019, data from the cal care provided by office- United States, indicated that physician office visits for DVT tabulation using NAMCS¹⁰⁰).
- In 2021, there were 210 712 DVT primary diagnosis tabulation).
- According to an analysis of ≈1 with PE in the ED, even after fied as low-risk PE according Embolism Severity Index, these patients were not (discharge rate of low-risk PE, 21.6%–47%)).⁴
- A study that examined 133 414 DVT diagnosis in the ED mal the DVT site was, the rate was (28% distal, 54% and 78% inferior vena cava; difference in major bleeding among apixaban, rivaroxaban, and warfarin prescriptions.⁷²

Costs

- In 2020, the aggregate charges in hospitalized ≈\$10 billion in 2018. Medicare and Medicaid cov-insurance accounted for more than one-quarter of

patients amounted to ≈\$15.5 billion compared with ered two-thirds of the total charge, whereas private all payments.³

- The incidence of VTE causes a 2-fold increase in annual costs in rheumatoid arthritis (adjusted annual total health care cost ratio for DVT and PE in the disease-modifying antirheumatic drug-naïve population, 2.04 [95% CI, 1.77–2.35] and 2.58 [95% CI, 2.06–3.24], respectively).¹⁰² In those with inflammatory bowel disease, VTE increases 1-year costs 3-fold (cost after VTE, \$67 054 versus \$22 424; $P<0.01$).¹⁰³
- In a registry of 3 million patients who underwent cardiac surgery, an additional mean cost of \$13 000 was observed among those with postoperative VTE.
- The Computerized Registry of Patients With Venous Thromboembolism registry, a database from 26 countries (including 6 US centers) that includes ≈121 000 patients, found a 30-day mortality of 1.95% for lower-limb DVT, 2.7% for upper-limb DVT, and 5.05% for PE.¹⁰⁵ The risk of death was lower for distal DVT compared with proximal DVT at the 1-year follow-up (HR, 0.72 [95% CI, 0.64–0.82]).¹⁰³
- In hospitalized patients with COVID-19, the incidence of DVT was higher in Asia (unadjusted pooled incidence, 40.8% [interquartile range, 24.6%–54.5%]) compared with the Middle East (15.6% [interquartile range, 8.6%–16.4%]), North America (12.8% [interquartile range, 3.8%–24.2%]), and Europe (8.0% [interquartile range, 3.9%–14.9%]).¹⁰⁶
 - However, the incidence of PE was higher in the Middle East (unadjusted pooled incidence, 16.2% [interquartile range, 8.1%–24.4%]) and Europe (14.6% [interquartile

based on studies from >20 years ago.¹⁰⁸ Meta-analyses with global data continue to use this figure to define the prevalence in North America.

- Pain is the most common symptom (29%) followed by swelling, heaviness, fatigue, and cramping. Spider veins are seen in 7%, and varicosities and skin changes are seen in 4% each. Stasis ulcer is present in 1% of all patients with CVI.¹⁰⁹

Incidence

- range, 6.4%–26.3%]) than in North America (5.0% [interquartile range, 3.0%–11.8%]) and Asia (3.2% [interquartile range, 1.9%–3.5%]).
- In a Swedish cohort comprising >950 000 patients with COVID-19, those who were hospitalized retained a higher risk of both PE (HR, 2.01 [95% CI, 1.51–2.68]) and DVT (HR, 1.46 [95% CI, 1.05–2.01]) even after 180 days compared with those without COVID-19.¹⁰⁷

Chronic Venous Insufficiency

ICD-10 I87.2.

2022, United States: Underlying cause mortality—62. Any-mention mortality—977.

2021, United States: Hospital discharges—5805 (principal diagnosis), 234 655 (all-listed diagnoses).

Prevalence

- No updated data are currently available on the prevalence of CVI in the United States. Practically all studies rely on a US prevalence of CVI of 28%

of varicose veins, 7.3% [95% CI, 7.0%–7.6%]).¹¹⁰

Risk Factors

- This study identified risk factors for varicose veins, including age (HR: 35–40 years of age, 1.61 [95% CI, 1.48–1.77]; 40–50 years of age, 1.66 [95% CI, 1.51–1.84]; and >50 years of age, 1.91 [95% CI, 1.63–2.23] compared with individuals <35 years of age), number of births (HR: 1 delivery, 1.78 [95% CI, 1.55–1.99]; ≥6 deliveries, 4.83 [95% CI, 2.15–10.90]), excessive weight gain during pregnancy (HR, 1.44 [95% CI, 1.09–1.91]), and postterm pregnancy (HR, 1.12 [95% CI, 1.02–1.21]).¹¹⁰
- The ARIC researchers found an association between low physical function (evaluated by a score that analyzes components such as chair stands, standing balance, and gait speed) and incidence of varicose veins (HR, 1.77 [95% CI, 1.04–3.00] between those with scores ≤6 and >6).¹¹¹
- PTS, a subset of CVI, has specific risk factors that can be identified at the time of or after DVT:
 - Using data from the GARFIELD-VTE registry, the predictors for severe PTS (assessed by the Villalta score) were chronic HF (OR, 3.3 [95% CI, 1.46–7.49]), prior VTE episode (OR, 1.82 [95% CI, 1.32–2.51]), and chronic immobilization (OR, 1.78 [95% CI, 1.03–3.08]).¹¹²

Social Determinants of Health/Health Equity

- A prospective study involving 449 US patients observed a linear association between CVI severity, measured by clinical-etiology-anatomy-pathophysiology classes and lower SES ($P<0.003$).¹¹³ Patients classified with the 2 most severe categories based on clinical-etiology-anatomy-pathophysiology classification system for chronic venous disorders had a median annual household income of <\$40 000.

Family History and Genetics

- Varicose veins are more likely to occur in the setting of a positive family history, consistent with a

heritable component.
and CVI has been estimated

- Although a number of genes
cated.¹¹⁵ to date, no causal
proven.¹¹⁶
- GWASs in >400 000 individuals
candidate loci for varicose
European ancestry.
CASZ1, PIEZO1, PPP3R1,
GATA2, NFATC2, and SOX9

complications (incidence rate
6.1% versus 8.6%; $P=0.001$).
dence rate, 0.4% versus
procedure-induced venous
rate, 1.1% versus 2.2%;

- Oral phlebotonics (eq.
synthetic products, and other
contribute to reducing edema
[95% CI, 0.60–0.78]), pain
CI, 0.48–0.83]), swelling

Prevention

- In a meta-analysis of ≈60 000 patients with VTE
on anticoagulant therapy, the use of rivaroxaban
reduced the risk of PTS by half compared with
war- farin (OR, 0.52 [95% CI, 0.43–0.63]).¹¹⁸

Awareness, Treatment, and Control

- In Medicare, the endovascular treatment of CVI
increased by 66% from 2010 to 2018 (6466 to
10 860 per 1 000 000 beneficiaries), driven by
an increase in traditional sclerotherapy (2883 to
3969 per 1 000 000 beneficiaries; 38% increase)
and radiofrequency ablation (1385 to 3270 per
1 000 000 beneficiaries; 136% increase).¹¹⁹ On
the other hand, the study observed a 66% decrease
in surgical approach (181 to 61 per 1 000 000
beneficiaries).
- Several treatment options are available for
patients with severe varicose veins, but
evidence for the best approach is scarce. A
2021 Cochrane metaanalysis found a borderline
benefit in technical success up to 5 years after
endoscopic laser ablation over ultra-sound-

guided foam sclerotherapy (pooled
OR, 6.47 [95% CI, 2.60–16.10]; 3
studies) and surgery (pooled OR,
2.31 [95% CI, 1.27–4.23]; 6 studies),
in addition to the benefit of the
surgery over ultrasound-guided foam
sclerotherapy (pooled OR, 0.09 [95%
CI, 0.03–0.30]; 3 studies). None of
the procedures showed a solid
benefit over the others when the
recurrence rate was analyzed.¹²⁰ The
success of these procedures is
critically compromised according to
the progressive increase in weight,
especially in those with a BMI ≥35
kg/m².¹²¹ Compiled data from the
Vascular Quality Initiative Varicose
Vein Registry and the American Vein
& Lymphatic Society PRO Venous
Registry showed that patients
undergoing these procedures

CI, 0.50–0.80]), and paresthesia (pooled RR, 0.67 [95% CI, 0.50–0.88]). In addition, there is likely to be a slight improvement in trophic changes (pooled RR, 0.87 [95% CI, 0.81–0.95]).^{.124}

- Balneotherapy compared with no treatment demonstrated marginal improvement in symptoms (pooled mean difference of the Venous Clinical Severity Score, –1.75 [95% CI, –3.02 to –0.49]; 3 studies) and pain (mean difference of Visual Analog Scale, –1.12 [95% CI, –1.35 to –0.88]; 2 studies) but with no evidence of benefit in edema, incidence of leg ulcers, thromboembolic events, and erysipelas (P =not significant).^{.125}

Complications

- The presence of varicose veins was associated a higher risk of VTE in patients undergoing lower-limb arthroplasty (OR, 2.37 [95% CI, 1.54–3.63]).^{.126}
- Leg wound is one of the most critical complications of CVI:
 - A study of the American Vein & Lymphatic Society PRO Venous Registry involving ≈270 000 patients found a leg wound prevalence of 1.1%.^{.127}
 - In a retrospective analysis of the Medicare Limited Data Set spanning from 2015 to 2019, among ≈1 225 000 beneficiaries with a claim diagnosis of CVI, 42% developed a confirmed diagnosis of venous leg ulcer during the follow-up period.^{.128}
 - Compression bandages or stockings are associated with improved wound healing time (pooled HR, 2.17 [95% CI, 1.52–3.10]), a higher rate of fully healed wounds (pooled RR, 1.77 [95% CI, 1.41–2.21]), and reduced pain (pooled median difference in 10-point pain scale, –1.39 [95% CI, –1.79 to –0.98]) with no adverse effects (P =0.97).^{.129}
- in accredited centers experience greater benefit than those in nonaccredited centers. There was an absolute reduction in Venous Clinical

Costs

Severity Score (5.61±3.6 versus 4.98±4.0; P <0.001), in addition

- Annual US spending on venous leg ulcers, a com-mon complication of CVI, is estimated at ≈\$5 bil-lion, most of which is for practitioner and hospital expenses.¹³⁰
 - to a lower incidence of complications (absolute incidence, 0.1% versus 0.4%; $P<0.001$).¹²²
 - sex-related differences in outcomes: Females have fewer local
 - Among those treated with endovenous ablation, data for ≈10 000 patients from the Vascular Quality Initiative's Varicose Vein Registry found

- A cost-effectiveness analysis found a dominance of compression therapy with early endovenous ablation over deferred ablation (per-patient cost, \$12 527 versus \$15 208; QALY, 2.011 versus 1.985 in a 3-year scenario).¹³¹

Health Care Use: Hospital Discharges/Ambulatory Care Visits

- In 2020, varicose veins and CVI/PTS were the main diagnosis in >66 000 ED visits.

Furthermore, ≈11 600 discharges were attributed to CVI/PTS and varicose veins.³

Global Burden

- A nationwide analysis in Korea revealed that ≈220 000 patients were undergoing treatment for CVI in 2020, which represents a 1.5-fold leg ulcer decreased from 3.1% in 2010 to 1.7% in 2020.

higher prevalence of PAH both in hospitalized patients¹⁴⁰ and in the outpatient setting.¹⁴¹

- Data from the US kidney transplantation registry observed a PH prevalence of 8.2% before the transplantation.¹⁴² The cumulative incidence after 3 years after transplantation was 10.6% (95% CI, 10.3%–11.0%).

- Among ≈600 000 Medicare patients

- In a Spanish registry covering 5.8 million people,

Lifetime Risk and Cumulative Incidence

- In a US health care claim database study involving 2011

CVI incidence was 3.37 per 1000 PY (95% CI, 3.31–3.43), increasing with age: 0.61 per 1000 PY in those <30 years of age and up to 10.95 per 1000 PY in those ≥80 years of age. Females presented ≈2.5-fold more CVI incidence than males (4.77 and 1.95 per 1000 PY, respectively). Venous stasis ulcer incidence was 0.23 per 1000 PY (95% CI, 0.21–0.24).¹³³

- A Brazilian study with ≈870 000 public health care surgeries between 2009 and 2018 observed a rate of 4.52 CVI procedures per 10 000 PY at a cost of US \$230 million.¹³⁴ The in-hospital mortality rate was 0.0056%.

- An online-based survey of 16 015 individuals from different nations showed a 22% prevalence

ing ≈170 000 patients after a VTE between

and 2018¹³⁹:

of CVI, from 14% in French respondents to 37% in Russian respondents, and fewer than half of those with CVI sought medical attention.¹³⁵ Among 19 104 work-ers in Germany in a population-based study, the prevalence of CVI was similar (22.3%).¹³⁶

Pulmonary Hypertension

ICD-10 I27.0, I27.2.

2022, United States: Underlying cause mortality—9635. Any-mention mortality—33 796.

2021, United States: Hospital discharges—12 855 (principal diagnosis), 1 131 494 (all-listed diagnoses).

- The 1-, 2-, and 5-year cumulative incidence of CTEPH was 2.09% (95% CI, 2.01%–2.17%), 3.54% (95% CI, 3.43%–3.65%), and 7.24% (95% CI, 7.01%–7.48%), respectively.
- In individuals with a PE diagnosis, the 1-, 2-, and 5- year cumulative incidence of CTEPH was 3.82% (95% CI, 3.68%–3.97%), 6.24% (95% CI, 6.03%–6.45%), and 12.12% (95% CI, 11.69%–12.56%), respectively.

Secular Trends

• In the United States, data from HCUP NIS show an upward trend in hospitalizations for PH between 2000 and 2014 in both principal and all-listed diagnoses. However, since 2016, a plateau in PH admissions has been observed.³

Risk Factors

• PH incidence is somewhat higher in females than males (PH incidence rate per 1000 PY after a VTE, 20.1 [95% CI, 19.4–20.8] in females versus 15.9 [95% CI, 15.3–16.6] in males),^{137,139} and females have at least 3-fold higher prevalence of PAH in a study of US hospitalized patients.¹⁴⁰

• Risk factors are implicit in the WHO disease classification of the 5 mechanistic subtypes of PH. The most common risk factors are left-sided HD and lung disease.

- In patients with WHO group I PH, a 10-year

Incidence

- A 2023 analysis of a US claims database with ≈61 000 000 patients found a PH diagnosis in

analysis from HCUP data found a high prevalence of 5.2% of ≈855 000 of those who had chronic unexplained dyspnea. Furthermore, 0.1% had a diagno-

lence of CHF (32.0%), hypertension (19.7%), chronic pulmonary disease (17.7%), valvular HD (12.5%), congenital HD (13.5%), and hypo-thyroidism (12%).¹⁴⁰ A study of the REVEAL registry showed that males with newly diagnosis of PAH.¹³⁷

nosed PAH with a smoking history had worse outcomes (HR for mortality, 1.80 [95% CI, 1.10–3.00]; HR for composite of transplanta-

ED).¹³⁸

- PH incidence is somewhat higher in females than males,^{137,139} and females have at least a 3-fold

tion or death, 2.23 [95% CI, 1.39–3.56]; and HR for time to first hospitalization, 1.77 [95% CI, 1.18–2.68]).¹⁴⁴

- The Pulmonary Hypertension Association Registry researchers found that 21.8% of the 541 patients in the registry had methamphetamine use as the underlying cause of PAH in the United States in 2015 to 2020.¹⁴⁵
- A US health care data analysis found higher risk of CTEPH after a VTE in initial presentation as a PE (HR, 5.04 [95% CI, 4.72–5.38]), HF (HR, 2.17 [95% CI, 2.04–2.31]), chronic pulmonary disease (HR, 2.01 [95% CI, 1.90–2.14]), alcohol abuse (HR, 1.66 [95% CI, 1.29–2.13]), AF (HR, 1.55 [95% CI, 1.43–1.68]), MI (HR, 1.53 [95% CI, 1.40–1.67]), hypertension (HR, 1.52 [95% CI, 1.43–1.61]), CKD (HR, 1.46 [95% CI, 1.36–1.58]), diabetes (HR, 1.42 [95% CI, 1.34–1.50]), liver disease (HR, 1.33 [95% CI, 1.23–1.45]), hematological disorders (HR, 1.32 [95% CI, 1.24–1.41]), older age (HR per decade, 1.26 [95% CI, 1.24–1.28]), female sex (HR, 1.24 [95% CI, 1.17–1.31]), autoimmune disease (HR, 1.23 [95% CI, 1.15–1.31]), and metastatic cancer (HR, 1.17 [95% CI, 1.06–1.30]).¹³⁹
- In patients undergoing kidney transplantation, newly diagnosed PH was associated with older age (HR: >60 years of age, 2.88 [95% CI, 2.15–3.86]; 45–59 years of age, 2.18 [95% CI, 1.63–2.91]; and 31–44 years of age, 1.55 [95% CI, 1.15–2.10], all compared with individuals between 18 and 30 years of age), valvular HD (HR, 1.51 [95% CI, 1.37–1.67]), chronic obstructive pulmonary disease (HR, 1.44 [95% CI, 1.28–1.61]), smoking history (HR, 1.32 [95% CI, 1.03–1.70]), female sex (HR, 1.29 [95% CI, 1.15–2.10]), OSA (HR, 1.28 [95% CI, 1.11–1.49]), >5 years of hemodialysis (HR, 1.26 [95% CI, 1.07–1.47]), diabetes (HR, 1.23 [95% CI, 1.07–1.42]), obesity (HR, 1.18 [95% CI, 1.05–1.33]), and
- prevalence year <\$50 ($P<0.001$).
- Veterans (>\$100 those with 0.74 [95% CI, 0.61–0.89]).
- The risk of among compared CAD (HR, 1.15 [95% CI, 1.02–1.30]).¹⁴²
- Social Determinants of Health/Health Equity**
- An analysis of patients in the Pulmonary Hypertension Association Registry showed an important impact of annual income, education level, and health insurance on death/lung transplantation in the Hispanic population with PAH. After adjustment for these social factors, the difference in transplantation-free survival between the Hispanic and NH population was attenuated, and there was no significant difference (HR for transplantation-free survival, 0.70 [95% CI, 0.35–1.62] after social determinants of health adjustment; $P=0.474$).¹⁴⁶
- Among the patients with WHO group I PH:
- Those with methamphetamine-related PAH had a clearly lower SES compared with the other patients in this group (prevalence of patients with college education, 17% versus 34%;

Family History and Genetics

- A 2018 study reported clustering of CTEPH in family factors influence an individual's risk of developing
- A Japanese family study identified *BMPR2* (bone factor for PAH).¹⁴⁹ In whole-exome sequencing, a noted to carry nonsynonymous variants associated CTEPH with acute PE.¹⁵⁰
- GWASs in >11 000 individuals have identified risk *DPB1*.¹⁵¹
- Exome sequencing in 2572 individuals and case-cases and 12 771 controls identified candidate risk *GDCX*, and *GDF2*.¹⁵²

Awareness, Treatment, and Control

- There is a meaningful delay between the beginning (median interval time, 2.26 years [interquartile range, 2–4] echocardiograms, 6 2 (interquartile range, 1–4) hospitalizations until nosis affects several outcomes, including length [95% CI, 1.29–2.12] compared to ≤12 months' 1.16–3.73]), ICU length of stay (IRR, 2.15 [95% [95% CI, 1.08–1.41]).¹⁵³
- As nonpharmacological therapy, exercise-based cardiovascular fitness, including 6-minute walk distance V_{O2peak} (+2.96 mL·kg⁻¹·min⁻¹ [95% CI, 2.49–3.43]).¹⁵⁴
 - Data from the TRIO comprehensive and inte-

ilies, providing novel evidence that heritable genetic CTEPH.¹⁴⁸ morphogenetic protein receptor type 2) as a risk Japanese cohort of patients with CTEPH were with acute PE, indicating a partial genetic overlap of

loci for PAH, including *SOX17* and *HLA-DPA1*/

control gene-based association analyses in 1832 genes for idiopathic PAH, including *KLK1*,

ning of the symptoms and PAH diagnosis range, 0.73–4.22 years]), requiring a median of (interquartile range, 3–12) specialist visits, and a definitive diagnosis is made.¹³⁷ This late diagnosis of hospital stay (IRR for >24 months' delay, 1.71 delay), 30-day readmission (IRR, 2.22 [95% CI, CI, 1.45–2.88]), and outpatient visits (IRR, 1.26

rehabilitation programs have shown improvements in tance (+47.7 m [95% CI, 33.9–61.7]) and

- In the WHO group 1 PH:
 - grated patient data repository showed that 40%

were on monotherapy, 43% were on dual therapy, and 17% were on triple therapy.¹⁴¹ Among all patients in the registry, 61% were using phosphodiesterase 5 inhibitors, 55% were receiving some endothelin receptor antagonist, and 51% were prescribed prostacyclin.

- Phosphodiesterase 5 inhibitors showed a clear benefit in 6-minute walk distance (+48 m [95% CI, 40–56]), WHO functional class (OR, 8.59 [95% CI, 3.95–18.72]), and mortality (OR, 0.22 [95% CI, 0.07–0.78] [95% CI, 17–33]) and WHO functional class (OR, 1.41 [95% CI, 1.16–1.70]) without a statistically significant reduction in mortality (OR, 0.78 [95% CI, 0.58–1.07]).¹⁵⁶

Mortality

- An analysis of CDC WONDER data revealed a progressive increase in PH-related mortality from 2003

to 2020.¹⁵³ The age-standardized mortality rate per 1 000 000

PY rose from 17.81 in 2003 to 23.89 in

2020 (annual percentage change, 2.3% [95% CI, 2.0%–2.6%]),

driven by a pronounced increase in deaths in PH groups 2 through 5

(annual percent-age

- In symptomatic patients with intermediate risk of 1-year mortality, the REPLACE investigators found benefit of switching from other phosphodi-

- Data from HCUP show that the in-hospital PH mortality rate rose from 3.9% in 2016 to 5.9% in 2020.³ In a 2019 study of US veterans with PH, 5-year survival was 66.1% for group 1 (PAH), 42.4% for group 2 (left-sided HD), 52.3% for group 3 (lung disease), 72.7% for group 4 (CTEPH), 67.8% for group 5 (miscellaneous), and 34.9% for PH with multiple causes.¹⁶²
- Intravenous prostacyclin exhibited improvements in WHO functional class (OR, 2.78 [95% CI, 1.53–5.06]) with no clinical worsening (OR, 0.10 [95% CI, 0.01–0.73]).¹⁵⁷
- Intravenous prostacyclin exhibited improvements in WHO functional class (OR, 14.96 [95% CI, 4.76–47.04]), 6-minute walk distance (+91 m [95% CI, 59–124]), and mortality (OR, 0.29 [95% CI, 0.12–0.69]).¹⁵⁸ However, serious adverse events may occur in 12% to 25% of cases, including sepsis, hemorrhage, pneumothorax, and

- The Pulmonary Hypertension Association Registry, a US multicenter cohort of ≈1000 patients with group I PH, observed a 1-, 2-, and 3-year composite of death/lung transplantation of 8.6% (95% CI, 6.8%–10.7%), 16.9% (95% CI, 14.1%–20.2%), and 23.1% (95% CI, 19.4%–27.7%), respectively.¹⁶³ In high-risk strata, the 3-year mortality rate was from 28% to 56% according to risk tool used.
- In the United States, patients with PH admitted to the hospital have high in-hospital mortality (4.2% PE. versus 2.6% for all other patients). Furthermore,
- Anticoagulation therapy showed no benefit in mortality regardless of the underlying cause of PH ($P=0.11$), in addition to worsening of quality of life (adjusted mean difference of emPHa-sis-10 score, 1.74 [95% CI, 0.40–3.09]), more ED visits (aIRR, 1.41 [95% CI, 1.28–1.56]), hos-

the mortality risk increases according to the age of age.¹³⁸

- In PH group 3, patients with PH and lung dis-
pitalization (aIRR, 1.33 [95% CI, 1.14–1.55]),
and days in the hospital (aIRR, 1.30 [95% CI,
1.23–1.37]).¹⁵⁹
- In the CTEPH scenario, pulmonary thromboen-
doarterectomy surgery resulted in better WHO
functional class (rate in WHO functional class I/
II, 82.9% versus 56% versus 48.2% in operated,

group, reaching a 10-fold risk in those ≥80 years

ease had an increased in-hospital mortality com-

1.73–2.07]).¹⁴³

operable but not operated, and inoperable, respec- tively;
 $P<0.001$) and less use of oxygen ($P<0.001$ versus
inoperable cohort), diuretics ($P<0.001$ ver- sus
inoperable cohort), and specific medications for PH
($P<0.001$ versus operable but not operated and

- Data from the US CTEPH Registry showed an over-all 1-, 2- and 3- year survival rate of 93%, 91%, and 87%, respectively.^{.164} When stratified by pulmo-nary thromboendarterectomy status, the 1-, 2- and 3-year survival was 95%, 93%, and 90%, respec-tively, for operated patients; 91%, 85%, and 74% for those in whom surgery was feasible but who decided not to have the procedure; and 88%, 84%, and 80% in inoperable patients ($P=0.001$).
- Mortality rates also vary according to WHO func-tional class. A meta-analysis including 10 stud-ies found a 1-, 2-, and 3-year survival rate for inoperable).^{.160} those exposed to pulmonary vasodilators (HR, 1.31 [95% CI, 1.25–1.37]).^{.161}
- A comprehensive study of data from 132 552 vet-erans with PH diagnosed in groups 2 and 3 found a 39% increased mortality or organ failure in

patients with PAH in WHO functional class I/II of 93.3%, 85.5%, and 78.4%, respectively. However, in patients with worse functional class (WHO functional class III/IV), the survival rates were 81.2% at year 1, 66.7% at year 2, and 54.8% at year 3.¹⁶⁵

- In an analysis using NIS 2014, which involved > 5 hospitals, patients presenting with total sample) had a higher [95% CI, 1.15–1.55].¹⁶⁶
- Among group 1 PH in WHO post hoc analysis including participants found that those with shuttle walk distance ≥ 440 m had (HR, 0.225 [95% CI, 0.098–0.525]) compared with groups 2 through 4 PH, 2019 findings from the ASPIRE registry demonstrated that greater incremental shuttle walking test distance was
- Delayed PH diagnosis of higher total costs (mean [95% CI, \$2107–\$8524]), (mean cost overrun, \$4266 [\$6477]), medical expenses \$4237 [95% CI, \$907–\$7567], hospitalization costs (mean cost \$1401–\$6342), compared with 6 months' delay in the
- In an analysis of administrative data associated with better survival (AUC, 0.693 [95% CI, 0.64–0.74])

per-month total all-cause health care costs for patients with PH who were commercially insured were \$9503 for those on monotherapy and \$16 240 for those on combination therapy. Among patients with PH with
0.646–0.739]).¹⁶⁸ Medicare Advantage and Part D, the monthly costs
• In noncardiac surgery setting, in a 2023 meta-analysis with >18 million patients (predominantly US individuals), the presence of PH was associ-
ated with higher risk of mortality compared with no PH (pooled aOR, 2.09 [95% CI, 1.51–2.90]; 8

- Among patients diagnosed with PH referred to the Mayo Clinic specialty center, half had their previously prescribed medications discontinued (eg, sildenafil,

- Among patients diagnosed with PH referred to the Mayo Clinic specialty center, half had their previously prescribed medications discontinued (eg, sildenafil,

tadalafil, riociguat, ambrisentan, treprostinil,

- In terms of pregnancy, a systematic review of 13 studies (4 in the United States) observed a 12%

tan, and selexipag), resulting in a monthly savings of ≈\$7000 per patient with an inappropriate diagnosis.¹⁷⁵
overall maternal mortality rate. Of all deaths, 61% occurred within the first 4 days of *Global Burden*

tion, 58% of births were PTBs.

- Despite the mortality rate noted previously, only 5.8% of patients enrolled in the Pulmonary Hypertension Association Registry were referred for palliative care. Among them, 43% were referred in the last appointment before death.¹⁷¹
- A retrospective analysis of 6169 US patients with PH observed a higher mortality in those living in small urban counties (HR, 1.48 [95% CI, 1.14–1.92]) and rural areas (HR, 2.01 [95% CI, 1.13–

3.57]) compared with individuals in metropolitan counties.¹⁷²

Health Care Use: Hospital Discharges/Ambulatory Care Visits

- In 2021, there were 12 855 hospital discharges with PH as the principal diagnosis (HCUP,³ unpublished NHLBI tabulation).
- In 2019, PH was the principal diagnosis for 278 000 physician office visits (NAMCS,¹⁰⁰ unpublished NHLBI tabulation).

(See Table 24-1 and Chart 24-3 and Chart 24-4)

- The number of prevalent cases of PAH was 0.19 million (95% UI, 0.16–0.24) million, with an age-standardized rate of 2.28 (95% UI, 1.85–2.80) per 100 000. There were 0.02 (95% UI, 0.02–0.03) million total deaths estimated for PAH, with an age-standardized rate of 0.27 (95% UI, 0.23–0.32) per 100 000 (Table 24-1).
- Among regions, PAH prevalence was highest for Western Europe and central Latin America (Chart 24-3).
- Mortality estimated for PAH among regions was highest for North Africa and the Middle East and Central and east Asia and lowest for central Latin America and Eastern Europe (Chart 24-4).
- A systematic review from the GBD Study 2020 showed a wide range of prevalence of PAH (WHO group I PH) worldwide, ranging from 0.7 to 15 per 100 000 inhabitants in France and Australia, respectively.¹⁷⁷ When stratified by diagnosis through

Costs

- Health care costs associated with PH are substantial. In inpatient scenarios, the mean charge increased progressively from \$82 000 in 2016 to \$125 000 in 2020.³
 - In patients with acute exacerbated chronic obstructive pulmonary disease, an additional

right-sided heart catheterization, the mean PAH diagnosis of WHO group 3 PH results in an increase in hospitalization costs of \$2785 (mean difference [95% CI, \$2602–\$2967]).¹⁴³

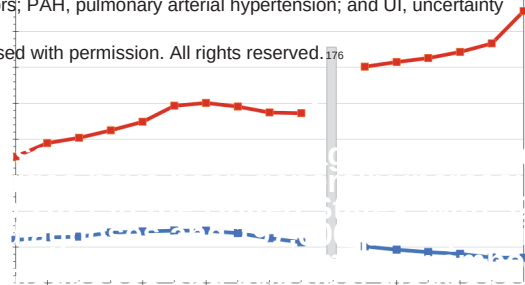
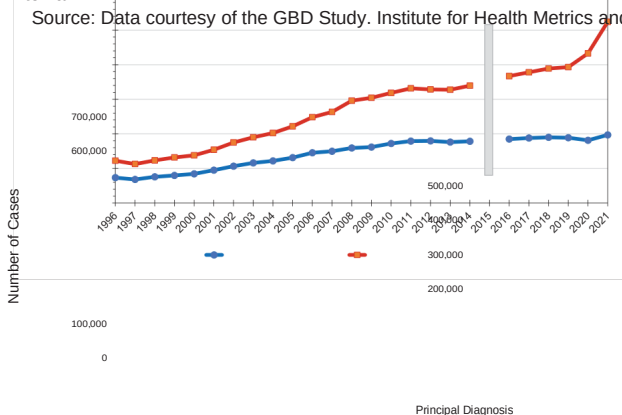
prevalence across 37 low-, middle-, and high-income countries was 3.7 per 100 000 people.

- A meta-analysis with 5834 patients observed an overall CTEPH incidence after acute PE of 2.82% (95% CI, 2.11%–3.53%).¹⁷⁸ In this scenario, Asian individuals showed a higher risk of CTEPH compared with European individuals (pooled incidence, 5.08% [95% CI, 2.67%–7.49%] versus 1.96% [95% CI, 1.29%–2.63%], respectively).

Table 24-1. Global Mortality and Prevalence of PAH, by Sex, 2021

	Both sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions), 2021	0.02 (0.02 to 0.03)	0.19 (0.16 to 0.24)	0.01 (0.01 to 0.01)	0.07 (0.06 to 0.09)	0.01 (0.01 to 0.02)	0.12 (0.10 to 0.15)
Percent change (%) in total	48.36 (20.97 to 78.48)	81.46 (73.47 to 89.06)	30.74 (7.31 to 64.57)	85.50 (76.33 to 94.03)	65.53 (27.24 to 135.23)	79.06 (71.54 to 86.05)
Percent change (%) in total	4.34 (-5.12 to 16.68)	21.32 (18.30 to 24.07)	-1.02 (-14.42 to 13.13)	21.76 (18.81 to 24.66)	8.88 (-3.28 to 27.03)	21.04 (18.05 to 23.87)
Rate per 100 000, age	0.27 (0.23 to 0.32)	2.28 (1.85 to 2.80)	0.27 (0.21 to 0.33)	1.78 (1.44 to 2.17)	0.28 (0.22 to 0.34)	2.75 (2.24 to 3.39)
Percent change (%) in rate, age	-22.08 (-34.52 to -7.57)	-0.92 (-1.64 to -0.30)	-27.55 (-42.72 to -6.33)	1.86 (1.03 to 2.67)	-17.12 (-34.21 to 11.89)	-2.20 (-3.03 to -1.44)
Percent change (%) in rate, age	-20.29 (-27.32 to -11.71)	-1.63 (-2.11 to -1.20)	-23.36 (-33.69 to -12.60)	-0.98 (-1.63 to -0.35)	-17.64 (-26.93 to -4.78)	-1.92 (-2.52 to -1.29)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles. GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; PAH, pulmonary arterial hypertension; and UI, uncertainty interval.



PE indicates pulmonary embolism.

*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.³

Chart 24-1. Trends in hospitalized PE, United States, 1996 to 2021.

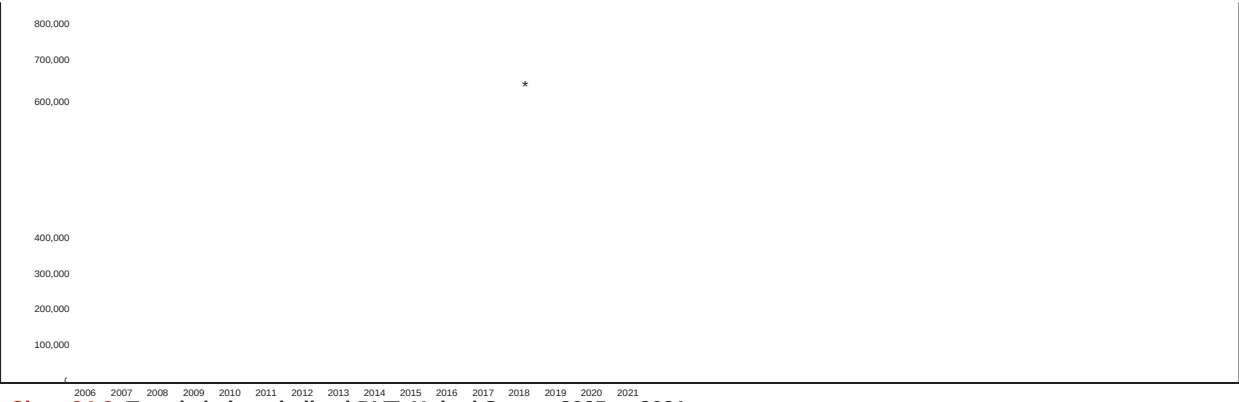


Chart 24-2. Trends in hospitalized DVT, United States, 2005 to 2021.

DVT indicates deep vein thrombosis.

*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.³

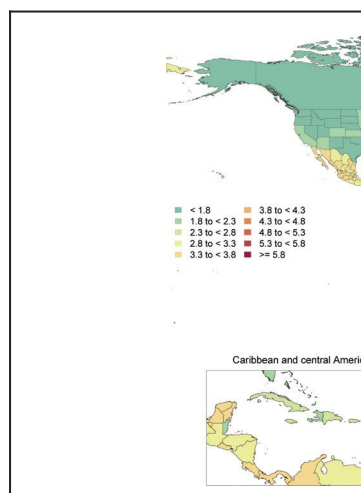


Chart 24-3. Age-standardized prevalence rates of PAH per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and PAH, pulmonary arterial hypertension.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁷⁶

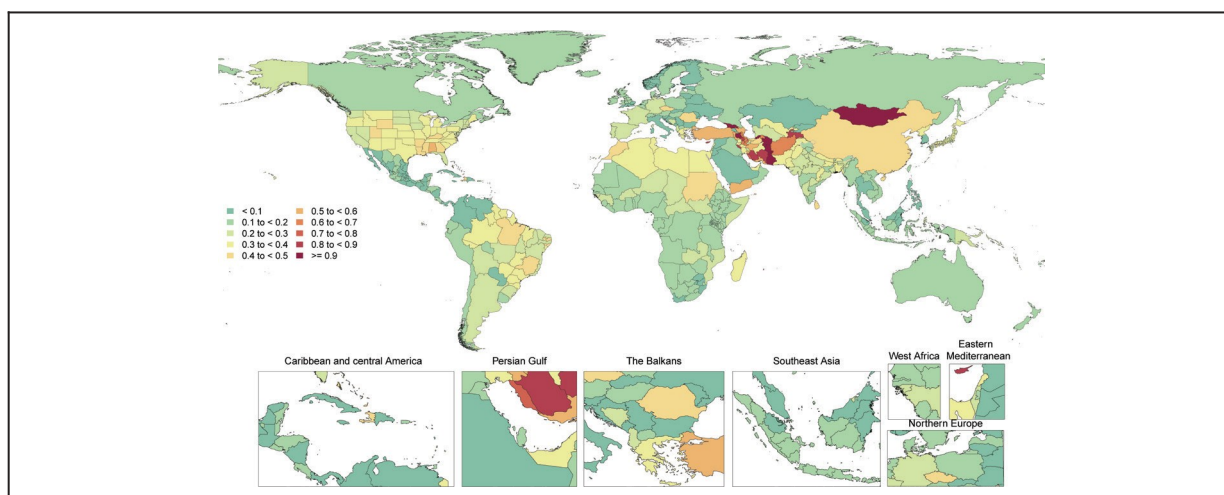


Chart 24-4. Age-standardized mortality rates of PAH per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and PAH, pulmonary arterial hypertension.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.¹⁷⁶

REFERENCES

1. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data files.

immediate and short-term cardiovascular readmissions following COVID-19-related hospitalisations in the USA. *BMJ Open*. 2023;13:e073959. doi: 10.1136/bmjopen-2023-073959

20. Elkin PL, Brown SH, Resendez S, McCray W, Resnick M, Hall K, Franklin G, Connors JM, Cushman M. COVID-19 vaccination and venous thromboembolism risk in older veterans. *J Clin Transl Sci*. 2023;7:e55. doi: 10.1017/cts.2022.527

21. Gaddh M, Scott D, Wysokinski WE, McBane RD, Casanegra AI, Baumann Kreuziger L, Houghton DE. Comparison of venous thromboembolism outcomes after COVID-19 and influenza vaccinations. *TH Open*. 2023;7:e303–e308. doi: 10.1055/a-2183-5269

22. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Folsom AR. Lifetime risk of venous thromboembolism in two

cohort studies. *Am J Med*. 2016;129:339.e19 doi: 10.1016/j.amjmed.2015.10.014

5. Wendelboe AM, Campbell J, Ding K, Bratzler DW, Beckman MG, Reyes NL, Raskob GE. Incidence of venous thromboembolism in a racially diverse population of Oklahoma County, Oklahoma. *Thromb Haemost*.

23. Zuin M, Bikdeli B, Armero A, Porio N, Rigatelli G, Bilato C, Piazza G. Trends in pulmonary embolism deaths among young adults aged 25 to 44 years in the United States, 1999 to 2019. *Am J Cardiol.* 2023;202:169–175. doi: 10.1055/s-0040-1722189
6. Weze KO, Obisesan OH, Dardari ZA, Cainzos-Achirica M, Dzaye O, Graham G, Miedema MD, Yeboah J, DeFilippis AP, Nasir K, et al. The interplay of race/ethnicity and obesity on the incidence of venous thromboembolism. *Am J Prev Med.* 2022;63:e11–e20. doi: 10.1016/j.amepre.2021.12.023
7. Brown CS, Osborne NH, Nuliyalu U, Obi A, Henke PK. Characterizing

24. Stein PD, Matta F, Hughes PG, Hughes MJ. Nineteen-year trends in mortality of patients hospitalized in the United States with high-risk pulmonary embolism. *Am J Med.* 2021;134:1260–1264. doi: 10.1016/j.amjmed.2021.01.026
25. Farmakis IT, Barco S, Hobohm L, Braekkan SK, Connors JM, Giannakoulas. Geographic variation in postoperative venous thromboembolism. *J Vasc Surg Venous Lymphat Disord.* 2023;11:986–994.e3. doi: 10.1016/j.jvsv.2023.04.004
8. Simon SJ, Patel R, Zwicker JI, Kazi DS, Hollenbeck BL. Venous thromboembolism in total hip and total knee arthroplasty. *JAMA Netw Open.* 2023;6:e2345883. doi: 10.1001/jamanetworkopen.2023.45883
9. Krenitsky N, Friedman AM, Yu K, Gyamfi-Bannerman C, Williams-Kane J, O'Shaughnessy F, Huang Y, Wright JD, D'Alton ME, Wen T. Trends in venous thromboembolism and associated risk factors during delivery hospitalizations from 2000 to 2018. *Obstet Gynecol.* 2022;139:223–234. doi: 10.1097/AOG.0000000000004648

- al. Maternal mortality related to pulmonary embolism in the United States, 2003-2020. *Am J Obstet Gynecol MFM*. 2023;5:100754. doi: 10.1016/j.ajogmf.2022.100754
26. Alabbadi S, Roach A, Chikwe J, Egorova NN. National trend in failure to rescue after cardiac surgeries. *J Thorac Cardiovasc Surg*. 2022;166:1157–1165.e6. doi: 10.1016/j.jtcvs.2022.02.037
27. Halawi MJ, Gronbeck C, Metersky ML, Wang Y, Eckenrode S, Mathew J, Suter LG, Eldridge N. Time trends in patient characteristics and in-hospital adverse events for primary total knee arthroplasty in the United States: 2010-2017. *Arthroplast Today*. 2021;11:157–162. doi: 10.1016/j.artd.2021.08.010
10. Martens KL, Li A, La J, May SB, Swinnerton KN, Tosi H, Elbers DC, Do NV, Brophy MT, Gaziano JM, et al. Epidemiology of cancer-associated venous thromboembolism in patients with solid and hematologic neoplasms in the Veterans Affairs Health Care System. *JAMA Netw Open*. 2023;6:e2317945. doi: 10.1001/jamanetworkopen.2023.17945
11. Martin KA, McCabe ME, Feinglass J, Khan SS. Racial disparities exist across age groups in Illinois for pulmonary embolism hospitalizations. *Arterioscler Thromb Vasc Biol*. 2020;40:2338–2340. doi: 10.1161/ATVBAHA.120.314573

28. Iyer GS, Tesfaye H, Khan NF, Zakoul H, Bykov K. Trends in the use of oral anticoagulants for adults with venous thromboembolism in the US, 2010-2020. *JAMA Netw Open*. 2023;6:e234059. doi: 10.1001/jamanetworkopen.2023.4059
29. Raskob GE, Spyropoulos AC, Cohen AT, Weitz JI, Ageno W, De Sanctis Y, Lu W, Xu J, Albanese J, Sugarmann C, et al. Association between asymptomatic proximal deep vein thrombosis and mortality in acutely ill medical patients. *J Am Heart Assoc*. 2021;10:e019459. doi: 10.1161/JAHA.120.019459
12. Teichman AL, Walls D, Choron RL, Butts CA, Krumrei N, Amro C, Swaminathan S, Arcomano N, Parekh A, Romeo P. The utility of lower extremity screening duplex for the detection of deep vein thrombosis in trauma. *J Surg Res*. 2022;269:151–157. doi: 10.1016/j.jss.2021.08.010
13. Cheong JY, Connelly TM, Russell T, Valente M, Bhama A, Lightner A, Hull T, Steele SR, Holubar SD. Venous thromboembolism risk stratification for patients undergoing surgery for IBD using a novel six factor scoring system using NSQIP-IBD registry. *ANZ J Surg*. 2023;93:1620–1625. doi: 10.1016/j.anzsurg.2023.08.010

30. Neeman E, Liu V, Mishra P, Thai KK, Xu J, Clancy HA, Schlessinger D, Liu R. Trends and risk factors for venous thromboembolism among hospitalized medical patients. *JAMA Netw Open.* 2022;5:e2240373. doi: 10.1001/jamanetworkopen.2022.40373
31. Gregson J, Kaptoge S, Bolton T, Pennells L, Willeit P, Burgess S, Bell S, Sweeting M, Rimm EB, Kabrhel C, et al; Emerging Risk Factors Collaboration. Cardiovascular risk factors associated with venous thromboembolism. *10.1111/ans.18242*
14. Bahl A, Alsbrooks K, Gala S, Hoerauf K. Symptomatic deep vein thrombosis associated with peripherally inserted central catheters of different diameters: a systematic review and meta-analysis. *Clin Appl Thromb Hemost.* 2019;4:163–173. doi: 10.1001/jamacardio.2018.4537

32. Fanola CL, Norby FL, Shah AM, Chang PP, Lutsey PL, Rosamond WD, Cushman M, Folsom AR. Incident heart failure and long-term risk for venous thromboembolism. *J Am Coll Cardiol*. 2020;75:148–158. doi: 10.1016/j.jacc.2019.10.058
15. Bello N, Meyers KJ, Workman J, Marcano Belisario J, Cervera R. Systematic literature review and meta-analysis of venous thromboembolism events in systemic lupus erythematosus. *Rheumatol Ther*. 2023;10:7–34. doi: 10.1007/s40744-022-00513-1
16. Fang MC, Reynolds K, Tabada GH, Prasad PA, Sung SH, Parks AL, Garcia E, Portugal C, Fan D, Pai AP, et al. Assessment of the risk of venous thromboembolism in nonhospitalized patients with COVID-19. *JAMA Netw Open*. 2023;6:e232338. doi: 10.1001/jamanetworkopen.2023.2338
17. Deitelzweig S, Luo X, Nguyen JL, Malhotra D, Emir B, Russ C, Li X, Lee TC, Ferri M, Wiederkehr D, et al. Thrombotic and bleeding events, mortality, and anticoagulant use among 546,656 hospitalized patients with COVID-19 in the United States: a retrospective cohort study. *J Thromb Thrombolysis*. 2022;53:766–776. doi: 10.1007/s11239-022-02644-2
18. Wu C, Liu Y, Cai X, Zhang W, Li Y, Fu C. Prevalence of venous thromboembolism in critically ill patients with coronavirus disease 2019: a meta-analysis. *Front Med (Lausanne)*. 2021;8:603558. doi: 10.3389/fmed.2021.603558
19. Vardar U, Shaka H, Kumi D, Gajjar R, Bess O, Kanemo P, Shaka

33. Michailidou D, Zhang T, Stamatis P, Ng B. Risk of venous and arterial thromboembolism in patients with giant cell arteritis and/or polymyalgia rheumatica: a Veterans Health Administration population-based study in the United States. *J Intern Med*. 2022;291:665–675. doi: 10.1111/joim.13446
 34. Kupelian V, Viscidi E, Hall S, Li L, Eaton S, Dilley A, Currier N, Ferguson T, Fanning L. Increased risk of venous thromboembolism in patients with amyotrophic lateral sclerosis: results from a US insurance claims database study. *Neurol Clin Pract*. 2023;13:e200110. doi: 10.1212/CPJ.0000000000200110
 35. Walker RF, Zakai NA, MacLehose RF, Cowan LT, Adam TJ, Alonso A, Lutsey PL. Association of testosterone therapy with risk of venous thromboembolism among men with and without hypogonadism. *JAMA Intern Med*. 2019;180:190–197. doi: 10.1001/jamainternmed.2019.5135
 36. Gartlehner G, Patel SV, Reddy S, Rains C, Schwimmer M, Kahwati L. Hormone therapy for the primary prevention of chronic conditions in post-menopausal persons: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2022;328:1747–1765. doi: 10.1001/jama.2022.18324
- A, Baskaran N. Gender disparities, causes and

37. Lo Re V 3rd, Dutcher SK, Connolly JG, DeFor TA, Diiho DA, Harrington LB, Hou L. of COVID-19 vs influenza with risk of events among hospitalized patients. *JAMA*. 10.1001/jama.2022.13072
38. Srivastava PK, Klonmhaus AM, Tehrani DM, PS, Rafique A, de Lemos J, Parikh RV. ant time period on clinical presentation and coronavirus disease 2019 patients. *Mayo* 2023;7:411–429. doi:
39. Harris DA, Haves KN, Zullo AR, Mor V, EP, Diiho DA, McMahon-Walraven CN. risks of potential adverse events following tion among older US adults. *JAMA Netw Open*. 2023;6:e2326852. doi: 10.1001/jamanetworkopen.2023.26852
40. Kotamarti VS, Greige N, Heiman AJ, Patel A, Ricci JA. Risk for venous thromboembolism in transgender patients undergoing cross-sex hormone treatment: a systematic review. *J Sex Med*. Biobank Japan, CHARGE Hemostasis vestigation of venous 2022;146:1225–1242. doi:
54. Ghouse J, Traquante V, Ahlberg G, Rand Vissina CR, Trudso L, Jonsdottir I. analysis identifies 93 risk loci and monogenic forms of venous 409. doi: 10.1038/s41588-022-01286-
55. Fernando SM, Tran A, Cheng W, Moller MH, Mehta S, Fowler RA. critically ill adults: a systematic review 2022;161:418–428. doi:
56. Raimas-George MR, Ross SW, Yang H 2021;18:1280–1291. doi: 10.1016/j.jsxm.2021.04.006
41. Jerjes-Sanchez C, Rodriguez D, Farjat AE, Kayani G, MacCallum P, Lopes RD, Turpie AGG, Weitz JI, Haas S, Ageno W, et al; GARFIELD-

CE. Just what the doctor ordered: missed ordering of venous thrombo- embolism chemoprophylaxis is associated with increased VTE events in high-risk general surgery patients. *Ann Surg.* 2022;278:e614–e619. doi: 10.1097/SLA.0000000000005779

57. Tran A, Fernando SM, Carrier M, Siegal DM, Inaba K, Vogt K, Engels PT, English SW, Kanji S, Kyeremanteng K, et al. Efficacy and safety of low molecular weight heparin versus unfractionated heparin for prevention of venous thromboembolism in trauma patients: a systematic review and meta-analysis. *Thromb Res.* 2017;149:82–87. doi: 10.1016/j.thromres.2017.05.005

lism: insights from GARFIELD-VTE. *TH Open.* 2021;5:e24–e34. doi: 10.1055/s-0040-1722611

42. Edwards MA, Muraleedharan D, Spaulding A. Racial disparities in reasons for mortality following bariatric surgery. *J Racial Ethn Health Disparities.* 2023;10:526–535. doi: 10.1007/s40615-022-01242-5

43. Nathan AS, Geng Z, Dayoub EJ, Khatana SAM, Eberly LA, Kobayashi T, Pugliese SC, Adusumalli S, Giri J, Groeneveld PW. Racial, ethnic, and socioeconomic inequities in the prescription of direct oral anti-coagulants in patients with venous thromboembolism in the United States. *Circ Cardiovasc Qual Outcomes.* 2019;12:e005600. doi: 10.1161/CIRCOUTCOMES.119.005600

44. Cohen AT, Sah J, Dhamane AD, Lee T, Rosenblatt L, Hlavacek P, Emir B, Keshishian A, Yuce H, Luo X. Effectiveness and safety of apixaban versus warfarin among older patients with venous thromboembolism with different demographics and socioeconomic status. *Adv Ther.* 2021;38:5519–5533. doi: 10.1007/s12325-021-01918-0

45. Zoller B, Ohlsson H, Sundquist J, Sundquist K. A sibling based de-sign to quantify genetic and shared environmental effects of venous thromboembolism in Sweden. *Thromb Res.* 2017;149:82–87. doi: 10.1016/j.thromres.2017.05.005

10.1097/SLA.00000000000005157

58. Liu M, Wang G, Li Y, Wang H, Liu H, Guo N, Han C, Peng Y, Yang M, Liu Y, et al. Efficacy and safety of thromboprophylaxis in cancer patients: a systematic review and meta-analysis. *Ther Adv Med Oncol*. 2020;12:1758835920907540. doi: 10.1177/1758835920907540
59. Bistervels IM, Buchmüller A, Wiegers HMG, Ní Áinle F, Tardy B, Donnelly J, Verhamme P, Jacobsen AF, Hansen AT, Rodger MA, et al; Highlow Block Writing Committee; Highlow Investigators. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2022;400:1777–1787. doi: 10.1016/S0140-6736(22)02128-6
60. Middleton P, Shepherd E, Gomersall JC. Venous thromboembolism prophylaxis for women at risk during pregnancy and the early post-natal period. *Cochrane Database Syst Rev*. 2021;3:CD001689. doi: 10.1002/14651858.CD001689.pub4
61. Nederpelt CJ, Bijman Q, Krijnen P, Schipper IB. Equivalence of DOACS and LMWH for thromboprophylaxis after hip fracture surgery: systematic review and meta-analysis. *Injury*. 2022;53:1169–1176. doi: 10.1016/j.injury.2021.11.052
46. Kujovich JL. Factor V Leiden thrombophilia. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. *GeneReviews*®; 1993-2020.
47. Simone B, De Stefano V, Leoncini E, Zacho J, Martinelli I, Emmerich J, Rossi E, Folsom AR, Almawi WY, Scarabin PY, et al. Risk of venous thromboembolism associated with single and combined effects of factor V Leiden, prothrombin 20210A and methylenetetrahydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. *Eur J Epidemiol*. 2013;28:621–647. doi: 10.1007/s10654-013-9825-8
48. Croles FN, Borjas-Howard J, Nasserinejad K, Leebeek FWG, Meijer K. Risk of venous thrombosis in antithrombin deficiency: a systematic review and bayesian meta-analysis. *Semin Thromb Hemost*. 2018;44:315–326. doi: 10.1055/s-0038-1625983
49. Croles FN, Nasserinejad K, Duvekot JJ, Kruip MJ, Meijer K, Leebeek FW. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. *BMJ*. 2017;359:j4452. doi: 10.1055/s-0038-1625983

62. Wang Y, Wang M, Ni Y, Liang Z. Direct oral anticoagulants for thromboprophylaxis in ambulatory patients with cancer. *Hematology*. 2020;25:63–70. doi: 10.1080/16078454.2020.1719726
63. Flumignan RL, Civile VT, Tinôco JDS, Pascoal PI, Areias LL, Matar CF, Tendal B, Trevisani VF, Atallah AN, Nakano LC. Anticoagulants for people hospitalised with COVID-19. *Cochrane Database Syst Rev*. 2022;3:CD013739. doi: 10.1002/14651858.CD013739.pub2
64. Liu HZ, Liang J, Hu AX. The efficacy and safety of aspirin in preventing venous thrombosis in major orthopedic surgery: an updated meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2023;102:e35602. doi: 10.1097/MD.00000000000035602
65. Clarke MJ, Broderick C, Hopewell S, Juszczak E, Eisinga A. Compression stockings for preventing deep vein thrombosis in airline passengers. *Cochrane Database Syst Rev*. 2021;4:CD004002. doi: 10.1002/14651858.CD004002.pub4
66. Meng J, Liu W, Wu Y, Xiao Y, Tang H, Gao S. Is it necessary to wear compression stockings and how long should they be worn for preventing postoperative deep vein thrombosis? A meta-analysis. *Journal of Thrombosis and Haemostasis*. 2023;23:1023–1032. doi: 10.1136/bmj.j4452
50. Lee EJ, Dykas DJ, Leavitt AD, Camire RM, Ebberink E, Garcia de Frutos P, Gnanasambandan K, Gu SX, Huntington JA, Lentz SR, et al. Whole-exome sequencing in evaluation of patients with venous thromboembolism. *Blood Adv*. 2017;1:1224–1237. doi: 10.1182/bloodadvances.2017005249
51. Klarin D, Emdin CA, Natarajan P, Conrad MF, Kathiresan S; INVENT Consortium. Genetic analysis of venous thromboembolism in UK Biobank identifies the *ZFPM2* locus and implicates obesity as a causal risk factor. *Circ Cardiovasc Genet*. 2017;10:e001643. doi: 10.1161/CIRCGENETICS.116.001643
52. de Haan HG, Bezemer ID, Doggen CJ, Le Cessie S, Reitsma PH, Arellano AR, Tong CH, Devlin JJ, Bare LA, Rosendaal FR, et al. Multiple SNP testing improves risk prediction of first venous thrombosis. *Blood*. 2012;120:656–663. doi: 10.1182/blood-2011-12-397752
53. Thibord F, Klarin D, Brody JA, Chen MH, Levin MG, Chasman DI, Goode EL, Hveem K, Teder-Laving M, Martinez-Perez A, et al; 23andMe Research Team, et al. Genetic analysis of venous thromboembolism in UK Biobank identifies the *ZFPM2* locus and implicates obesity as a causal risk factor. *Circ Cardiovasc Genet*. 2017;10:e001643. doi: 10.1161/CIRCGENETICS.116.001643

- thrombotic syndrome? A meta-analysis of randomized controlled trials. *Thromb Res.* 2023;225:79–86. doi: 10.1016/j.thromres.2023.03.016
- Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. *Cochrane Database Syst Rev.* 2022;1:CD005258. doi: 10.1002/14651858.CD005258.pub4
68. Ho KM, Rao S, Honeybul S, Zellweger R, Wibrow B, Lipman J, Holley A, et al. Filters in severely injured patients. *N Engl J Med.* 2019;381:328–337. doi: 10.1056/NEJMoa1806515
69. Heijkoop B, Nadi S, Spornat D, Kiroff G. Extended versus inpatient thromboprophylaxis with heparins following major open abdominopelvic surgery (*Lond*). 2020;9:7. doi: 10.1186/s13741-020-0137-8
67. Kakkos S, Kirkilesis G, Caprini JA, Geroulakos G, Nicolaides A, Stansby G, et al. sion and pharmacological prophylaxis for prevention of venous throm-

70. Zayed Y, Kheiri B, Barbarawi M, Banifadel M, Abdalla A, Chahine A, Obeid M, Haykal T, Yelangi A, Malapati S, et al. Extended duration of thromboprophylaxis for medically ill patients: a systematic review and meta-analysis of randomised controlled trials. *Intern Med J*. 2020;50:192–199. doi: 10.1111/imj.14417
71. Kirkilesis G, Kakkos SK, Bicknell C, Salim S, Kakavia K. Treatment of distal deep vein thrombosis. *Cochrane Database Syst Rev*. 2020;4:CD013422. doi: 10.1002/14651858.CD013422.pub2
72. Pawar A, Gagne JJ, Gopalakrishnan C, Iyer G, Tesfaye H, Brill G, Chin K, Bykov K. Association of type of oral anticoagulant dispensed with adverse clinical outcomes in patients extending anticoagulation therapy beyond 90 days after hospitalization for venous thromboembolism. *JAMA Netw Open*. 2023;6:e2328033. doi: 10.1001/jamanetworkopen.2023.28033
74. Haas S, Farjat AE, Pieper K, Ageno W, Angchaisuksiri P, Bounameaux H, Goldhaber SZ, Goto S, Mantovani L, Prandoni P, et al. On-treatment comparative effectiveness of vitamin K antagonists and direct oral anticoagulants in GARFIELD-VTE, and focus on cancer and renal disease. *TH Open*. 2022;6:E354–E364. doi: 10.1055/s-0042-1757744
75. Khan AM, Chiasakul T, Redd R, Patell R, McCarthy EP, Neuberger D, Zwicker JI. Survival outcomes with warfarin compared with direct oral anticoagulants in cancer-associated venous thromboembolism in the United States: a population-based cohort study. *PLoS Med*. 2022;19:e1004012. doi: 10.1371/journal.pmed.1004012
76. Cohen AT, Sah J, Dhamane AD, Lee T, Rosenblatt L, Hlavacek P, Emir B, Keshishian A, Yuce H, Luo X. Effectiveness and safety of apixaban vs warfarin among venous thromboembolism patients at high-risk of bleeding. *PLoS One*. 2022;17:e0274969. doi: 10.1371/journal.pone.0274969
77. Cohen AT, Sah J, Dhamane AD, Lee T, Rosenblatt L, Hlavacek P, Emir B, Delinger R, Yuce H, Luo X. Effectiveness and safety of apixaban versus warfarin in venous thromboembolism patients with chronic kidney disease. *Thromb Haemost*. 2022;122:926–938. doi: 10.1055/s-0041-1740254
78. Wetmore JB, Herzog CA, Yan H, Reyes JL, Weinhandl ED, Roetker NS, Agarwal MA, Dhaliwal JS, Yang EH, Aksoy O, Press M, Watson K, Ziaieian B, Fonarow GC, Moriarty JM, Saggart R, et al. Sex differences in outcomes of percutaneous pulmonary artery thrombectomy in patients with pulmonary embolism. *Chest*. 2023;163:216–225. doi: 10.1016/j.chest.2022.07.020
88. Kobayashi T, Pugliese S, Sethi SS, Parikh SA, Goldberg J, Alkhafan F, Vitarello C, Rosenfield K, Lookstein R, Keeling B, et al. Contemporary management and outcomes of patients with high-risk pulmonary embolism. *J Am Coll Cardiol*. 2023;81:1016–1025. doi: 10.1016/j.jacc.2023.07.043
- Apixaban versus warfarin for treatment of venous thromboembolism in patients receiving long-term dialysis. *Clin J Am Soc Nephrol*. 2022;17:693–702. doi: 10.2215/CJN.14021021
79. Xie Y, Choi T, Al-Aly Z. Association of treatment with nirmatrelvir and the risk of Post-COVID-19 condition. *JAMA Intern Med*. 2023;183:554–564. doi: 10.1001/jamainternmed.2023.0743
80. Xie Y, Choi T, Al-Aly Z. Molnupiravir and risk of post-acute sequelae of covid-19: cohort study. *BMJ*. 2023;381:e074572. doi: 10.1136/bmj-2022-074572
81. Liu Y, Lu H, Bai H, Liu Q, Chen R. Effect of inferior vena cava filters on pulmonary embolism-related mortality and major complications: a systematic review and meta-analysis of randomized controlled trials. *J Vasc Surg Venous Lymphat Disord*. 2021;9:792–800.e2. doi: 10.1016/j.jvs.2021.02.008
82. Shafi I, Zlotshewer B, Zhao M, Lakhter V, Bikdeli B, Comerota A, Zhao H, Bashir R. Association of vena cava filters and catheter-directed thrombolysis for deep vein thrombosis with hospital readmissions. *J Vasc Surg Venous Lymphat Disord*. 2024;12:101677. doi: 10.1016/j.jvs.2023.08.016
83. Balabhadra S, Kuban JD, Lee S, Yevich S, Metwalli Z, McCarthy CJ, Huang SY, Tam A, Gupta S, Sheth SA, et al. Association of inferior vena cava filter placement with rates of pulmonary embolism in patients with cancer and acute lower extremity deep venous thrombosis. *JAMA Netw Open*. 2020;3:e2011079. doi: 10.1001/jamanetworkopen.2020.11079
84. Broderick C, Watson L, Armon MP. Thrombolytic strategies versus standard anticoagulation for acute deep vein thrombosis of the lower limb. *Cochrane Database Syst Rev*. 2021;1:CD002783. doi: 10.1002/14651858.CD002783.pub5
85. Javed A, Machin M, Gwozdz AM, Turner B, Onida S, Shalhoub J, Davies AH. Meta-analysis of lytic catheter-based intervention for acute proximal deep vein thrombosis in the reduction of post-thrombotic syndrome. *J Vasc Surg Venous Lymphat Disord*. 2023;11:866–875.e1. doi: 10.1016/j.jvs.2023.07.043

- cer on cancer- or venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE. *Cochrane Database Syst Rev*. 2021;10:CD010837. doi: 10.1002/14651858.CD010837.pub5
91. Martin KA, Harrington K, Huang X, Khan SS. Pulmonary embolism-related mortality during the COVID-19 pandemic: data from the United States. *Res Pract Thromb Haemost*. 2022;6:e12845. doi: 10.1002/rth2.12845
 92. Turpie AGG, Farjat AE, Haas S, Ageno W, Weitz JI, Goldhaber SZ, Goto S, Angchaisuksiri P, Kayani G, Lopes RD, et al; GARFIELD-VTE Investigators. 36-Month clinical outcomes of patients with venous thromboembolism: GARFIELD-VTE. *Thromb Res*. 2023;222:31–39. doi: 10.1016/j.thromres.2022.11.016
 93. Wang C, Zhang H, Zhou M, Cheng Y, Ye L, Chen J, Wang M, Feng Z. Prognosis of COVID-19 in patients with vein thrombosis: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2020;24:10279–10285. doi: 10.26355/eurrev_202010_23252
 94. Fu AZ, Feng X, Ashton V, Kharat A. Risk factors for recurrent venous thromboembolism: a real-world analysis. *Blood Coagul Fibrinolysis*. 2022;33:301–309. doi: 10.1097/MBC.0000000000001140
 95. Wiegers HMG, Knijp J, van Es N, Coppens M, Moll S, Klok FA, Middeldorp S. Risk of recurrence in women with venous thromboembolism related to estrogen-containing contraceptives: systematic review and meta-analysis. *J Thromb Haemost*. 2022;20:1158–1165. doi: 10.1111/jth.15661
 96. Lakhter V, Zack CJ, Brailovsky Y, Azizi AH, Weinberg I, Rosenfield K, Schainfeld R, Kolluri R, Katz P, Zhao H, et al. Predictors of intracranial hemorrhage in patients treated with catheter-directed thrombolysis for deep vein thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2021;9:627–634. doi: 10.1016/j.jvsv.2020.08.029
 97. Shah NB, Sharedalal P, Shafi I, Tang A, Zhao H, Lakhter V, Kolluri R, Rao AK, Bashir R. Prevalence and outcomes of heparin-induced thrombocytopenia in hospitalized patients with venous thromboembolic disease: insight from National Inpatient Sample. *J Vasc Surg Venous Lymphat Disord*. 2023;11:723–730. doi: 10.1016/j.jvsv.2023.02.001
 98. Mir T, Uddin M, Shafi O, Qureshi W, Kaur J, Zghouzi M, Lohia P, Soubani A, Burket M, Sheikh M, et al. Thrombotic superior vena cava syndrome: a national emergency department database study. *J Thromb Thrombolysis*. 2022;53:372–379. doi: 10.1007/s11239-021-02548-7
 99. Espitia O, Raimbeau A, Planquette B, Katsahian S, Sanchez O, Espinasse B, Bénichou A, Murris J. A systematic review and meta-analysis of the incidence of post-thrombotic syndrome, recurrent thromboembolism, and bleeding after upper extremity vein thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2024;12:101688. doi: 10.1016/j.jvsv.2023.09.002
 100. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed May 1, 2024.
 101. Stein PD, Matta F, Hughes MJ. Site of deep venous thrombosis and age in the selection of patients in the emergency department for hospitalization versus home treatment. *Am J Cardiol*. 2021;146:95–98. doi: 10.1016/j.amjcard.2021.01.024
 102. Dore RK, Antonova JN, Burudpakdee C, Chang L, Gorritz M, Genovese MC. The incidence, prevalence, and associated costs of anemia, malignancy, venous thromboembolism, major adverse cardiovascular events, and infections in rheumatoid arthritis patients by treatment history in the United States. *ACR Open Rheumatol*. 2022;4:473–482. doi: 10.1002/acr2.11376
 103. Setyawan J, Mu F, Zichlin ML, Billmyer E, Downes N, Yang H, Azimi S. Deep vein thrombosis: a systematic review and meta-analysis. *Vasa*. 2021;50:59–67. doi: 10.1024/0301-1526/a000875
86. Lichtenberg MKW, Stahlhoff S, Mlynczak K, Golicki D, Gagne P, Razavi MK, de Graaf R, Kolluri R, Kolasa K. Endovascular mechanical thrombectomy versus thrombolysis in patients with iliofemoral deep

- N, Strand V, Yarur A. Risk of thromboembolic events and associated healthcare costs in patients with inflammatory bowel disease. *Adv Ther.* 2022;39:738–753. doi: 10.1007/s12325-021-01973-7
104. Khoury H, Lyons R, Sanaiha Y, Rudasill S, Shemin RJ, Benharash P. Deep venous thrombosis and pulmonary embolism in cardiac

surgical patients. *Ann Thorac Surg*. 2020;109:1804–1810. doi: 10.1016/j.athoracsur.2019.09.055

105. RIETE Registry. Death within 30 days: venous thromboembolism. Accessed February 28, 2024.

106. Kurata S, Miyawaki N, Onawa K, Watanabe K, Asano K, Fujii T. Thromboembolic events in hospitalized patients with COVID-19: ecological assessment with a scoping review. *BMJ Open*. 2023;13:e066218. doi: 10.1136/bmjopen-2022-066218

107. Sioland H, Lindgren M, Toska T, Hansson PO, Sandblad KG, Alex C, Björck L, Cronie O, Björk J, Lundberg CE, et al. Pulmonary embolism and deep venous thrombosis after COVID-19: long-term risk in a population-based cohort study. *Res Pract Thromb Haemost*. 2023;7:100284. doi: 10.1016/j.rpth.2023.100284

108. Criqui MH, Jansky M, Fronck A, Denenberg JO, Langer RD, Bergan J, Golomb BA. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. *Am J Epidemiol*. 2003;158:448–456. doi: 10.1093/aje/kwg016

109. Cher BAY, NH. Women's tions: *J Vasc Sur*. 2010;1016/10.1016/

110. Martinez-Stein AT. venous doi: 10.1016/

111. de Moraes for chronic 2023;1:CD01

112. Westby D

- Varicose veins as a risk factor for venous thromboembolism in arthroplasty patients: meta-analysis. *Phlebology*. 2023;38:150–156. doi: 10.1177/02683555221150563
127. Schul MW, Melin MM, Keaton TJ. Venous leg ulcers and prevalence of surgically correctable reflux disease in a national registry. *J Vasc Surg* 2022;57:312–321. doi: 10.1007/s11239-023-02895-7
 109. Pappas PJ, Pappas SF, Nguyen KQ, Lakhanpal S. Racial disparities in the outcomes of superficial vein treatments for chronic venous insufficiency. *J Vasc Surg Venous Lymphat Disord*. 2020;8:789–798.e3. doi: 10.1016/j.jvsv.2019.12.076
 110. DeCarlo C, Boitano LT, Waller HD, Pendleton AA, Latz CA, Tanious A, Kim Y, Mohapatra A, Dua A. Pregnancy conditions and complications associated with the development of varicose veins. *J Vasc Surg Venous Lymphat Disord*. 2022;10:872–878.e68. doi: 10.1016/j.jvsv.2022.01.003
 111. Mok Y, Ishigami J, Sang Y, Kucharska-Newton AM, Salameh M, Schrack JA, Palta P, Coresh J, Windham BG, Lutsey PL, et al. Clinically recognized varicose veins and physical function in older individuals: the ARIC study. *J Gerontol A Biol Sci Med Sci*. 2022;77:1637–1643. doi: 10.1093/gerona/glab287
 112. Prandoni P, Haas S, Fluharty ME, Schellong S, Gibbs H, Tse E, Carrier M, Jacobson B, Ten Cate H, Panchenko E, et al; GARFIELD-VTE Investigators. Incidence and predictors of post-thrombotic syndrome in patients with proximal DVT in a real-world setting: findings from the GARFIELD-VTE registry. *J Thromb Thrombolysis*. 2024;57:312–321. doi: 10.1007/s11239-023-02895-7
 113. Natour AK, Rteil A, Corcoran P, Weaver M, Ahsan S, Kabbani L. Socioeconomic status and clinical stage of patients presenting for treatment of chronic venous disease. *Ann Vasc Surg*. 2022;83:305–312. doi: 10.1016/j.avsg.2021.12.010
 114. Fiebig A, Krusche P, Wolf A, Krawczak M, Timm B, Nikolaus S, Frings

128. *Lymphat Disord.* 2023;11:511–516. doi: 10.1016/j.jvsv.2022.11.005
129. Tettelbach WH, Driver V, Oropallo A, Kelso MR, Niezgoda JA, Wahab N, De Jong JL, Hubbs B, Forsyth RA, Magee GA. Treatment patterns and out- comes of Medicare enrollees who developed venous leg ulcers. *J Wound Care.* 2023;32:704–718. doi: 10.12968/jowc.2023.32.11.704
130. Shi C, Dumville JC, Cullum N, Connaughton E, Norman G. Compression bandages or stockings versus no compression for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2021;7:CD013397. doi: 10.1002/14651858.CD013397.pub2
131. Kolluri R, Lugli M, Villalba L, Varcoe R, Maleti O, Gallardo F, Black S, Forgues F, Lichtenberg M, Hinahara J, et al. An estimate of the economic burden of venous leg ulcers associated with deep venous disease. *Vasc Med.* 2022;27:63–72. doi: 10.1177/1358863X211028298
132. Zheng H, Magee GA, Tan TW, Armstrong DG, Padula WV. Cost-effectiveness of compression therapy with early endovenous ablation in venous ulcer- ation for a Medicare population. *JAMA Netw Open.* 2022;5:e2248152. doi: 10.1001/jamanetworkopen.2022.48152
133. Shon S, Kim H, Kim HC, Cho S, Lee SH, Joh JH. National trend of the treatment for chronic venous diseases in Korea between 2010 and 2020. *Ann Surg Treat Res.* 2023;104:27–33. doi: 10.4174/astr.2023.104.1.27
134. Homs-Romero E, Romero-Collado A, Verdu J, Blanch J, Rascon-Hernan C, Marti- Lluch R. Validity of chronic venous disease diagnoses and epi- demiology using validated electronic health records from primary care: a real-world data analysis. *J Nurs Scholarsh.* 2021;53:296–305. doi: 10.1111/jnu.12639
135. N, Schreiber S. Heritability of chronic venous disease. *Hum Genet.* 2010;127:669–674. doi: 10.1007/s00439-010-0812-9
136. Slonkova V, Slonkova V Jr, Vasku A, Vasku V. Genetic predisposition for chronic venous insufficiency in several genes for matrix metalloprotein- ases (MMP-2, MMP-9, MMP-12) and their inhibitor TIMP-2. *J Eur Acad Dermatol Venereol.* 2017;31:1746–1752. doi: 10.1111/jdv.14447
137. Raffetto JD, Ligi D, Maniscalco R, Khalil RA, Mannello F. Why ve-nous leg ulcers have difficulty healing: overview on pathophysiol-

134. Silva MJ, Louzada ACS, da Silva MFA, Portugal MFC, Teivelis MP, Wolosker N. Epidemiology of 869,220 varicose vein surgeries over 12 years in Brazil: trends, costs and mortality rate. *Ann Vasc Surg.* 2022;82:1–6. doi: 10.1016/j.avsg.2021.11.016
135. Rabe E, Regnier C, Goron F, Salmat G, Pannier F. The prevalence, disease characteristics and treatment of chronic venous disease: an international web-based survey. *J Comp Eff Res.* 2020;9:1205–1218. doi: 10.2217/ce-2020-0158
136. Kirsten N, Mohr N, Gensel F, Alhumam A, Bruning G, Augustin M. Efficacy of rivaroxaban in prevention of post-thrombotic syndrome: a systematic review and meta-analysis. *J Vasc Surg Venous*
117. Shadrina AS, Sharapov SZ, Shashkova TI, Tsepilov YA. Varicose veins of lower extremities: insights from the first large-scale genetic study. *PLoS Genet.* 2019;15:e1008110. doi: 10.1371/journal.pgen.1008110
118. Karathanos C, Nana P, Spanos K, Kouvelos G, Brotis A, Matsagas M, Giannoukas A. Efficacy of rivaroxaban in prevention of post-thrombotic syndrome: a systematic review and meta-analysis. *J Vasc Surg Venous*
119. Population-ogy, clinical consequences, and treatment. *J Clin Med.* 2020;10:29. doi: 10.3390/jcm10010029

- based epidemiologic study in venous diseases in Germany: prevalence, co-
Risk Manag. 2021;17:679–687. doi: 10.2147/VHRM.S323084
137. Didden E-M, Lee E, Wyckmans J, Quinn D, Perchenet L. Time to diagnosis
sis of nationwide US healthcare data. *Pulm Circ.* 2023;13:e12188. doi:
10.1016/j.jvsv.2021.04.016
119. Parikh D, Choksi E, Reeves R, Winokur RS, Tan A, Weinstein J, Ford
RW. Characterizing trends in chronic superficial venous disease treatment
among Medicare beneficiaries from 2010 to 2018. *J Vasc Interv
Radiol.* 2024;35:301–307. doi: 10.1016/j.jvir.2023.11.003
120. Whing J, Nandhra S, Nesbitt C, Stansby G. Interventions for great
saphe-nous vein incompetence. *Cochrane Database Syst Rev.*
2021;8:CD005624.
doi: 10.1002/14651858.CD005624.pub4
121. Deol ZK, Lakhanpal S, Franzon G, Pappas PJ. Effect of obesity on
morbidity, and medical needs in a cohort of 19,104 workers. *Vasc Health
of pulmonary hypertension and diagnostic burden: a retrospective analy-
10.1002/pul2.12188*
- chronic venous insufficiency treatment outcomes. *J Vasc
Surg Venous Lymphat Disord.* 2020;8:617–628.e1. doi:
10.1016/j.jvsv.2020.04.006
122. Obi AT, Afridi S, Lurie F. Management and treatment
outcomes of pa-tients undergoing endovenous ablation are
significantly different between Intersocietal Accreditation
Commission-accredited and nonaccredited vein centers. *J
Vasc Surg Venous Lymphat Disord.* 2021;9:346–351. doi:
10.1016/j.jvsv.2020.07.007

138. Wilcox SR, Faridi MK, Camargo CA Jr. Demographics and outcomes of pulmonary hypertension patients in United States emergency departments. *West J Emerg Med.* 2020;21:714–721. doi: 10.5811/westjem.2020.2.45187

139. Lutsey PL, Evensen LH, Thenappan T, Prins KW, Walker RF, Farley JF, MacLehose RF, Alonso A, Zakai NA. Incidence and risk factors of pulmonary hypertension after venous thromboembolism: an analysis of a large health care database. *J Am Heart Assoc.* 2022;11:e024358. doi: 10.1161/JAHA.121.024358

140. Chaturvedi A, Kanwar M, Chandrika P, Thenappan T, Raina A, Benza RL. Data on clinical and economic burden associated with pulmonary arterial hypertension related hospitalizations in the United States. *Data Brief.* 2020;32:106303. doi: 10.1016/j.dib.2020.106303

141. Farber HW, Chakinala MM, Cho M, Frantz RP, Frick A, Lancaster L, Milligan S, Oudiz R, Panjabi S, Tsang Y, et al. Characteristics of patients

with pulmonary arterial hypertension from an innovative, comprehensive real-world patient data repository. *Pulm Circ*. 2023;13:e12258. doi: 10.1002/pul2.12258

142. Lentine KL, Lam NN, Caliskan Y, Xiao H, Axelrod DA, Costa SP, Levine DJ, Runo JR, Te HS, Rangaswami J, et al. Incidence, clinical correlates, and outcomes of pulmonary hypertension after kidney transplantation: analysis of linked US registry and Medicare billing claims. *Transplantation*. 2022;106:666–675. doi: 10.1097/TP.0000000000003783

143. Munshi RF, Pellegrini JR Jr, Patel P, Kashin M, Kang J, Sexton R, Russe JR, Makaryus AN, Patel P, Thakkar S, et al. Impact of pulmonary hypertension in patients with acute exacerbation of chronic obstructive pulmonary disease and its effect on healthcare

144. Frost AE, Zhao C, Farber HW, Benza R, Yen J, Selej M, Elliott CG.

Smoking history and pulmonary arterial hypertension: demographics, onset, and outcomes. *J Heart Lung Transplant*. 2022;42:377–389. doi: 10.1016/j.healun.2022.10.007

145. Kolaitis NA, Zamanian RT, de Jesus Perez VA, Badesch DB, Benza

Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9:573–584. doi: 10.1016/S2213-2600(20)30532-4

158. Barnes H, Yeoh HL, Fothergill T, Burns A, Humbert M, Williams T.

Prostacyclin for pulmonary arterial hypertension. *Cochrane Database Syst Rev*. 2019;5:CD012785.

doi: 10.1002/14651858.CD012785.pub2 159. Garry JD, Kolaitis NA, Kronmal R, Thenappan T, Hemnes A, Grinnan D, Bull T, Chakinala MM, Horn E.

RL, Burger CD, Chakinala MM, Elwing JM, Feldman J, Lammi MR, et al;

Pulmonary Hypertension Association Registry Investigators. Clinical differences and outcomes between methamphetamine-associated and idiopathic pulmonary arterial hypertension in the Pulmonary Hypertension Association Registry. *Ann Am Thorac Soc*. 2021;18:613–622. doi:

10.1016/j.healun.2022.08.019

160. Kerr KM, Elliott CG, Chin K, Benza RL, Channick RN, Davis RD, He F, LaCroix A, Madani MM, McLaughlin VV, et al. Results From the United States Chronic Thromboembolic Pulmonary Hypertension Registry: enrollment characteristics and 1-year follow-up. *Chest*. 2021;160:1822–1831. doi: 10.1016/j.chest.2021.05.052
161. Gillmeyer KR, Miller DR, Glickman ME, Qian SX, Klings ES, Maron BA, Hanlon JT, Rinne ST, Wiener RS. Outcomes of pulmonary vasodilator use in veterans with pulmonary hypertension associated with left heart disease and lung disease. *Pulm Circ*. 2021;11:20458940211001714. doi: 10.1513/AnnalsATS.202007-774OC
146. Bernardo RJ, Lu D, Ramirez RL 3rd, Hedlin H, Kawut SM, Bull T, De Marco T, Ford HJ, Grinnan D, Klinger JR, et al. Hispanic ethnicity and social de-terminants of health in pulmonary arterial hypertension: the Pulmonary

162. Trammell AW, Shah AJ, Phillips LS, Michael Hart C. Mortality in US veterans with pulmonary hypertension: a retrospective analysis of survival by sub-type and baseline factors. *Pulm Circ.* 2019;9:2045894019825763. doi: 10.1177/2045894019825763
- Hypertension Association Registry. *Ann Am Thorac Soc.* 2022;19:1459–1468. doi: 10.1513/AnnalsATS.202109-1051OC
147. Gillmeyer KR, Rinne ST, Qian SX, Maron BA, Johnson SW, Klings ES, Wiener RS. Socioeconomically disadvantaged veterans experience treatment delays for pulmonary arterial hypertension. *Pulm Circ.* 2022;12:e12171. doi: 10.1177/2045894022111111

163. Chang KY, Duval S, Badesch DB, Bull TM, Chakinala MM, De Marco T, Frantz RP, Hemnes A, Mathai SC, Rosenzweig EB, et al; PHAR Investigators. Mortality in pulmonary arterial hypertension in the modern era: early insights from the Pulmonary Hypertension Association Registry. *J Am Heart Assoc.* 2022;11:e024969. doi: 10.1002/pul2.12171
148. Dodson MW, Allen-Brady K, Brown LM, Elliott CG, Cannon-Albright LA. Chronic thromboembolic pulmonary hypertension cases cluster in families. *Chest.* 2019;155:384–390. doi: 10.1016/j.chest.2018.10.004
149. Gamou S, Kataoka M, Aimi Y, Chiba T, Momose Y, Isobe S, Hirayama T, Yoshino H, Fukuda K, Satoh T. Genetics in pulmonary arterial hypertension in a large homogeneous Japanese population. *Clin Genet.* 2018;94:70–80.

164. Chin KM, Auger WR, Benza RL, Channick RN, Davis RD, Elliott CG, He F, Jain S, Madani MM, McLaughlin VV, et al. Long-term survival and quality of life: results from the United States Chronic Thromboembolic Pulmonary Hypertension Registry. *CHEST Pulm.* 2023;1:100008. doi: <https://doi.org/10.1016/j.chpulm.2023.100008> doi: 10.1111/cge.13154
150. Yaoita N, Satoh K, Satoh T, Shimizu T, Saito S, Sugimura K, Tatebe S, Yamamoto S, Aoki T, Kikuchi N, et al. Identification of the novel variants in patients with chronic thromboembolic pulmonary hypertension. *J Am Heart Assoc.* 2020;9:e015902. doi: 10.1161/JAHA.120.015902
151. Rhodes CJ, Batai K, Bleda M, Haimel M, Southgate L, Germain M, Pauciulo MW, Hadinnapola C, Aman J, Girerd B, et al; UK NIHR BioResource Rare Diseases Consortium; UK PAH Cohort Study
165. Kim NH, Fisher M, Poch D, Zhao C, Shah M, Bartolome S. Long-Consortium; US PAH Biobank Consortium. Genetic determinants of risk in pulmonary arterial hypertension: international genome-wide association studies and meta-analysis. *Lancet Respir Med.* 2019;7:227–238. doi: 10.1016/S2213-2600(18)30409-0
152. Zhu N, Pauciulo MW, Welch CL, Lutz KA, Coleman AW, Gonzaga-Jauregui C, Wang J, Grimes JM, Martin LJ, He H, et al; PAH Biobank Enrolling Centers' Investigators. Novel risk genes and mechanisms implicated by exome sequencing of 2572 individuals with pulmonary arterial hyperten-

doi: 10.1177/2045894020935291

166. Rubens M, Ramamoorthy V, Saxena A, Jimenez J, George S, Baker J, Ruiz J, Chaparro S. Hospital outcomes in patients with pulmonary hypertension with atrial fibrillation in the United States. *Am J Cardiol.* 2024;212:67–72. doi: 10.1016/j.amjcard.2023.11.050
167. Heresi GA, Rao Y. Follow-up functional class and 6-minute walk distance identify long-term survival in pulmonary arterial hypertension. *Lung.* 2020;198:933–938. doi: 10.1007/s00408-020-00402-w
168. Billings CG, Lewis R, Hurdman JA, Condliffe R, Elliot CA, Thompson AAR, Smith IA, Austin M, Armstrong IJ, Hamilton N, et al. The incremental shuttle walk test predicts mortality in non-group 1 pulmonary hypertension: results from the ASPIRE Registry. *Pulm Circ.* 2019;9:2045894019848649. doi: 10.1186/s13073-019-0685-z
153. Singh H, Agarwal L, Jani C, Bhatt P, Hartley A, Shalhoub J, Kurman JS, Al Omari O, Ahmed A, Marshall DC, et al. Pulmonary hypertension associated mortality in the United States from 2003 to 2020: an observational analysis of time trends and disparities. *J Thorac Dis.* 2023;15:3256–3272. doi: 10.1177/2045894019848649

169. Binbraik Y, Wang MK, Riekk T, Conen D, Marcucci M, Borges FK, Hambly N, Devereaux PJ. Pulmonary hypertension and associated outcomes in noncardiac surgery: a systematic review and meta-analysis. *Heart Lung*. 2023;58:21–27. doi: 10.1016/j.hrtlng.2022.10.015
doi: 10.21037/jtd-22-1468
154. Yan L, Shi W, Liu Z, Zhao Z, Luo Q, Zhao Q, Jin Q, Zhang Y, Li X, Duan A. The benefit of exercise-based rehabilitation programs in patients with pulmonary hypertension: a systematic review and meta-analysis of randomized controlled trials. *Pulm Circ*. 2021;11:20458940211007810. doi: 10.1177/20458940211007810
155. Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. *Cochrane Database Syst Rev*. 2019;1:CD012621.
170. Low TT, Guron N, Ducas R, Yamamura K, Charla P, Granton J, Silversides
doi: 10.1002/14651858.CD012621.pub2
156. Liu C, Chen J, Gao Y, Deng B, Liu K. Endothelin receptor antagonists for pulmonary arterial hypertension. *Cochrane Database Syst Rev*. 2021;3:CD004434. doi: 10.1002/14651858.CD004434.pub6
157. Hoeper MM, Al-Hiti H, Benza RL, Chang SA, Corris PA, Gibbs JSR, Grunig E, Jansa P, Klinger JR, Langleben D, et al; REPLACE Investigators.

- CK. Pulmonary arterial hypertension in pregnancy: a systematic review of outcomes in the modern era. *Pulm Circ.* 2021;11:20458940211013671. doi: 10.1177/20458940211013671
171. Rohlfing AB, Bischoff KE, Kolaitis NA, Kronmal RA, Kime NA, Gray MP, Bartolome S, Chakinala MM, Frantz RP, Ventetuolo CE, et al; PHAR Investigators. Palliative care referrals in patients with pulmonary arterial hypertension: the Pulmonary Hypertension Association Registry. *Respir Med.* 2023;206:107066. doi: 10.1016/j.rmed.2022.107066
172. Macias CG, Wharam JF, Maron BA, Ong MS. Urban-rural disparities in pulmonary hypertension mortality. *Ann Am Thorac Soc.* 2020;17:1168–1171. doi: 10.1513/AnnalsATS.202003-234RL
173. DuBrock HM, Germack HD, Gauthier-Loiselle M, Linder J, Satija A, Manceur AM, Cloutier M, Lefebvre P, Panjabi S, Frantz RP. Economic

- burden of delayed diagnosis in patients with pulmonary arterial hypertension (PAH). *Pharmacoecon Open*. 2024;8:133–146. doi: 10.1007/s41669-023-00453-8
174. Studer S, Hull M, Pruett J, Koen E, Tsang Y, Drake W. Treatment patterns, healthcare resource utilization, and healthcare costs among patients with pulmonary arterial hypertension in a real-world US database. *Pulm Circ*. 2019;9:2045894018816294. doi: 10.1177/2045894018816294
175. Saunders H, Helgeson SA, Abdelrahim A, Rottman-Pietrzak K, Reams V, Zeiger TK, Moss JE, Burdett CD. Comparing diagnosis and management of pulmonary hypertension patients at a pulmonary hypertension center versus community centers. *Diseases*. 2022;10:5. doi: 10.3390/diseases10010005
176. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. 2024. doi: 10.1007/s41669-023-00453-8
177. Emmons-Bell S, Johnson C, Yacoub M. Global Burden of Disease Study and Institute for Health Metrics and Evaluation. 2024. doi: 10.1007/s41669-023-00453-8
178. Pan W, Zhang Z, Wang Z, Zhen S, Tao X, Wan J, et al. Higher incidence of chronic pulmonary hypertension after acute pulmonary embolism in Chinese adults: a nationwide population-based study. *European Respiratory Journal*. 2021;52(10):2100055. doi: 10.1183/1399-6613.2100055

25. PERIPHERAL ARTERY
DISEASE AND AORTIC DISEASES

ICD-9 440.20 to 440.24, 440.30 to 440.32, 440.4, 440.9, 443.9, 445.02; ICD-10 I70.2, I70.9, I73.9, I74.3, I74.4.

See Tables 25-1 through 25-3 and Charts 25-1 through 25-5

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Peripheral Artery Disease

- Black participants had an increased risk of incident PAD compared with White participants (multivariable-adjusted HR, 1.09 [95% CI, 1.02–1.16]). This increased overall risk was attributed to a greater risk of amputation (multi-variable-adjusted HR, 1.20 [95% CI, 1.08–1.33]) (Table 25-1, Figure 25-1).
- Black participants had an increased risk of incident PAD compared with White participants (multivariable-adjusted HR, 1.04 [95% CI, 0.95–1.13]).

Lifetime Risk and Cumulative Incidence

- The lifetime risk (90-year horizon)

and 30% in White individuals, Hispanic individuals, and Black individuals, respectively, from pooled data

Prevalence

(See Charts 25-1 and 25-2)

- Data from the GBD Study 2019 estimate that the US prevalence of PAD among those ≥ 40 years of age was 12 461 375 individuals (95% UI, 11 235 661–13 740 797).¹
- Estimates of PAD prevalence by age, sex, and race and ethnicity are shown in Charts 25-1 and 25-2.
 - PAD prevalence increases with age, approximately doubling per decade.^{2,3}
 - PAD prevalence in males and females varies by age, race, and ethnicity.^{1,2}
 - PAD prevalence is greater in Black compared with NH White individuals, particularly after 50 and 60 years of age in males and females, respectively.^{2,3}

Incidence

- In the GBD Study 2019, the age-standardized incidence rate of PAD in the United States was

from 6 US community-based cohorts.⁵

193.5 per 100 000 (95% UI, 173.7–215.6 per 100 000).¹

- Among 77 041 individuals in the Veterans Affairs birth cohort born between 1945 and 1965 with normal baseline ABIs, risk of incident PAD, defined as subsequent ABI < 0.90 , surgical or percutaneous revascularization, or nontraumatic amputation, varied by sex and race.⁴

– Females were at lower risk of incident PAD compared with males (multivariable-adjusted HR, 0.49 [95% CI, 0.41–0.59]).

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Secular Trends

- Based on the GBD, the US prevalence of PAD among those ≥ 40 years of age increased from 9 903 935 (95% UI, 8 490 068–11 331 986) in 1990 to 12 461 375 (95% UI, 11 235 661–13 740 797) in 2019.¹
 - Despite an increase in the number of individuals with PAD, the age-standardized rate decreased by 27.7 (95% UI, 32.7–21.4) per 100 000.
- From 2011 to 2017, the proportion of hospitalizations for PAD increased from 4.5% to 8.9% ($P_{\text{trend}} < 0.0001$) according to NIS data.⁶
- Similarly, from 2011 to 2017, the proportion of hospitalizations for CLTI increased from 0.9% to 1.4% ($P_{\text{trend}} < 0.0001$) in the NIS.⁶
- From 2011 to 2021, principal discharge diagnosis for PAD decreased from 135 969 to 74 105 (HCUP, unpublished NHLBI tabulation).
- Between 2011 and 2017, the annual rate of endovascular lower-extremity peripheral artery interventions increased from 464.47 to 509.99 per 100 000 individuals among Medicare beneficiaries.⁷
- Rates of lower-extremity amputation are also increasing.
 - Between 2009 and 2015, a 50% increase in the rate of nontraumatic lower-extremity amputation was observed in adults with diabetes according to NIS data.⁸
 - Among patients in the Veterans Affairs health care system, rates of lower-extremity amputation increased from 12.89 (95% CI, 12.53–13.25) per 10 000 individuals to 18.12 (95% CI, 17.70–18.54) per 10 000 individuals from 2008 to 2018.⁹

Risk Factors

- Modifiable PAD risk factors largely parallel those for atherosclerosis in other vascular beds such as CAD and include smoking, diabetes, hypertension, and atherogenic dyslipidemia.^{3,5,10,11}

- Current or former smoking is PAD risk factors, with ORs (all $P < 0.05$) and relatively recent smokers.^{3,5}
 - Heavy smoking, defined by duration, or smoking factor for PAD compared
- Diabetes is associated with with ORs ranging from 1.38 to
- Hypertension, defined as BP associated with $\approx 50\%$

1.67 [95% CI, 1.50–1.86]).¹⁰

– Each 20-mm Hg increase in SBP was associ-

Social Determinants of

- Lower SES (defined as living median household income associated with greater risk for [95% CI, 1.06–1.17]).²³
- Among patients with PAD tion or amputation in the neighborhood social the Area Deprivation Index, later presentation and a lower salvage.²⁴

ated with an OR of 1.27 (95% CI, 1.22–1.32) for

- Compared with those in the lowest quintile of the Area Deprivation Index, those in the high-est quintile were more likely to present with rest

PAD.⁵

[95%

pain compared with claudication (RR, 2.0

- Among patients treated for hypertension, SBP is more strongly associated with incident PAD (HR

CI, 1.8–2.2]; $P < 0.001$) or tissue loss compared with claudication (RR, 1.4 [95% CI, 1.3–1.6];
per 1-SD increase in SBP, 1.46 [95% CI, 1.29–

$P < 0.001$).

1.65]) than DBP (HR per 1-SD increase in
DBP, 1.12 [95% CI, 0.97–1.30]).¹³

incident PAD (all $P > 0.05$) but was
associated with incident

• In both ARIC and WHS, each 1-SD increase in
both TC and LDL-C was not associated with

- Compared with those in the lowest quintile of the Area Deprivation Index, those in the highest quintile were also less likely to undergo attempts at revascularization (RR, 0.59 [95% CI, 0.51–0.70]; $P<0.001$).

CAD.^{14,15}

geo-

- In contrast, each 1-SD decrease in HDL-C is strongly associated with incident PAD (HR, 1.39 [95% CI, 1.16–1.67] and 1.92 [95% CI, 1.49–2.50], respectively).^{14,15}

- The rate of lower-extremity amputation varies

– Further lipid subfraction analyses suggest that markers of atherogenic dyslipidemia, including

graphically within the United States and may be influenced by patient rurality and race.²⁵

– Among Medicare beneficiaries, zip codes in the top quartile of amputation rates had a larger mean proportion of Black residents than zip codes in the bottom quartile (17.5% versus 4.4%;

elevated concentrations of triglyceride-rich lipoproteins such as small LDL particles (HR, 2.17 [95% CI, 1.10–4.27]) and total HDL particles (HR, 0.29 [95% CI, 0.16–0.52]), are independently associated with PAD.^{14–17}

– With the use of mendelian randomization, apolipoprotein B-lowering therapy was predicted to have a greater reduction in CAD risk (per 1-SD reduction: OR, 0.66 [95% CI, 0.63–0.69]; $P=4\times10^{-73}$) than PAD risk (per 1-SD reduction: OR, 0.87 [95% CI, 0.84–0.91]; $P=9\times10^{-9}$).¹⁸

– Mendelian randomization also suggests a causal link between lipoprotein(a) and PAD among individuals of both European (per 1-SD increase: OR,

$P<0.001$).²⁵

1.22 [95% CI, 1.11–1.34]; $P=2.97\times10^{-5}$) and African (per 1-SD increase: OR, 1.16 [95% CI, 1.01–1.33]; $P=0.034$) ancestries.¹⁹

• Smoking, type 2 diabetes, hypertension, and hypercholesterolemia accounted for 75% (95% CI, 64%–87%) of risk associated with the development of clinical PAD in the HPFS of males.²⁰

• MetS was associated with increased risk for incident PAD according to data from the CHS (HR, 1.47 [95% CI, 1.11–1.94]) and WHS (HR, 1.48 [95% CI, 1.00–2.19]).^{21,22}

- Data from the Vascular Quality Initiative suggest that individuals from underrepresented racial and ethnic groups living in rural areas have a 52% greater odds of amputation than people from underrepresented racial and ethnic groups living in urban areas (95% CI, 1.19–1.94).²⁶

Risk Prediction

- Models for predicting the probability of an ABI
Included variables were age, sex, race, pulse pres-
sta- tus, with a C statistic of 0.76 (95% CI, 0.72–0.79).²⁷
included diabetes and history of CAD or stroke,
- In a study using electronic medical record data to
machine-learning method had a C statistic of 0.68
demic health care systems.²⁹

<0.9 have been developed from NHANES data.^{5,27}
sure, TC and HDL (or their ratio), and smoking
Another model with NHANES data additionally
which yielded a similar C statistic of 0.75.^{5,28}
identify patients at high risk of an abnormal ABI, a
in 2 validation cohorts derived from separate aca-

Genetics/Family History

- Atherosclerotic PAD is heritable. Monozygotic twins
for PAD with an OR of 17.7 (95% CI, 11.7–26.6) and

compared with dizygotic twins had a greater risk

5.7 (95% CI, 4.1–7.9), respectively, in the Swedish Twin Registry, with heritable factors accounting for 58% of phenotypic variance between twins.³⁰ Chip-

based genetic analyses similarly suggest that the heritability of PAD is 55%.³¹

• GWASs have identified genetic loci associated with common atherosclerotic PAD, including the CHD-associated chromosome 9p21 genetic locus associated with PAD, AAA, and intracranial aneurysm.³² – Other common *CDKN2B*, *DAB21P*, and *CYBA* genes.³³

– A large-scale GWAS in >31 000 cases with PAD and >211 000 controls from the MVP and the UK Biobank identified 18 new PAD loci. Eleven of the loci were associated with atherosclerotic disease in 3 vascular beds, including *LDLR*, *LPA*, and *LPL*, whereas 4 of the variants were specific for PAD (including variants in *TCF7L2* and *F5*).³⁴ – Given this overlap between genetic risk factors between different vascular beds, a GRS composed of genetic variants associated with CAD has been shown to be associated with PAD in the UK Biobank (OR, 1.28 [95% CI, 1.23–1.32]).³⁵ In another study, targeted sequencing of 41 genome regions associated with CAD performed in 1749 cases with PAD and 1855 controls found

higher levels of HDL-C are associated with lower PAD risk.

Prevention (Primary)

• Approaches to primary prevention of PAD are extrapolated from recommendations for prevention of atherosclerotic disease with a focus on optimization of healthy lifestyle behaviors (healthy diet, PA, and never-smoking), avoidance of the

overlap of several genes between CAD and PAD.³⁶

• Mendelian randomization, primarily in populations of European descent, has been used to examine evidence of causality for several putative PAD risk factors, including hemostatic measures, lipoproteins, smoking, and BP phenotypes. These studies reported that factor VIII, von Willebrand factor, apolipoprotein B, very-low-density lipoprotein, smoking, BP, and gut microbiota taxa affect PAD.^{18,37–40}

• One GWAS of 449 548 participants of European ancestry (12 086 PAD cases) examined evidence of SNP-by-smoking and SNP-by-type 2 diabetes interaction on PAD.³¹ The authors reported a lead variant near *CCSER1* that showed genome-wide significant evidence of association with PAD only in those with diabetes ($P=2.5\times10^{-9}$; $P_{\text{interaction}}=5.3\times10^{-7}$). This potentially suggests unique pathways of PAD development in those with

Awareness, Treatment, and Control

Awareness

- Awareness of PAD, its risk factors, and its complications is relatively low.
 - In a US-based survey of 2501 adults ≥ 50 years of age in 2006, only 25% of individuals expressed familiarity with PAD compared with 67% for CAD and 74% for stroke.⁴² Income and education levels were positively associated with all knowledge domains.
- Physicians may underappreciate and undertreat PAD.
 - Patients with PAD receive optimal medical therapy less frequently than patients with CAD. Data from the MarketScan and Medicare databases showed that only 34% of patients with PAD were prescribed guideline-recommended statins compared with 52% of patients with CAD.⁴³
 - Similarly, only 24.5% of patients with PAD in the MarketScan database achieved a target LDL-C < 70 mg/dL.⁴⁴
 - In the BEST-CLI trial, an RCT comparing revascularization strategies for patients undergoing treatment of CLTI, only 25% of participants were receiving optimal medical treatment defined as smoking abstinence, controlled BP, use of an antiplatelet agent, and use of at least 1 lipid-lowering agent.⁴⁵

Treatment

- Treatment of patients with lower-extremity PAD is summarized in the 2024 AHA/ACC guideline and includes addressing modifiable risk factors such as PA, smoking cessation, dyslipidemia, diabetes. BP and glycemic control, and revascularization approaches.⁴¹
- The proportion of variance that 2 traits share attributable to genetic causes (ie, genetic correlation) of PAD with CAD, BMI, HDL-C, LDL-C, triglycerides, type 2 diabetes, and SBP has been reported.³¹ C, triglycerides, and SBP also showed evidence of positive genetic correlation with PAD. HDL-C showed evidence of negative genetic correlation with PAD, suggesting that Strong genetic correlation between PAD and CAD was reported ($r_g=0.58$). BMI, type 2 diabetes, LDL-C SNPs associated with

• Optimal exercise programs for patients with PAD are summarized in a 2019 AHA scientific statement.⁴⁶ – In a randomized trial of optimal medical care versus supervised exercise training versus iliac artery stent placement, supervised exercise resulted in superior treadmill walking time at 6 months compared with stenting (mean increase from base-line, 5.8±4.6 minutes versus 3.7±4.9 minutes; $P=0.04$). Results in the exercise group and stent

- group were superior to optimal medical care alone
- Smoking cessation compared with continued smoking is associated with lower risk of amputation (19% versus 40%; HR, 0.40 [95% CI, 0.22–0.86]) over a follow-up of 10 years.⁵⁶
 - In a retrospective analysis of patients with intermittent claudication and intermittent claudication in the Veterans Affairs system, smokers were at higher risk of lower-limb wound complications (absolute risk difference, 4.05% [95% CI, 2.12%–5.99%]; $P < 0.001$) or
 - Glycemic control may be associated with better outcomes among patients with peripheral artery disease in observational studies^{56,57}:
 - In 149 patients with peripheral artery disease after infrapopliteal revascularization, the risk of amputation was greater among patients with higher HbA1c levels compared with those with lower levels (1.2–2.8%).⁵⁶
 - Among 197 Japanese patients who underwent revascularization for CLTI, an HbA1c of $\geq 7.0\%$ was associated with a higher risk of amputation for CLTI.

with 2.91 times greater risk for major amputation (95% CI, 1.61–5.26) over a mean follow-up of

graft failure (absolute risk difference, 1.50% [95% CI, 0.63%–2.37%]; $P=0.001$) compared

endo-

with nonsmokers.⁴⁹

- Lipid-lowering therapy with a high-intensity statin and, in some cases, a PCSK9 inhibitor is recommended for the treatment of PAD.^{41,49,50}
 - Among 155 647 patients with incident PAD in the Veterans Affairs health system, high-intensity statin use was associated with a lower risk of

1.7 years.⁵⁷

- Surgical revascularization may be superior to

vascular therapy in select patients with CLTI.⁵⁸

both amputation (HR, 0.67 [95% CI, 0.61–0.74]) and

mortality (HR, 0.74 [95% CI, 0.70–0.77]).⁵¹

– In a subanalysis of the FOURIER trial, compared

- In the BEST-CLI trial, 1 cohort of 1434 patients with CLTI and an adequate great saphenous vein for grafting underwent randomization to either initial surgical or endovascular revascularization. Initial surgical revascularization was associated with a reduction in the primary outcome of major adverse limb events or death resulting from any cause compared with initial endovascular revascularization (HR, 0.68 [95% CI, 0.59–0.79]; $P < 0.001$).⁵⁸
 - with placebo, the PCSK9 inhibitor evolocumab reduced the risk of major adverse limb events, including acute limb ischemia, major amputation, and urgent revascularization (HR, 0.58 [95% CI, 0.38–0.88]), in patients with and without existing PAD and already receiving statin therapy.⁵²
- In a subanalysis of the ODYSSEY Outcomes

- In a second cohort of 396 patients with CLTI but without an adequate great saphenous vein, initial surgical revascularization did not reduce major adverse limb events or death resulting from any cause compared with initial endovascular revascularization (HR, 0.79 [95% CI, 0.58–1.06]; trial, compared with placebo, the PCSK9 inhibitor alirocumab similarly reduced the risk of major adverse limb events, including CLTI, limb revascularization, or amputation (HR, 0.69 [95% CI, $P=0.12$]).⁵⁸

- Revascularization for patients with claudication or CLTI may be associated with improvement in quality of life and limb preservation. A

0.54–0.80]).⁵³

- The antithrombotic medication rivaroxaban, in addition to aspirin, may reduce the risk of adverse limb outcomes (eg, revascularization or amputation) among patients with PAD.⁵⁴
 - In a subanalysis of the COMPASS trial, among the 6391 subjects with PAD at baseline, compared with aspirin alone, the combination of rivaroxaban 2.5 mg

meta-analysis of 10 studies found that rivaroxaban twice daily plus aspirin 100 mg daily was associated with lower risk of major adverse limb events (2.6% versus 1.5%; HR, 0.57 [95% CI, 0.37–0.88]; $P=0.01$).⁵⁴

– In the VOYAGER trial, among 6564 subjects with

larization was associated with improved quality of life on the basis of a 6.1-point improvement (95% CI, 3.0–9.2) in the Short Form-36 Physical Functioning domain.⁵⁹

– Similarly, in a propensity-matched sample from the PORTRAIT registry, those who underwent early invasive management for claudication had a greater improvement in health status at 1 year compared with those treated noninvasively according to the Peripheral Artery Questionnaire ($P<0.001$ for all questionnaire domains).⁶⁰

PAD who recently underwent lower-extremity revascularization, compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily reduced the risk of a composite of major adverse

Mortality
(See Table 25-1)

cardiovascular and limb events (17.3% versus 19.9%; HR, 0.85

• In 2022, PAD was the underlying cause in 11 596 deaths. The number of any-mention deaths attrib-utable to PAD was 60 000 (Table 25-1; unpub-lished NHLBI tabulation using NVSS⁶¹ and CDC WONDER).⁶² [95% CI, 0.76–0.96]; *P*=0.009).⁵⁵

-
- In 2022, the overall underlying cause age-adjusted death rate for PAD was 2.7 per 100 000 (unpublished NHLBI tabulation using CDC WONDER).⁶² Age-adjusted death rates for PAD by race, ethnicity, and sex are listed in Table 15-1.
 - A meta-analysis of 16 cohorts including a total of 48 294 individuals (48% female) demonstrated a continuous association between ABI and mortality. Increased all-cause mortality between 1.11 and 1.40 had the lowest risk.⁶³
 - ABI ≤ 0.9 was associated with approximately tri-Black individuals compared with White individuals (25.03% [95% CI, 24.45%–25.61%] versus 18.62% [95% CI, 18.39%–18.85%]).⁶⁹
 - Patients with microvascular disease, defined as retinopathy, neuropathy, and nephropathy, were at increased risk for amputation (HR, 3.7 [95% CI, 3.0–4.6]), independently of traditional risk factors and prevalent PAD,

ity amputation was estimated at 48.3% among 186 338 Medicare patients ≥ 65 years of age with ple the risk of all-cause death compared with ABI of 1.11 to 1.40 in both males (RR, 3.33 [95% CI, 2.74–4.06]) and females (RR, 2.71 [95% CI, 2.03–3.62]).⁶³

- In EUCLID, females with symptomatic PAD were at lower risk of both all-cause and cardiovascular mortality (HR, 0.61 [95% CI, 0.53–0.71], $P < 0.001$; HR, 0.65 [95% CI, 0.54–0.78], $P < 0.001$, respectively).⁶⁴ – In contrast, based on data from 2011 to 2017 in the NIS, in-hospital mortality for patients with CLTI was higher for females compared with males (OR, 1.13 [95% CI, 1.11–1.14]).⁶
 - Among participants with type 2 diabetes or prediabetes plus additional cardiovascular risk factors in 3 randomized trials, ABI < 1 was associated with an increased risk of all-cause mortality compared to those with ABI ≥ 1.2 (HR, 1.68 [95% CI, 1.56–1.82]; $P < 0.0001$).⁶⁵

Complications

Cardiovascular Disease

PAD.⁷¹

- Individuals with PAD are at heightened risk for other types of CVD.

- In EUCLID, participants with PAD had a cumulative incidence of stroke and TIA of 0.87 per 100 patient-years and 0.27 per 100 patient-years, respectively.⁶⁶
- Similarly, the incidence of type 1 MI in EUCLID was 2.4 events per 100 patient-years.⁶⁷

Tissue (Limb) Loss

- Among 6 493 141 veterans followed up from 2008 to 2018, PAD was independently associated with an increased risk of lower-limb amputation (HR, 3.04 [95% CI, 2.95–3.13]).⁹
- In an analysis of 393 017 patients in the Premier Healthcare Database who underwent lower-extremity arterial revascularization, 50 750 patients (12.9%) had at least 1 subsequent hospitalization for major adverse limb events.⁶⁸
- Among Medicare beneficiaries who underwent peripheral vascular interventions from 2016 to 2018, the age- and sex-adjusted incidence of death or major amputation was greater among

death

Impaired Quality of Life

- Even individuals with borderline ABI (0.90–0.99) are at risk for mobility loss, defined as the loss of ability to walk one-quarter of a mile or up and down 1 flight of stairs independently (HR, 3.07 [95% CI, 1.21–7.84]).⁷²
- Among patients with PAD, lower PA levels are associated with faster rates of functional decline measured by 6-minute walk distance performance, 4-m walking velocity, and the Short Performance Physical Battery (all $P<0.05$).⁷³
- In the GBD Study 2019, the age-standardized rate of DALYs attributable to PAD was 40.0 per 100 000 (95% UI, 22.3–69.5) compared with 1629.4 per 100 000 (95% UI, 1539.9–1712.3) for IHD.⁷⁴

Health Care Use: Hospital Discharges and Ambulatory Care Visits

- In 2019, primary diagnosis of PAD accounted for 1 377 000 physician office visits (NAMCS,⁷⁵ unpublished NHLBI tabulation) and, in 2021, 74 105 primary diagnoses hospital discharges (HCUP,⁷⁶ unpublished NHLBI tabulation) and 58 981 ED visits (HCUP,⁷⁶ unpublished NHLBI tabulation).

Cost

- Among patients with PAD hospitalized in 2014, median hospitalization costs were \$15 755 (95% CI, \$8972–\$27 800) in 2017 US dollars.⁷⁷ This corresponded to an annual cost of hospitalization for PAD of approximately \$6.31 billion dollars.
- Among 25 695 patients with PAD between 2009 and 2016 in the Optum Integrated Database, the health care costs incurred over 1 year were substantially higher in those who had a MACE (mean difference, \$44 659) or major limb event (mean difference, \$34 216) compared with patients without these events.⁷⁸
- In a cohort of 22 203 patients with PAD in Minnesota, total health care costs were approximately \$18 000 (2011 US dollars) greater among tobacco users (9.0%) compared with nonusers (\$64 041 versus \$45 918) over 1 year.⁷⁹

*Global Burden**Prevalence**(See Table 25-2 and Charts 25-3)*

- Based on 204 countries and Study 2021.⁸⁰
 - PAD was prevalent among 98.50–131.22) million
 - PAD prevalence was North America, followed by southern Latin America
- Approximately 6.6% of the years of age, or 45 million according to a population-conducted between 2012 and
- PAD estimates in sub-Saharan Africa range from 3.1% to 24% in adults ≥50 years of age, with the variability possibly caused by differences in the prevalence of cardiovascular risk factors in the communities surveyed.⁸²
- In a cross-sectional analysis of individuals living in rural South Africa, 6.6% of adults 40 to 69 years of age had ABI ≤0.90.⁸³

*Mortality**(See Table 25-2 and Chart 25-4)*

- In the GBD Study 2021.⁸⁰
 - The age-standardized mortality estimated for PAD was 0.85 (95% UI, 0.75-0.93) per 100 000 individuals (Table 25-2).

- Approximately 1% of males years of age have an AAA decade thereafter, the increases by 2% to 4%.^{89,90} of age, the prevalence of Tromsø study was 4.1%.⁸⁹

Incidence

- In 2010, the estimated annual AAA per 100 000 individuals 0.61–1.11) and 164.57 (95% in individuals 40 to 44 and 75 respectively, according to a studies.⁹¹
 - PAD age-standardized mortality among regions was highest for Eastern and Central Europe and lowest for East and Southeast Asia, Oceania, and Andean Latin America (Chart 25-4).

*Aortic Diseases**ICD-9 440, 441, 444, and 447; ICD-10 I70, I71, I74, I77, and I79.**Aortic Aneurysm and Acute Aortic Syndromes ICD-9 441; ICD-10 I71. Prevalence*

Lifetime Risk and Cumulative Incidence

- Between 1995 and 2015, the cumulative incidence dissection was ≈0.74% and 0.09%, respectively, Health Register databases.^{.92}

of hospitalizations for aortic aneurysm and aortic on the basis of *ICD* codes from Swedish National

Secular Trends

- Between 1995 and 2015, the incidence of aortic aortic ulcer remained stable at 10.2 (males) and 5.7 the Rochester Epidemiology Project.^{.93}

dissection, intramural hematoma, or penetrating (females) per 100 000 PY according to data from

Risk Factors

- TAAs in younger individuals are more likely congenital conditions, the prototype examples disease. In older individuals 60 to 74 years of tension (OR, 1.8 [95% CI, 1.5–2.1]), and family the risk of TAA.^{.94}
- In a mendelian randomization analysis from the UK DBP, and mean arterial pressure were all associated with diameter (all
- Estimating the prevalence of TAA is challenging because of the relatively few studies in which screening has been performed in the general

caused by heritable thoracic aortic disease or being Marfan syndrome and bicuspid aortic valve age, male sex (OR, 1.9 [95% CI, 1.1–3.1]), hyper-history (OR, 1.6 [95% CI, 1.1–2.2]) contribute to

Biobank and MVP, genetically predicted SBP, increased ascending thoracic aortic

P<0.05).^{.95}

- In a meta-analysis of 4 563 501 patients, patients with a history of hypertension were more likely to have aortic dissection than those without hypertension.
 - Among 5662 patients who underwent chest CT imaging for any reason in 2016, 121 (2.14%) were incidentally found to have an ascending

sion (RR, 3.07 [95% CI, 2.15–4.38]).⁹⁶

- Inflammatory conditions such as giant-cell arteritis, Takayasu arteritis, or infectious aortitis also may cause TAA.
 - AAA is more common in males than females, and its prevalence increases with age.^{85,86}
 - AAA is ≈4 times more common in males than females according to data from an ultrasound screening study of 125 722 veterans 50 to 79 years of age conducted between 1992 and

– Giant-cell arteritis is associated with a 2-fold higher risk for developing a thoracoabdominal aortic aneurysm (sub-HR, 1.92 [95% CI, 1.52–2.41]) even after adjustment for competing risks according to data from the United Kingdom.⁹⁷• Risk factors for AAA were assessed in a retrospective analysis of 3.1 million

1997.^{87,88}

2003 and 2008.⁹⁸ Male sex (OR, 5.71 [95% CI, 5.57–5.85]), family history (OR, 3.80 [95% CI, 3.66–3.95]), and hypertension (OR, 1.25 [95% CI, 1.21–1.28]) were strongly associated with developing AAA. Individuals of all groups ≥ 55 years of age were at greater risk of developing AAA compared with those < 55 years of age (all $P < 0.0001$).

- Mendelian randomization suggests that genetically predicted greater height and higher pulse pressure are associated with larger infrarenal aortic diameter (all $P < 0.05$).⁹⁹

- Data suggest that lipoprotein(a) is linked to AAA risk. In ARIC, individuals with baseline lipoprotein(a) measures in the top quartile were at greater risk of incident AAA than those in the bottom quartile (HR, 1.57 [95% CI, 1.19–2.08]).¹⁰⁰

- Mendelian randomization analyses also suggest a causal link between genetically determined

lipoprotein(a) levels and AAA in individuals of HIV and time-updated CD4⁺ T-cell counts < 200 cells/mm³ (HR, 1.29 [95% CI, 1.02–1.65]) or HIV viral load ≥ 500 copies/mL (HR, 1.29 [95% CI, 1.09–1.52]) were at greater risk of incident AAA than those without HIV.¹⁰¹

- Diabetes may be associated with lower risk of aortic aneurysmal disease.^{94,102,103} A 2014 systematic review of 17 community-based observational studies demonstrated a consistent, inverse association between diabetes and prevalent AAA (OR, 0.80 [95% CI, 0.70–0.90]).¹⁰²

- Evidence suggests that there may be a temporal relationship between fluoroquinolone use and aortic disease. A study analyzing > 9 million fluoroquinolone prescriptions showed an increased risk of newly diagnosed AAA in

Social Determinants of Health/Health Equity

- Few data exist on social determinants of health for TAA.

- In a retrospective study of 60 784 patients who underwent thoracic aortic repair procedures between 2005 and 2008, thoracic endovascular

aortic repair was more common than open surgical repair among Black individuals (OR, 1.71 [95% CI, 1.37–2.13]), Hispanic individuals (OR,

1.70 [95% CI, 1.22–2.37]), and Native American individuals (OR, 2.37 [95% CI, 1.44–3.91]) compared with White individuals. Those with a mean annual income below \$25 000 were also more likely to undergo endovascular rather than open

surgical repair than those with a mean annual income exceeding \$35 000 (OR, 1.24 [95% CI, 1.03–1.62]).¹⁰⁷

patients > 35 years of age prescribed a fluoroquinolone compared with those prescribed other antibiotics (HR, 1.31 [95% CI, 1.25–1.37]).¹⁰⁴

- In a case-crossover analysis of patients in Taiwan, fluoroquinolone use was associated with an increased risk of aortic dissection or aneurysm (OR, 2.71 [95% CI, 1.14–6.46]), and there was a greater risk with more prolonged fluoroquinolone exposure.¹⁰⁵

- In a case-crossover analysis of patients in the United Kingdom, fluoroquinolone use was associated with an increased odds of aortic aneurysm or dissection hospitalization compared with nonuse (OR, 1.58 [95% CI, 1.37–1.83]).¹⁰⁶ However, there was no increased risk for fluoroquinolone use compared with use of other antibiotic classes.

Subclinical/Unrecognized Disease

- TAAs typically expand slowly, increasing in size at descending aorta, respectively.^{109,110} TAAs with rates of expansion ($P<0.0001$).¹¹¹ rates of 0.1 and 0.3 cm/y in the ascending and familial and genetic causes may display faster
- One-time screening for AAA in males 65 to 80 years of age had a number needed to screen of 350 to prevent a single AAA-related death over 7 to 15 years in a meta-analysis of 4 randomized trials.¹¹² In a nationwide Swedish program targeting males ≥ 65 years of age, the initiation of an AAA screening program found a number needed to screen of 667 to prevent a single premature death.¹¹³ ies on small AAAs (3.0–5.4 cm) demonstrated not vary significantly by age and
- A meta-analysis of 15 475 individuals from 18 studies on small AAAs (3.0–5.4 cm) demonstrated a mean aneurysm growth rate of 0.22 cm/y, which did not vary significantly by age and sex.¹¹⁴ mer or never-smokers (by 0.35 mm/y) and lower in people with diabetes than in those without diabetes (by 0.51 mm/y).¹¹⁴

Genetics/Family History

- Aortic dissection is heritable. In a study using the Taiwan National Health Insurance database of >23 000 patients, a family history of aortic dissection in first-degree relatives was associated with an RR of aortic dissection of 6.82 (95% CI, 5.12–9.07) with an estimated heritability of 57.0%.¹¹⁵
- In a study of UK Biobank participants, a PRS for aortic diameter was associated with an increased risk of TAA (HR, 1.42 per SD [95% CI, 1.34–1.50]).¹¹⁶

- There are syndromic thoracic caused by rare genetic syndrome (caused primarily gene). Loeys-Dietz syndrome related genes, including *TGFB2*, and *TGFB3*, drome (*COL3A1*), arterial (*SLC2A10*), and familial TAA *TGFB2*, and variants in
- Genetic variants associated with of TAA/dissection include in *FBN1* (rare variants cause Marfan syndrome), *LRP1* (LDL receptor protein–related 1), and *ULK4* (unc-51–like kinase 4).^{.117,118}
- AAA is heritable, and twin studies suggest that the degree of heritability ranges from 70% to 77%.^{.119,120}• A GWAS of individuals in the MVP identified 24 common genetic variants associated with AAA, including a locus on chromosome 9p21, as well as SNPs in *LPA*, *IL6R*, *LDLR*, and *APOE* (all $P < 5 \times 10^{-8}$).^{.121}• A GWAS of TAAs/dissections was also conducted in the

with spontaneous coronary $P < 5 \times 10^{-8}$).^{.128}

- In a case series of patients coronary artery dissection, with connective tissue that 8.2% of patients ant. with the most common Ehlers-Danlos syndrome. testing may be useful in these

Awareness, Treatment, and

MVP (n=8626 cases).^{.122} The authors identified 21 loci, 17 of which were novel and highlighted the role of extracellular matrix integrity. Unlike other CVDs, lipoprotein loci did not appear to be associated with TAAs/dissections. These results suggested that genetic pathways for TAA/dissections may be distinct from those for other CVDs, including

- Aortic aneurysmal disease is typically asymptomatic
 - Screening for AAA is recommended in males 65 a history of smoking.¹³⁰ Awareness of this recommendation, however, appears to be low, with 1.4% of eligible individuals screened on the basis of 2015 estimates from Centers for Medicare & Medicaid Services data.¹³¹

until complications occur.

to 75 years of age who currently smoke or have a history of smoking, however, appears to be low, with of 2015 estimates from Centers for Medicare &

- Treatment of TAA and AAA is aimed at slowing progression and preventing complications, namely rupture and dissection.
 - Thresholds for surgical repair of TAAs are based on size, rate of growth, presence of syndromic or nonsyndromic heritable thoracic aortic disease, specific genetic variants, and concomitant valve disease and are outlined in the “2022 ACC/AHA

AAAs.

of

- Genetic variants associated with intracranial aneurysms have been found in several genes, including *RBBP8*, *STRAD13/KL*, *SOX17*, and *CDKN2A/B* (all $P < 5 \times 10^{-8}$).¹²³ Rare variants in *ANGPTL6* are

Guideline for the Diagnosis and Management

Aortic Disease.”¹³²

associated with familial cases of intracranial aneurysms

– In a sample of 12 573 and 2732 Medicare patients from 1998 to 2007, for intact TAA, perioperative mortality was similar for open and endovascular repair (7.1% versus 6.1%; $P=0.56$).

($P<0.05$).¹²⁴

mor-

- GWAS data demonstrate that 16 common genetic variants associated with AAA are also associated with cerebral and lower-extremity arterial aneurysms (all $P<0.05$).¹²¹
- Genetic associations with nonatherosclerotic arterial diseases such as fibromuscular dysplasia and spontaneous coronary artery dissection have been challenging because of the lower prevalence of disease, but studies of these diseases are ongoing.
 - A noncoding SNP in *PHACTR1* (phosphatase and actin regulator 1) has been associated with

In contrast, for ruptured TAA, perioperative

fibromuscular dysplasia ($P<10^{-4}$).¹²⁵ and functional analyses have demonstrated that this locus regulates endothelin-1 expression.¹²⁶

– In the UK Biobank, a PRS for AAA was also associated with an increased risk of fibromuscular dysplasia (OR, 1.03 [95% CI, 1.01–1.05];

tality was greater for open compared with endovascular repair (45% versus 28%; $P<0.001$), although 5-year survival rates were higher (70% versus 56%; $P<0.001$).¹³³

- Racial disparities in perioperative 30-day mortality after TAA repair are present with open (Black people, 18% versus White people, 10%; $P<0.001$) compared with endovascular (8% versus 9%; $P=0.54$) approaches on the basis of Medicare data from 1999 to 2007.¹³³
- Elective AAA repair is typically not recommended among asymptomatic individuals until the diameter exceeds 5.5 cm or if the annual expansion rate is ≥ 0.5 cm/y because open or endovascular repair of small AAAs (4.0–5.5 cm) did not demonstrate a benefit compared with routine ultrasound surveillance according to results from 4 trials including a total of 3314 participants.^{132,134}
 - A variant at chromosome 1q21.2 that affects *ADAMTSL4* expression and variants in 116 *PHACTR1*, *LRP1*, and *LINC00310* are associated with patients undergoing ruptured AAA repair, patients

treated at low-volume centers had a greater over-all mortality risk than those treated at high-volume centers (OR, 1.39 [95% CI, 1.22–1.59]). In multivariable-adjusted models, patients treated at low-volume centers had a greater mortality risk for open repair (OR, 1.68 [95% CI, 1.21–2.33]) but not endovascular repair (OR, 1.42 [95% CI, 0.84–2.41]).¹³⁵ In the United States, data from NIS showed that the risk of death after volume hospitals was significantly greater than at high-volume hospitals (OR, 1.921 [95% CI,

– Between 1999 and 2016, deaths attributable to ruptured TAA declined significantly from 5.5 to 1.8 per million according to US NVSS data.¹⁴²
– From 1996 to 2018, the mortality rate in IRAD for type A thoracic aortic dissection over the first 48 hours was 5.8%. This rose to 23.7% for those treated medically.

likely to be treated with endovascular therapies, but mortality rates remained similar between 1.458–2.532]; $P < 0.001$).¹³⁶

- After elective AAA repair, survival after endovascular versus open surgical repair varies on the basis of timing since the intervention. Among Medicare patients, open versus endovascular AAA repair had a higher risk of all-cause mortality (HR, 1.24 [95% CI,

1996 and 2013).¹⁴⁴

1.05–1.47]), AAA-related mortality (HR, 4.37 [95% CI, 2.51–7.66]), and complications at 1 year.¹³⁷ After 8 years of follow-up, however, survival was similar between the 2 groups ($P = 0.76$). The rate of eventual aneurysm

- Among patients with acute type B aortic dis-section in IRAD, heterogeneous in-hospital out-comes exist. In-hospital mortality was higher (20.0%) among patients with complications (eg, mesenteric ischemia, renal failure, limb ischemia, or refractory pain) compared with patients with-out complications (6.1%). Among patients with complications, in-hospital mortality was higher with open surgical (28.6%) compared with endo-vascular (10.1%) repair ($P=0.006$).¹⁴⁵
- rupture was higher with endovascular (5.4%) compared with open (1.4%) repair.¹³⁸
- Similarly, in the OVER Veterans Affairs Cooperative Study of 881 patients, compared with open repair, endovascular repair was
- Among Medicare beneficiaries hospitalized with acute type B aortic dissections from 2011 to 2018, initial thoracic endovascular aortic asso-ciated with lower mortality at 2 years (HR, 0.63 [95% CI, 0.40–0.98]) and 3 years (HR, 0.72

[95% CI, 0.51–1.00]) but no survival difference in up to 9 years (mean, 5 years) of follow-up (H 0.97 [95% CI, 0.77–1.22]).¹³⁹

- AAA

those with 49–198 cases/y; $P<0.01$). Perioperative mortality after open repair was inversely associated with case volume for both surgeon (6.4% in ≤ 3 cases versus 3.8% in 14–62 cases; $P<0.01$) and hospital (6.3% in ≤ 5 cases versus 3.8% in 14–62 cases;

- From 1999 to 2016, the death rate attributable to ruptured AAA declined from 26.3 to 7.9 per million according to US NVSS data.¹⁴²
- Data from 23 838 patients with ruptured AAAs collected through the NIS 2005 to 2010 demonstrated in-hospital mortality of 53.1% (95% CI, 51.3%–54.9%) with 80.4% of patients (95% CI, 79.0%–81.9%) undergoing intervention for repair. Of individuals who underwent repair, 20.9% (95% CI, 18.6%–23.2%) underwent endovascular repair with a 26.8% (95% CI, 23.7%–30.0%) postintervention mortality rate, and 79.1% (95% CI, 77.0%–81.2%) underwent open repair. Furthermore, associated health care costs rose during this time period despite reductions in in-hospital mortality and length of stay.¹⁴¹
- Of all AAA repairs, endovascular AAA repair increased from 5% to 74% between 2000 and 2010 despite a stable overall number of AAAs (≈45 000 per year) according to NIS data.

CI, 76.8%–81.4%) underwent open repair with a 45.6% (95% CI, 43.6%–47.5%) postintervention mortality rate.¹⁴⁷

- A meta-analysis of 619 068 patients who underwent elective AAA repair observed a higher 30-day mortality rate in females compared with males (mortality rate, 0.04 [95% CI, 0.04–0.05] versus 0.02 [95% CI, 0.02–0.03])

Mortality

2022, United States: Underlying cause mortality—
9999. Any-mention mortality—19 422.

- Similarly, in the Vascular Quality Initiative, females undergoing repair of ruptured AAAs had a greater likelihood of in-hospital mortality (OR, 1.36 [95%
- TAA

CI, 1.12–1.66]; $P=0.002$) (HR, 1.25 [95% CI, 1.04–1.49] compared with males).¹⁴⁹

- Among 4638 ruptured AAA in 2018 in the Vascular no difference in 5-year versus open repair (HR, 1.11; $P=0.28$) for 2004 to 2013 to 2018, endovascular associated with longer 5-year open repair (HR, 0.69 [95% $P<0.001$]).¹⁵⁰

Complications

Dissection and rupture are the predominant complications of aortic aneurysmal disease, and their risks are proportional to aortic diameter and expansion rate, as well as familial or genetic causes.

TAA:

- At a diameter of 4.0 to 4.9 and >6.0 cm, the annual rate of TAA dissection or rupture is estimated at $\approx 2\%$ and $\approx 7\%$, respectively.¹⁵¹
 - Most TAA dissections in absolute numbers, however, occur at relatively smaller diameters. In IRAD, 59.1% and 40.9% of dissections occurred at diameters <5.5 and <5.0 cm, respectively.¹⁵²
 - Annual age- and sex-adjusted incidences per 100 000 people were estimated at 3.5 (95% CI, 2.2–4.9) for TAA rupture and 3.5 (95% CI, 2.4–4.6) for acute aortic dissection according to data from Olmsted County, Minnesota.¹⁵³
- AAA:
- The risk of AAA rupture is also proportionately related to diameter.
 - Rates of rupture of small AAAs (3.0–5.4 cm in diameter) range from 0.71 to 11.03 per 1000

Global Burden

(See Table 25-3 and Chart 25-5)

- Based on a meta-analysis of trials, the 2019 global incidence at least 3.0 cm in people was 0.92% (95% CI, 0.65%–1.19%) and responded to 35.12 (95% CI, 28.12–42.12) individuals.¹⁵⁶
- Global mortality attributable to aortic aneurysm by sex according to the GBD countries and territories is shown
 - There were 0.15 (95% UI, 0.12–0.18)

PY with higher rupture rates in smokers (pooled HR, 2.02 [95% CI, 1.33–3.06]) and females (pooled HR, 3.76 [95% CI, 2.58–5.47]; $P<0.001$).¹¹⁴—A Canadian registry observed that small AAAs (<5.5 cm for males and <5.0 cm for females) account for only 10% of all ruptured AAAs.¹⁵⁴

Health Care Use: Hospital Discharges and

Ambulatory Care Visits

- In 2021, hospital discharges with aortic aneurysm as principal diagnoses totaled 65 260 (HCUP,⁷⁶ unpublished NHLBI tabulation).

Cost

- A study comprising 1207 Medicare patients from the Vascular Quality Initiative showed that the median cost of index endovascular repair of AAA was \$25 745 (IQR, \$21 131–\$28 774), whereas the median cost of subsequent reintervention was

- total deaths attributable to aortic aneurysm, an increase of 74.22% (95% UI, 62.98%–83.64%) from 1990.
- The highest age-standardized mortality rates estimated for aortic aneurysm among regions were for high-income Asia Pacific, tropical Latin America, and Eastern Europe. Rates were lowest for East Asia (Chart 25-5).
 - In New Zealand, the age-standardized rate of AAA-related hospitalizations decreased from 43.7 per 100 000 in 2001 to 15.4 per 100 000 in 2018.¹⁵⁷
 - Geographic variation in the management of AAA appears to be present. In a comparison of AAA management between the United Kingdom and United States, the United States demonstrated a higher rate of AAA repair, smaller AAA diameter at the time of repair, and lower rates of AAA rupture and AAA-related death (all $P<0.0001$).¹⁵⁸

Atherosclerotic Renal Artery Stenosis ICD-9 440.1; ICD-10 I70.1.

Prevalence

- The prevalence of renal artery disease by renal duplex ultrasonography was 6.8% in the North Carolina subcohort of the CHS between 1997 and 1998.¹⁵⁹ Among those with renal artery stenoses, 88% were unilateral and 12% were bilateral.
- The prevalence of renal artery stenosis by angiography ranged from 5.4% to 16.6% among patients undergoing coronary angiography on the basis of data ascertained from 2007 to 2008 in Italy (n=1298) and from 2014 to 2015 in Romania (n=181), respectively.^{160,161}
- In a French study of patients undergoing peripheral angiography for PAD, the prevalence of renal artery stenosis was 14%.¹⁶²

Incidence

- The incidence rate of renal artery stenosis was estimated at 3.09 per 1000 patient-years from Medicare claims data between 1992 and \$22 165 (IQR, \$17 152–\$29 605).¹⁵⁵ 2004.¹⁶³

Lifetime Risk and Cumulative Incidence

- The lifetime risk and cumulative incidence of renal artery stenosis have not been established.

Secular Trends

- The risk for a claim for renal artery stenosis was higher in 2004 (HR, 3.35 [95% CI, 3.17–3.55]) compared with 1992 according to Medicare claims data, even with adjustment for demographics and comorbidities.
- In a multiple logistic regression analysis of 1298 patients undergoing both coronary and renal artery angiography, PAD (OR, 2.98 [95% CI, 1.76–5.03]), dyslipidemia (OR, 2.82 [95% CI, 1.15–6.88]), eGFR <67 mL·min⁻¹·1.73 m⁻² (OR, 2.63 [95% CI, 1.54–4.47]), age >66 years (OR, 2.20 [95% CI, 1.26–3.85]), and multivessel CAD (OR, 1.82 [95% CI, 1.06–3.13]) were all associated with ≥50% renal artery stenosis (all *P*<0.05).¹⁶⁴

Risk Prediction

- On the basis of data from a retrospective single-center study of 4177 patients in Iran who under-

Awareness, Treatment, and Control

- Optimal medical therapy is the first-line treatment in the management of renal artery stenosis.¹⁶⁶ In CORAL, a randomized clinical trial of 943 patients with renal artery stenosis and either hypertension requiring ≥2 medications or CKD recruited between 2005 and 2010, renal artery stenting plus optimal medical therapy was not superior to medical therapy alone. In a study that included patients who went renal angiography between 2002 and 2016, a predictive model for the presence of renal artery stenosis, defined by ≥70% stenosis (prevalence, 14.1%), that included age, sex, history of hypertension, BMI, and eGFR had an AUC of 0.70 (95% CI, 0.67–0.72).¹⁶⁵

Table 25-1. PAD in the United States

Mortality

• An Irish study reported that among a total of 3987 the presence of renal artery stenosis conferred a great risk of mortality (HR, 2.01 [95% CI, 1.51–2.67]).¹⁶⁸

patients undergoing coronary angiography, risk of mortality (HR, 2.01 [95% CI,

Complications

• The main long-term complications of renal artery stenosis are decline in renal function and a height-ened risk of CVD.
– In the CHS, renal artery stenosis was associated with an increased risk of CHD (HR, 1.96 [95% CI, 1.00–3.83]).¹⁶⁹
– In an analysis of Medicare recipients, patients with atherosclerotic renal artery stenosis were at higher risk of incident congestive HF, stroke, death, and need for renal replacement therapy (all $P < 0.0001$).¹⁶³

stenosis are decline in renal function and a height-ened risk of CVD.
– In the CHS, renal artery stenosis was associated with an increased risk of CHD (HR, 1.96 [95% CI, 1.00–3.83]).¹⁶⁹
– In an analysis of Medicare recipients, patients with atherosclerotic renal artery stenosis were at higher risk of incident congestive HF, stroke, death, and need for renal replacement therapy (all $P < 0.0001$).¹⁶³

Population group	Mortality, 2022, all ages*	Age-adjusted mortality rates per 100 000 (95% CI)
Both sexes	11 596	2.7 (2.7–2.8)
Males	5708 (49.2%)†	3.1 (3.1–3.2)
Females	5888 (50.8%)†	2.4 (2.3–2.4)
NH White males	4347	3.2 (3.1–3.2)
NH White females	4479	2.4 (2.3–2.5)
NH Black males	770	4.8 (4.5–5.2)
NH Black females	805	3.4 (3.1–3.6)
Hispanic males	401	2.3 (2.1–2.6)
Hispanic females	398	1.7 (1.6–1.9)
NH Asian males	111‡	1.2 (1.0–1.5)‡
NH Asian females	133‡	1.0 (0.8–1.2)‡
NH American Indian/Alaska Native	55	2.2 (1.7–2.9)
NH Native Hawaiian or Pacific Islander	18	Unreliable (1.7–4.7)

Ellipses (...) indicate data not available; NH, non-Hispanic; and PAD, peripheral artery disease.

*Mortality for Hispanic people, American Indian or Alaska Native people, Asian people, and Native Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native decedents, Asian decedents, Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality attributable to PAD that is for males vs females.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Mortality (for underlying cause of PAD): Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System⁶¹ and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.⁶²

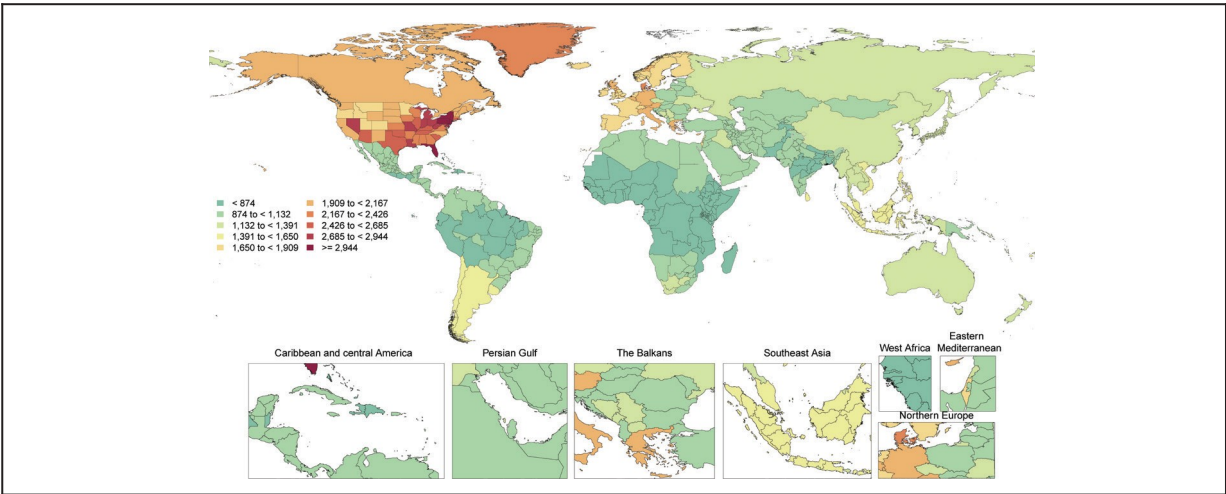


Chart 25-3. Age-standardized global prevalence of lower-extremity PAD per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and PAD, peripheral artery disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁸⁰

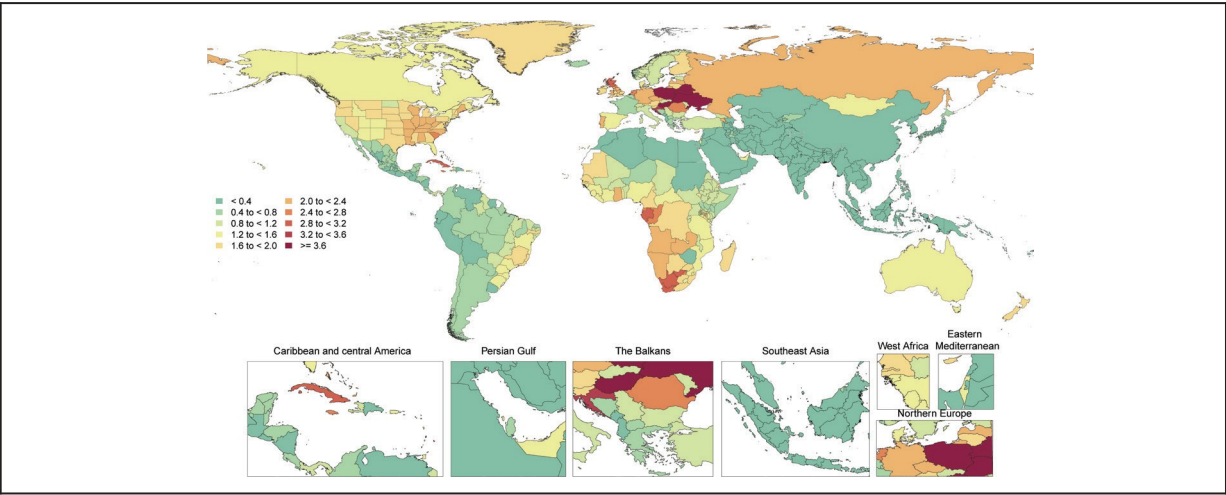


Chart 25-4. Age-standardized global mortality rates of lower-extremity PAD per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

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Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁸⁰

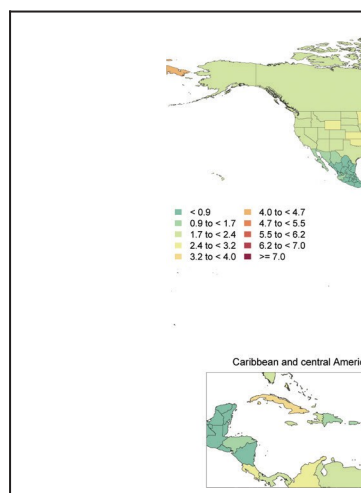


Chart 25-5. Age-standardized global mortality rates of aortic aneurysm per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. During each annual GBD Study cycle, population health estimates are produced for the full time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

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Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.⁸⁰

REFERENCES

1. GBD 2019 Peripheral Artery Disease Collaborators. Global burden of peripheral artery disease and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Glob Health*. 2023;11:e1553–e1565. doi: 10.1016/S2214-109X(23)00355-8
2. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med*. 2007;32:328–333. doi: 10.1016/j.amepre.2006.12.010
3. Eraso LH, Fukaya E, Mohler ER 3rd, Xie D, Sha D, Berger JS. Peripheral arterial disease, prevalence and cumulative risk factor profile analysis. *Eur J Prev Cardiol*. 2014;21:704–711. doi: 10.1177/2047487312452968
4. Aday AW, Duncan MS, Patterson OV, DuVall SL, Alba PR, Alcorn CW, Tindle HA, Creager MA, Bonaca MP, Damrauer SM, et al. Association of sex and race with incident peripheral artery disease among veterans with normal ankle-brachial indices. *JAMA Netw Open*. 2022;5:e2240188. doi: 10.1001/jamanetworkopen.2022.40188
5. Matsushita K, Sang Y, Ning H, Ballew SH, Chow EK, Grams ME, Selvin E, Allison M, Criqui M, Coresh J, et al. Lifetime risk of lower-extremity peripheral artery disease defined by ankle-brachial index in the United States. *J Am Heart Assoc*. 2019;8:e012177. doi: 10.1161/JAHA.119.012177

10. Song P, Rudan D, Zhu Y, Fowkes FJ, Rahimi K, Fowkes FGR, Rudan I. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health*. 2019;7:e1020–e1030. doi: 10.1016/S2214-109X(19)30255-4

11. Berger JS, Hochman J, Lobach I, Adelman MA, Riles TS, Rockman CB. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg*. 2013;58:673–681. doi: 10.1016/j.jvs.2013.01.053

12. Ding N, Sang Y, Chen J, Ballew SH, Kalbaugh CA, Salameh MJ, Blaha MJ, Allison M, Heiss G, Selvin E, et al. Cigarette smoking, smoking cessation, and long-term risk of 3 major atherosclerotic diseases. *J Am Coll Cardiol*. 2019;74:498–507. doi: 10.1016/j.jacc.2019.05.049

13. Lu Y, Ballew SH, Tanaka H, Szklo M, Heiss G, Coresh J, Matsushita K. 2017 ACC/AHA blood pressure classification and incident peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) study. *Eur J Prev Cardiol*. 2020;27:51–59. doi: 10.1177/2047487319865378

14. Kou M, Ding N, Ballew SH, Salameh MJ, Martin SS, Selvin E, Heiss G, Ballantyne CM, Matsushita K, Hoogeveen RC. Conventional and novel lipid measures and risk of peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2021;41:1229–1238. doi: 10.1161/ATVBAHA.120.315828

15. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein particle profiles, standard lipids, and peripheral artery disease incidence. *Circulation*. 2018;138:2330–doi:

F, Abbott JD, Shishehbor MH, Guzman RJ, Hiatt WR, Duval S, et al. Contemporary trends in hospital admissions and outcomes in patients with critical limb ischemia: an analysis from the National Inpatient Sample database. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007539. doi: 10.1161/CIRCOUTCOMES.120.007539

7. Schramm KM, DeWitt PE, Dybul S, Rochon PJ, Patel P, Hieb RA, Rogers RK, Ryu RK, Wolhauer M, Hong K, et al. Recent trends in clinical setting and provider specialty for endovascular peripheral artery disease interventions for the Medicare population. *J Vasc Interv Radiol*. 2020;31:614–621. doi: 10.1016/j.jvir.2019.10.025

8. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult U.S. population. *Diabetes Care*. 2019;42:50–54. doi:

- 10.1161/CIRCULATIONAHA.118.035432
16. Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD. Triglyceride-rich lipoprotein cholesterol, small dense LDL cholesterol, and incident cardiovascular disease. *J Am Coll Cardiol*. 2020;75:2122–2135. doi: 10.1016/j.jacc.2020.02.059
17. Dikilitas O, Satterfield BA, Kullo IJ. Risk factors for polyvascular involvement in patients with peripheral artery disease: a mendelian randomization study. *J Am Heart Assoc*. 2020;9:e017740. doi: 10.1161/JAHA.120.017740
18. Levin MG, Zuber V, Walker VM, Klarin D, Lynch J, Malik R, Aday AW, Bottolo L, Pradhan AD, Dichgans M, et al; on behalf of the VA Million Veteran Program. Prioritizing the role of major lipoproteins and subfractions as risk factors for peripheral artery disease. *Circulation*. 2021;144:353–364. doi: 10.1161/circulationaha.121.053797
9. Cai M, Xie Y, Bowe B, Gibson AK, Zayed MA, Li T, Al-Aly Z. Temporal trends in incidence rates of lower extremity amputation and associated risk factors among patients using Veterans Health Administration Services from 2008 to 2018. *JAMA Netw Open*. 2021;4:e2033953. doi: 10.1001/jamanetworkopen.2020.33953

19. Satterfield BA, Dikilitas O, Safarova MS, Clarke SL, Tcheandjieu C, Zhu X, Bastarache L, Larson EB, Justice AE, Shang N, et al. Associations of genetically predicted Lp(a) (lipoprotein [a]) levels with cardiovascular traits in individuals of European and African ancestry. *Circ Genom Precis Med*. 2021;14:e003354. doi: 10.1161/CIRCGEN.120.003354

20. Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, Mukamal KJ. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA*. 2012;308:1660–1667. doi: 10.1001/jama.2012.13415
21. Garg PK, Biggs ML, Carnethon M, Ix JH, Criqui MH, Britton KA, Djousse L, Sutton-Tyrrell K, Newman AB, Cushman M, et al. Metabolic syndrome and risk of incident peripheral artery disease: the Cardiovascular Health Study. *Hypertension*. 2014;63:413–419. doi: 10.1161/HYPERTENSIONAHA.113.01925
22. Conen D, Rexrode KM, Creager MA, Ridker PM, Pradhan AD. Metabolic syndrome, inflammation, and risk of symptomatic peripheral artery disease in women: a prospective study. *Circulation*. 2009;120:1041–1047. doi: 10.1161/HYPERTENSIONAHA.113.01925
23. Arya S, Binney Z, Khakharia A, Brewster LP, Goodney P, Patzer R, Hockenberry J, Wilson PWF. Race and socioeconomic status independently affect risk of major amputation in peripheral artery disease. *J Am Heart Assoc*. 2018;7:e007425. doi: 10.1161/jaha.117.007425
24. Mota L, Marcaccio CL, Zhu M, Moreira CC, Rowe VL, Hughes K, Liang P, Schermerhorn ML. Impact of neighborhood social disadvantage on the presentation and management of peripheral artery disease. *J Vasc Surg*. 2023;77:1477–1485. doi: 10.1016/j.jvs.2022.12.062
25. Fanaroff AC, Yang L, Nathan AS, Khatana SAM, Julien H, Wang TY, Armstrong EJ, Treat-Jacobson D, Glaser JD, Wang G, et al. Geographic and socioeconomic disparities in major lower extremity amputation rates in metropolitan areas. *J Am Heart Assoc*. 2021;10:e021456. doi: 10.1161/JAHA.121.021456
26. Minc SD, Goodney PP, Misra R, Thibault D, Smith GS, Marone L. The effect of rurality on the risk of primary amputation is amplified by race. *J Vasc Surg*. 2020;72:1011–1017. doi: 10.1016/j.jvs.2019.10.090
27. Zhang Y, Huang J, Wang P. A Prediction model for the peripheral arterial disease using NHANES data. *Medicine (Baltimore)*. 2016;95:e3454. doi: 10.1097/md.0000000000003454
28. Matsushita K, Sang Y, Ning H, Ballew SH, Chow EK, Grams ME, Selvin variation in blood pressure and increased lifetime risk of peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2021;41:2027–2034. doi: 10.1161/ATVBAHA.120.315482
29. Small AM, Huffman JE, Klarin D, Sabater-Lleal M, Lynch JA, Assimes TL, Sun YV, Miller D, Freiberg MS, Morrison AC, et al; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Hemostasis Working Group and the VA Million Veteran Program. Mendelian randomization analysis of hemostatic factors and their contribution to peripheral artery disease: brief report. *Arterioscler Thromb Vasc Biol*. 2021;41:380–386. doi: 10.1161/ATVBAHA.119.313847
30. Levin MG, Klarin D, Assimes TL, Freiberg MS, Ingelsson E, Lvnch J, Natarajan P, O'Donnell C, Rader DJ, Tsao PS, et al; E, Allison M, Criqui M, Coresh J, et al. Online calculator for "lifetime risk and prevalence of lower extremity peripheral artery disease (PAD)." 2019. Accessed March 15, 2024.
31. Sonderman M, Aday AW, Farber-Eger E, Mai Q, Freiberg MS, Liebovitz DM, Greenland P, McDermott MM, Beckman JA, Wells J. identify-ing patients with peripheral artery disease using the electronic health record: a pragmatic approach. *JACC Adv*. 2023;2:100566. doi: 10.1016/j.jacadv.2023.100566
32. Wahlen CM, Magnusson PK. Genetic influences on peripheral arterial disease in a twin population. *Arterioscler Thromb Vasc Biol*. 2011;31:678–682. doi: 10.1161/ATVBAHA.110.210385
33. van Zuydam NR, Stiby A, Abdalla M, Austin E, Dahlstrom EH, McLachlan S, Vlachopoulou E, Ahlqvist E, Di Liao C, Sandholm N, et al; GoLEAD Consortium and SUMMIT Consortium. Genome-wide association study of peripheral artery disease. *Circ Genom Precis Med*. 2021;14:e002862. doi: 10.1161/CIRCGEN.119.002862
34. Helgadottir A, Thorleifsson G, Magnusson KP, Gretarsdottir S, Steinthorsdottir V, Manolescu A, Jones GT, Rinkel GJ, Blankensteijn JD, Ronkainen A, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet*. 2008;40:217–224. doi: 10.1038/ng.72
35. Murabito JM, White CC, Kavousi M, Sun YV, Feitosa MF, Nambi V, Lamina C, Schillert A, Coassin S, Bis JC, et al. Association between chromosome 9p21 variants and the ankle-brachial index identified by a meta-analysis of 21 genome-wide association studies. *Circ Cardiovasc Genet*. 2012;5:100–112. doi: 10.1161/CIRCGENETICS.111.961292
36. Klarin D, Lynch J, Aragam K, Chaffin M, Assimes TL, Huang J, Lee KM, Shao Q, Huffman JE, Natarajan P, et al. Genome-wide association study of peripheral artery disease in the Million Veteran Program. *Nat Med*.

- cular diseases: a mendelian randomization study. *JAMA Netw Open*. 2021;4:e2034461. doi: 10.1001/jamanetworkopen.2020.34461
40. Shi H, Yuan X, Wu F, Li X, Fan W, Yang X, Liu G. Genetic support of the causal association between gut microbiota and peripheral artery disease: a bidirectional mendelian randomization study. *Aging (Albany NY)*. 2024;16:762–778. doi: 10.18632/aging.205417
41. Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VES guideline for the management of lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149:e1313–e1410. doi: 10.1161/CIR.0000000000001251
42. Hirsch AT, Murphy TP, Lovell MB, Twillman G, Treat-Jacobson D, Harwood EM, Mohler ER 3rd, Creager MA, Hobson RW 2nd, Robertson RM, et al; Peripheral Arterial Disease Coalition. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. *Circulation*. 2007;116:2086–2094. doi: 10.1161/CIRCULATIONAHA.107.725101
43. Colantonio LD, Hubbard D, Monda KL, Mues KE, Huang L, Dai Y, Jackson EA, Brown TM, Rosenson RS, Woodward M, et al. Atherosclerotic risk and statin use among patients with peripheral artery disease. *J Am Coll Cardiol*. 2020;76:251–264. doi: 10.1016/j.jacc.2020.05.048
44. Hess CN, Cannon CP, Beckman JA, Goodney PP, Patel MR, Hiatt WR, Mues KE, Orroth KK, Shannon E, Bonaca MP. Effectiveness of blood lipid management in patients with peripheral artery disease. *J Am Coll Cardiol*. 2021;77:3016–3027. doi: 10.1016/j.jacc.2021.04.060
45. Menard MT, Jaff MR, Farber A, Rosenfield K, Conte MS, White CJ, Beckman JA, Choudhry NK, Clavijo LC, Huber TS, et al. Baseline modern medical management in the BEST-CLI trial. *J Vasc Surg*. 2023;78:711–718.e5. doi: 10.1016/j.jvs.2023.05.006
46. Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui MH, Gardner AW, Hiatt WR, Regensteiner JG, Rich K; on behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Council on Cardiovascular and Stroke Nursing. Optimal exercise programs for patients with peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e10–e33. doi: 10.1161/CIR.0000000000000623
47. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, Massaro JM, Lewis BA, Cerezo J, Oldenburg NC, et al; CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. *Circulation*. 2012;125:130–139. doi: 10.1161/CIRCULATIONAHA.111.075770
48. Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, Laird JR. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg*. 2014;60:1565–1571. doi: 10.1038/s41591-019-0492-5
- 10.1016/j.jvs.2014.08.064
35. Ntalla I, Kanoni S, Zeng L, Giannakopoulou O, Danesh J, Watkins H, van Zuydam N, Hopewell J, Schaid DJ, Kullo IJ. Targeted sequencing study to uncover shared genetic susceptibility between peripheral artery disease and coronary heart disease: brief report. *Arterioscler Thromb Vasc Biol*. 2019;39:1227–1233. doi: 10.1161/ATVBAHA.118.312128
36. Samani NJ, Deloukas P, Schunkert H; UK Biobank CardioMetabolic Consortium CHD Working Group. Genetic risk score for coronary disease identifies predispositions to cardiovascular and noncardiovascular diseases. *J Am Coll Cardiol*. 2019;73:2932–2942. doi: 10.1016/j.jacc.2019.03.512
37. Safarova MS, Fan X, Austin EE, Assimes TL, Natarajan P, et al. Association between genetic

49. Reitz KM, Althouse AD, Meyer J, Arya S, Goodney PP, Shireman PK, Hall DE, Tzeng E. Association of smoking with postprocedural complications following open and endovascular interventions for intermittent claudication. *JAMA Cardiol.* 2022;7:45–54. doi: 10.1001/jamacardio.2021.3979
50. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol [published corrections appear in *Circulation*. 2019;139:e1182–e1186 and *Circulation*. 2023;148:e5]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625

51. Arya S, Khakharia A, Binney ZO, DeMartino PP, Wilson PWF. Association of statin dose in patients with peripheral artery disease. doi: 10.1161/CIRCULATIONAHA.120.046524
52. Bonaca MP, Nault P, Giuliano RP, Keech J, Murphy SA, Jukema JW, Lewis BS, et al. Effect of lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial. *Circulation*. 2018;137:338–350. doi: 10.1161/CIRCULATIONAHA.120.046524
53. Schwartz GG, Steg PG, Szarek M, Bittner U, Jukema JW, Pordv R, Roe MT, et al: for the Investigators. Peripheral artery disease and outcomes after acute coronary syndrome. *Circulation*. 2020;141:1608–1617. doi: 10.1161/CIRCULATIONAHA.120.046524
54. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. *J Am Coll Cardiol*. 2018;71:2306–2315. doi: 10.1016/j.jacc.2018.03.008
55. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, Fanelli F, Capell WH, Diao L, Jaeger N, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382:1994–2004. doi: 10.1056/NEJMoa2000052
56. Singh S, Armstrong EJ, Sherif W, Alvandi B, Westin GG, Singh GD, Amsterdam EA, Laird JR. Association of elevated fasting glucose with lower patency and increased major adverse limb events among patients with diabetes undergoing infrapopliteal balloon angioplasty. *Vasc Med*. 2014;19:307–314. doi: 10.1177/1358863X14538330
57. Takahara M, Kaneto H, Iida O, Gorogawa S, Katakami N, Matsuoka TA, artery disease: insights from the doi: 10.1001/iamacardio.2018.4171
68. Hess CN, Wang TY, Weleski Fu J, RK, Hiatt WR. Long-term outcomes limb events after peripheral artery 2020;75:498–508. doi: 10.1161/
69. Krawisz AK, Natesan S, Wadhera RK, Jaff MR, Giri J, Julien H. Secondary outcomes explain Black-White disparities in total endovascular intervention. doi: 10.1161/
70. Beckman JA, Duncan MS, Damrauer DH, Berlimo R, Ruff AA, Marconi VC. doi: 10.1056/NEJMoa2000052

- peripheral artery disease, and amputation. *Circulation*. 2019;140:449–458. doi: 10.1161/CIRCULATIONAHA.119.040672
71. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, Peterson ED. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J*. 2013;165:809–815, 815.e1. doi: 10.1016/j.ahj.2012.12.002
 72. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004;292:453–461. doi: 10.1001/jama.292.4.453
 73. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, Tan J, McDermott MM. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation*. 2006;114:242–248. doi: 10.1161/CIRCULATIONAHA.105.605246
 74. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. Accessed June 1, 2024. Ikeda M, Shimomura I. The influence of glycemic control on the prognosis of Japanese patients undergoing percutaneous transluminal angioplasty for critical limb ischemia. *Diabetes Care*. 2010;33:2538–2542. doi: 10.2337/dc10-0939
 58. Farber A, Menard MT, Conte MS, Kaufman JA, Powell RJ, Choudhry NK, Hamza TH, Assmann SF, Creager MA, Cziraky MJ, et al; BEST-CLI Investigators. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N Engl J Med*. 2022;387:2305–2316. doi: 10.1056/NEJMoa2207899
 75. Centers for Disease Control and Prevention and National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Accessed May 1, 2024.

76. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed April 1, 2024.
59. Vemulapalli S, Dolor RJ, Hasselblad V, Subherwal S, Schmit KM, Heidenfelder BL, Patel MR, Schuyler Jones W. Comparative effectiveness of medical therapy, supervised exercise, and revascularization for patients with intermittent claudication: a network meta-analysis. *Clin Cardiol*. 2015;38:378–386. doi: 10.1002/clc.22406
60. Angraal S, Hejjaji V, Tang Y, Gosch KL, Patel MR, Heyligers J, White CJ, Tutein Nolthenius R, Mena-Hurtado C, Aronow HD, et al. One-year health status outcomes following early invasive and noninvasive treatment in symptomatic peripheral artery disease. *Circ Cardiovasc Interv*. 2022;15:e011506. doi: 10.1161/circinterventions.121.011506
61. Centers for Disease Control and Prevention and National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
62. Centers for Disease Control and Prevention and National Center for Health Statistics. Multiple cause of death, CDC WONDER online database. Accessed May 1, 2024.

77. Kohn CG, Alberts MJ, Peacock WF, Bunz TJ, Coleman CI. Cost and National Inpatient Sample. *Atherosclerosis*. 2019;286:142–146. doi: 10.1016/j.atherosclerosis.2019.05.026
78. Berger A, Simpson A, Bhagnani T, Leeper NJ, Murphy B, Nordstrom B, Ting W, Zhao Q, Berger JS. Incidence and cost of major adverse cardiovascular events and major adverse limb events in patients with chronic coronary artery disease or peripheral artery disease. *Am J Cardiol*. 2019;123:1893–1899. doi: 10.1016/j.amjcard.2019.03.022
79. Duval S, Long KH, Roy SS, Oldenburg NC, Harr K, Fee RM, Sharma RR, Alesci NL, Hirsch AT. The contribution of tobacco use to high health care utilization and medical costs in peripheral artery disease: a state-based cohort analysis. *J Am Coll Cardiol*. 2015;66:1566–1574. doi: 10.1016/j.jacc.2015.06.1349
80. *Global Burden of Disease Study and Institute for Health Metrics and Evaluation*. University of Washington. Accessed July 1, 2024.
63. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, et al; Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300:197–208. doi: 10.1001/jama.300.2.197
64. Haine A, Kavanagh S, Berger JS, Hess CN, Norgren L, Fowkes FGR, Katona BG, Mahaffey KW, Blomster JI, Patel MR, et al; International Steering Committee and Investigators of the EUCLID Trial. Sex-specific risks of major cardiovascular and limb events in patients with symptomatic peripheral artery disease. *J Am Coll Cardiol*. 2020;75:608–617. doi: 10.1016/j.jacc.2019.11.057
65. Mohammadi K, Pigeyre M, Bosch J, Yusuf S, Gerstein HC. Arm and ankle blood pressure indices, and peripheral artery disease, and mortality: a cohort study. *Eur Heart J*. 2024;45:1738–1749. doi: 10.1093/eurheartj/ehae087
66. Kolls BJ, Sapp S, Rockhold FW, Jordan JD, Dombrowski KE, Fowkes FGR, Mahaffey KW, Berger JS, Katona BG, Blomster JI, et al. Stroke in patients with peripheral artery disease. *Stroke*. 2019;50:1356–1363. doi: 10.1161/STROKEAHA.118.023534
67. Olivier CB, Mulder H, Hiatt WR, Jones WS, Fowkes FGR, Rockhold FW, Berger JS, Baumgartner I, Held P, Katona BG, et al. Incidence, characteristics, and outcomes of myocardial infarction in patients with peripheral

81. Wang Z, Wang X, Hao G, Chen Z, Zhang L, Shao L, Tian Y, Dong Y, Zheng C, Kang Y, et al; China Hypertension Survey Investigators. A national study of the prevalence and risk factors associated with peripheral arterial dis-ease from China: the China Hypertension Survey, 2012-2015. *Int J Cardiol.* 2019;275:165–170. doi: 10.1016/j.ijcard.2018.10.047

82. Johnston LE, Stewart BT, Yangni-Angate H, Veller M, Upchurch GR Jr, Gyedu A, Kushner AL. Peripheral arterial disease in sub-Saharan Africa: a review. *JAMA Surg.* 2016;151:564–572. doi: 10.1001/jamasurg.2016.0446

83. Beidelman ET, Rosenberg M, Wade AN, Crowther NJ, Kalbaugh CA. Prevalence of and risk factors for peripheral artery disease in rural South Africa: a cross-sectional analysis of the HAALSI cohort. *J Am Heart Assoc.* 2024;13:e031780. doi: 10.1161/JAHA.123.031780

84. Mori M, Bin Mahmood SU, Yousef S, Shioda K, Faggion Vinholo T, Mangi AA, Elefteriades JA, Geirsson A. Prevalence of incidentally identified thoracic aortic dilations: insights for screening criteria. *Can J Cardiol.* 2019;35:892–898. doi: 10.1016/j.cjca.2019.03.023

85. Scott RA, Ashton HA, Kay DN. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. *Br J Surg.* 1991;78:1122–1125. doi: 10.1002/bjs.1800780929

86. Newman AB, Arnold AM, Burke GL, O'Leary DH, Manolio TA. Cardiovascular disease and mortality in older adults with small abdominal aortic aneurysms detected by ultrasonography: the aneurysm among 143 001 veterans. *Circulation*. 2001;103:182–190. doi: 10.1161/0000000000000008

87. Lederle FA, Johnson GR, Wilson SE; Aneurysm Detection and Management Veterans Affairs Cooperative Study. Abdominal aortic aneurysm in women. *J Vasc Surg*. 2001;34:122–126. doi: 10.1067/mva.2001.115275

88. Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, Barone GW, Bandyk D, Moneta GL, Makhoul RG. The Aneurysm Detection and Management Study screening program: validation cohort and final results: Aneurysm Detection and Management Veterans Affairs Cooperative Study investigators. *Arch Intern Med*. 2000;160:1425–1430. doi: 10.1001/archinte.160.10.1425

89. Singh K, Bonaa KH, Jacobsen BK, Bjork L, Solberg S. Prevalence of aneurysms and risk factors for abdominal aortic aneurysms in a population-based study: the Tromso Study. *Am J Epidemiol*. 2001;154:236–244. doi: 10.1093/ajep/154.3.236

2018;72:1369–1378. doi: 10.1016/j.jacc.2018.06.067

106. Brown JP, Wing K, Leyrat C, Evans SJ, Mansfield KE, Wong AYS, Smeeth use and hospitalization with aortic aneurysm or aortic dissection. *JAMA Cardiol.* 2023;8:865–870. doi: 10.1001/jamacardio.2023.2418
- 10.1093/aje/154.3.236
90. Powell JT, Greenhalgh RM. Clinical practice: small abdominal aortic aneurysms. *N Engl J Med.* 2003;348:1895–1901. doi: 10.1056/NEJMc012641
91. Sampson UK, Norman PE, Fowkes FG, Aboyans V, Song Y, Harrell FE Jr, Forouzanfar MH, Naghavi M, Denenberg JO, McDermott MM, et al. Estimation of global and regional incidence and prevalence of abdominal aortic aneurysms 1990 to 2010. *Glob Heart.* 2014;9:159–170.
- L, Galwey NW, Douglas IJ. Association between fluoroquinolone
107. Johnston WF, LaPar DJ, Newhook TE, Stone ML, Upchurch GR Jr, Ailawadi G. Association of race and socioeconomic status with the use of endovascular repair to treat thoracic aortic diseases. *J Vasc Surg.* 2013;58:1476–1482. doi: 10.1016/j.jvs.2013.05.095
- doi: 10.1016/j.gheart.2013.12.009
92. Avdic T, Franzen S, Zarrouk M, Acosta S, Nilsson P, Gottsater A, Svensson

108. Perlstein MD, Gupta S, Ma X, Rong LQ, Askin G, White RS. Abdominal aortic aneurysm repair readmissions and disparities of socioeconomic status: a multistate analysis, 2007-2014. *J Cardiothorac Vasc Anesth*. 2019;33:2737–2745. doi: 10.1053/j.jvca.2019.03.020
109. Coady MA, Davies RR, Roberts M, Goldstein LJ, Rogalski MJ, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Familial patterns of AM, Gudbjornsdottir S, Eliasson B. Reduced thoracic aortic aneurysms. *Arch Surg*. 1999;134:361–367. doi: 10.1001/archsurg.134.4.361
110. a nationwide observational study. *J Am Heart Assoc*. 2018;7:e007618. doi: 10.1161/JAHA.117.007618
111. to 2015. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004689. doi: 10.1161/CIRCOUTCOMES.118.004689
93. DeMartino RR, Sen I, Huang Y, Bower TC, Oderich GS, Pochettino A, Greason K, Kalra M, Johnstone J, Shuja F, et al. Population-based assessment of the incidence of aortic dissection, intramural hematoma, and penetrating ulcer, and its associated mortality from 1995
94. Obel LM, Diederichsen AC, Steffensen FH, Frost L, Lambrechtsen J, Busk M, Urbonaviciene G, Egstrup K, Karon M, Rasmussen LM, et al. Population-based risk factors for ascending, arch, descending, and abdominal aortic

110. Shang EK, Nathan DP, Sprinkle SR, Vigmostad SC, Fairman RM, Bavaria JE, Gorman RC, Gorman JH 3rd, Chandran KB, Jackson BM. Peak wall stress predicts expansion rate in descending thoracic aortic aneurysms. *Ann Thorac Surg.* 2013;95:593–598. doi: 10.1016/j.athoracsur.2012.10.025
111. Albornoz G, Coady MA, Roberts M, Davies RR, Tranquilli M, Rizzo JA, Elefteriades JA. Familial thoracic aortic aneurysms and dissections: incidence, modes of inheritance, and phenotypic patterns. *Ann Thorac Surg.* 2006;82:1400–1405. doi: 10.1016/j.athoracsur.2006.04.098
112. Eckstein HH, Bockler D, Flessenkamper I, Schmitz-Rixen T, Debus S, Lang W. Ultrasonographic screening for the detection of abdominal aortic aneurysms. *Dtsch Arztebl Int.* 2009;106:657–663. doi: 10.3238/arztebl.2009.0657
113. Dilations for 60-74-year-old individuals. *J Am Coll Cardiol.* 2021;78:201–211. doi: 10.1016/j.jacc.2021.04.094
95. DePaolo J, Levin MG, Tcheandjieu C, Priest JR, Gill D, Burgess S, Damrauer SM, Chirinos JA. Relationship between ascending thoracic aortic diameter and blood pressure: a mendelian randomization study. *Arterioscler Thromb Vasc Biol.* 2023;43:359–366. doi: 10.1161/ATVBAHA.122.318149
96. Hibino M, Otaki Y, Kobeissi E, Pan H, Hibino H, Taddese H, Majeed A, Verma S, Konta T, Yamagata K, et al. Blood pressure, hypertension, and the risk of aortic dissection incidence and mortality: results from the J-SCH study, the UK Biobank study, and a meta-analysis of cohort studies. *Circulation.* 2022;145:633–644. doi: 10.1161/CIRCULATIONAHA.121.056546

113. Wanhainen A, Hultgren R, Linne A, Holst J, Gottsater A, Langenskiöld M, Smidfelt K, Björck M, Svensjö S; Swedish Aneurysm Screening Study Group (SASS). Outcome of the Swedish Nationwide Abdominal Aortic Aneurysm Screening Program. *Circulation*. 2016;134:1141–1148. doi: 10.1161/CIRCULATIONAHA.116.022305
114. Sweeting MJ, Thompson SG, Brown LC, Powell JT; RESCAN Collaborators. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. *Br J Surg*. 2012;99:655–665. doi: 10.1002/bjs.8707
115. Chen SW, Kuo CF, Huang YT, Lin WT, Chien-Chia Wu V, Chou AH, Lin PJ, Chang SH, Chu PH. Association of family history with incidence and outcomes of aortic dissection. *J Am Coll Cardiol*. 2020;76:1181–1192. doi: 10.1016/j.jacc.2020.07.028
97. Robson JC, Kiran A, Maskell J, Hutchings A, Arden N, Dasgupta B, Hamilton W, Emin A, Culliford D, Luqmani RA. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. *Ann Rheum Dis*. 2015;74:129–135. doi: 10.1136/annrheumdis-2013-204113
98. Kent KC, Zwolak RM, Egorova NN, Riles TS, Manganaro A, Moskowitz AJ, Gelijns AC, Greco G. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. *J Vasc Surg*. 2010;52:539–548. doi: 10.1016/j.jvs.2010.05.090

116. Nekoui M, Pirruccello JP, Di Achille P, Choi SH, Friedman SN, Nauffal V, Ng K, Batra P, Ho JE, Philippakis AA, et al. Spatially distinct genetic determinants of aortic dimensions influence risks of aneurysm and stenosis. *J Am Coll Cardiol*. 2022;80:486–497. doi: 10.1016/j.jacc.2022.05.024
117. Guo DC, Grove ML, Prakash SK, Eriksson P, Hostetler EM, LeMaire SA, Body SC, Shalhoub S, Estrera AL, Safi HJ, et al; GenTAC Investigators. Genetic variants in *LRP1* and *ULK4* are associated with acute aortic dissections. *Am J Hum Genet*. 2016;99:762–769. doi: 10.1016/j.ajhg.2016.06.034
99. Portilla-Fernandez E, Klarin D, Hwang SJ, Biggs ML, Bis JC, Weiss S, Rosales S, Natarajan P, Hoffmann U, Rogers IS, et al. Genetic and clinical determinants of abdominal aortic diameter: genome-wide association studies, exome array data and mendelian randomization study. *Hum Mol Genet*. 2022;31:3566–3579. doi: 10.1093/hmg/ddac051
100. Kubota Y, Folsom AR, Ballantyne CM, Tang W. Lipoprotein(a) and abdominal aortic aneurysm risk: the Atherosclerosis Risk

118. LeMaire SA, McDonald ML, Guo DC, Russell L, Miller CC 3rd, Johnson RJ, Bekheirnia MR, Franco LM, Nguyen M, Pyeritz RE, et al. Genome-wide association study identifies a susceptibility locus for thoracic aortic aneurysms and aortic dissections spanning *FBN1* at 15q21.1. *Nat Genet.* 2011;43:996–1000. doi: 10.1038/ng.934
119. Wahlgren CM, Larsson E, Magnusson PK, Hultgren R, Swedenborg J. Genetic and environmental contributions to abdominal aortic aneurysm development in a twin population. *J Vasc Surg.* 2010;51:3–7. doi: 10.1016/j.atherosclerosis.2017.10.017
101. Filipkowski AM, Kundu S, Eden SK, Alcorn CW, Justice AC, 10.1016/j.jvs.2009.08.036
120. Joergensen TM, Christensen K, Lindholt JS, Larsen LA, Green A, Houliand K. Editor's choice: high heritability of liability to abdominal aortic aneurysms: So-Armah KA, Tindle HA, Wells QS, Beckman JA, Freiberg MS, et al. Association of HIV infection and incident abdominal aortic

- a population based twin study. *Eur J Vasc* doi: 10.1016/j.ejvs.2016.03.012
121. Klarin D, Verma SS, Judv R, Dikilitas O, Pan C, Tcheandjeu C, Snin JM, et al. Aortic aneurysm in the Million Veteran Program. doi: 10.1038/s41588-023-01420-z
 122. Klarin D, Devineni P, Sendamarai AK, YH, Levin MG, Pirruccello JP, Surakka I. A genome-wide association study of thoracic aortic aneurysm in the Million Veteran Program. *Nat Genet*. 2018;50:1038-1045. doi: 10.1038/s41588-023-01420-z
 123. Yasuno K, Bilalov K, Billenaa P, Low SK, M Krey D, Arlier Z, Navak N, et al. A genome-wide association study of intracranial aneurysms identifies three new risk loci. *Nat Genet*. 2010;42:420-425. doi: 10.1038/ng.563
 124. Bourcier R, Le Scouarnec S, Bonnaud S, Karakachoff M, Bourcureau E, Heurtebise-Chretien S, Menguy C, Dina C, Simonet F, Moles A, et al; ICAN Study Group. Rare coding variants in *ANGPTL6* are associated with familial forms of intracranial aneurysm. *Am J Hum Genet*. 2018;102:133-141. doi: 10.1016/j.ajhg.2017.12.006
 125. Kiando SR, Tucker NR, Castro-Vega LJ, Katz A, D'Escamard V, Treard C, Fraher D, Albuissou J, Kadian-Dodov D, Ye Z, et al. *PHACTR1* is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. *PLoS Genet*. 2016;12:e1006367. doi: 10.1371/journal.pgen.1006367
 126. Gupta RM, Hadaya J, Trehan A, Zekavat SM, Roselli C, Klarin D, Emdin CA, Hilvering CRE, Bianchi V, Mueller C, et al. A genetic variant associated with five vascular diseases is a distal regulator of endothelin-1 gene expression. *Cell*. 2017;170:522-533.e15. doi: 10.1016/j.cell.2017.06.049
 127. Katz AE, Yang ML, Levin MG, Tcheandjeu C, Mathis M, Hunker K, Blackburn S, Eliason JL, Coleman DM, Fendrikova-Mahlay N, et al. Fibromuscular dysplasia and abdominal aortic aneurysms are dimorphic sex-specific diseases with shared complex genetic architecture. *Circ Genom Precis Med*. 2022;15:e003496. doi: 10.1161/CIRCGEN.121.003496
 128. Saw J, Yang M-L, Trinder M, Tcheandjeu C, Xu C, Starovoytov A, Birt I, Mathis MR, Hunker KL, Schmidt EM, et al. Chromosome 1q21.2 and additional loci influence risk of spontaneous coronary artery dissection and myocardial infarction. *Nat Commun*. 2020;11:4432. doi: 10.1038/s41467-020-17558-x
 129. Kaadan MI, MacDonald C, Ponzini F, Duran J, Newell K, Pitler L, Lin A, Weinberg I, Wood MJ, Lindsay ME. Prospective cardiovascular genetics evaluation in spontaneous coronary artery dissection. *Circ Genom Precis Med*. 2018;11:e001933. doi: 10.1161/CIRCGENETICS.117.001933
 130. Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, Doubeni CA, Epling JW Jr, Kubik M, Landefeld CS, et al; US Preventive Services Task Force. Screening for abdominal aortic aneurysm: US Preventive Services Task Force recommendation statement. *JAMA*. 2013;309:2465-2472. doi: 10.1001/jama.2013.276522
 131. Jackson RS, Chang DC, Freischlag J. Aortic aneurysm repair: open vs endovascular. *Ann Surg*. 2012;255:1-11. doi: 10.1097/SLA.0b013e3182457778
 132. Schermerhorn ML, Buck DB, O'Malley D, Darling J, Landon BE. Long-term results of the Medicare population. *N Engl J Med*. 2010;362:1405-1414. doi: 10.1056/NEJMoa1005778
 133. Lederle FA, Freischlag JA, Kvriakides K, Kohler TR, Kounias P, Jean-Claude Veterans Affairs Cooperative Study Group. Endovascular and open repair of abdominal aortic aneurysms. *N Engl J Med*. 2012;367:1988-1997. doi: 10.1056/NEJMoa1209007
 134. Herb J, Strassle PD, Kalbaugh CA, Crowner JR, Farber MA, McGinley KL. Limited adoption of abdominal aortic aneurysm screening guidelines associated with no improvement in aneurysm rupture rate. *Surgery*. 2018;164:359-364. doi: 10.1016/j.surg.2018.04.009
 135. Isselbacher EM, Preventza O, Hamilton Black J 3rd, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, et al; Peer Review Committee Members. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;146:e334-e482. doi: 10.1161/CIR.0000000000001106
 136. Goodney PP, Brooke BS, Wallaert J, Travis L, Lucas FL, Goodman DC, Cronenwett JL, Stone DH. Thoracic endovascular aneurysm repair, race, and volume in thoracic aneurysm repair. *J Vasc Surg*. 2013;57:56-63. doi: 10.1016/j.jvs.2012.07.036
 137. Filardo G, Powell JT, Martinez MA, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. *Cochrane Database Syst Rev*. 2015;2015:CD001835. doi: 10.1002/14651858.CD001835.pub4
 138. Kontopodis N, Galanakis N, Akoumianakis E, Ioannou CV, Tsetis D, Antoniou GA. Editor's choice: systematic review and meta-analysis of the impact of institutional and surgeon procedure volume on outcomes after ruptured abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg*. 2021;62:388-398. doi: 10.1016/j.ejvs.2021.06.015
 139. Polanco AR, D'Angelo AM, Shea NJ, Allen P, Takayama H, Patel VI. Increased hospital volume is associated with reduced mortality after thoracoabdominal aortic aneurysm repair. *J Vasc Surg*. 2021;73:451-458. doi: 10.1016/j.jvs.2020.05.027

140. Zettervall SL, Schermerhorn ML, Soden PA, McCallum JC, Shean KE, Deery SE, O'Malley AJ, Landon B. The effect of surgeon and hospital volume on mortality after open and endovascular repair of abdominal aortic aneurysms. *J Vasc Surg*. 2017;65:626–634. doi: 10.1016/j.jvs.2016.09.036
141. Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg*. 2014;59:1512–1517. doi: 10.1016/j.jvs.2014.01.007
142. Abdulameer H, Al Taii H, Al-Kindi SG, Milner R. Epidemiology of fatal ruptured aortic aneurysms in the United States (1999-2016). *J Vasc Surg*. 2019;69:378–384.e2. doi: 10.1016/j.jvs.2018.03.435
143. Harris KM, Nienaber CA, Peterson MD, Woznicki EM, Braverman AC, Trimarchi S, Myrmel T, Pyeritz R, Hutchison S, Strauss C, et al. Early mortality in type A acute aortic dissection: insights from the International Registry of Acute Aortic Dissection. *JAMA Cardiol*. 2022;7:1009–1015. doi: 10.1001/jamacardio.2022.2718
144. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, Myrmel T, Larsen M, Harris KM, Greason K, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol*. 2015;66:350–358. doi: 10.1016/j.jacc.2015.05.029
145. Trimarchi S, Tolenaar JL, Tsai TT, Froehlich J, Pegorer M, Upchurch GR, Fattori R, Sundt TM 3rd, Isselbacher EM, Nienaber CA, et al. Influence of clinical presentation on the outcome of acute B aortic dissection: evidences from IRAD. *J Cardiovasc Surg (Torino)*. 2012;53:161–168.
146. Weissler EH, Osazuwa-Peters OL, Greiner MA, Hardy NC, Kougas P, O'Brien SM, Mark DB, Jones WS, Secemsky EA, Vekstein AM, et al. Initial thoracic endovascular aortic repair vs medical therapy for acute uncomplicated type B aortic dissection. *JAMA Cardiol*. 2023;8:44–53. doi: 10.1001/jamacardio.2022.4187
147. Karthikesalingam A, Holt PJ, Vidal-Diez A, Ozdemir BA, Poloniecki JD, Hinchliffe RJ, Thompson MM. Mortality from ruptured abdominal aortic aneurysms: clinical lessons from a comparison of outcomes in England and the USA. *Lancet*. 2014;383:963–969. doi: 10.1016/S0140-6736(14)60109-4
148. Tedjawirja VN, de Wit MCJ, Balm R, Koelemay MJW. Differences in comorbidities between women and men treated with elective repair for abdominal aortic aneurysms: a systematic review and meta-analysis. *Ann Vasc Surg*. 2021;76:330–341. doi: 10.1016/j.avsg.2021.03.049
149. Li B, Eisenberg N, Witheford M, Lindsay TF, Forbes TL, Roche-Nagle G. Sex differences in outcomes following ruptured abdominal aortic aneurysm repair. *JAMA Netw Open*. 2022;5:e2211336. doi: 10.1001/jamanetworkopen.2022.11336
150. Varkevisser RRB, Swerdlow NJ, de Guerre L, Dansey K, Stangenberg L, Giles KA, Verhagen HJM, Schermerhorn ML. Five-year survival following endovascular repair of ruptured abdominal aortic aneurysms is improving. *J Vasc Surg*. 2020;72:105–113.e4. doi: 10.1016/j.jvs.2019.10.074
151. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, Elefteriades JA. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg*. 2002;73:17–27. doi: 10.1016/s0003-4975(01)03236-2
152. Pape LA, Tsai TT, Isselbacher EM, Oh JK, O'Gara PT, Evangelista A, Fattori R, Meinhardt G, Trimarchi S, Bossone E, et al; International Registry of Acute Aortic Dissection (IRAD) Investigators. Aortic diameter $\geq$ 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2007;116:1120–1127. doi: 10.1161/CIRCULATIONAHA.107.702720
153. Clouse WD, Hallett JW Jr, Schaff HV, Spittell PC, Rowland CM, Ilstrup DM, Melton LJ 3rd. Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture. *Mayo Clin Proc*. 2004;79:176–180. doi: 10.4065/79.2.176

154. Bellamkonda KS, Nassiri N, Sadeghi MM, Zhang Y, Guzman RJ, Ochoa Chaar CI. Characteristics and outcomes of small abdominal aortic aneurysm rupture in the American College of Surgeons National Surgical Quality Improvement Program database. *J Vasc Surg.* 2021;74:729–737. doi: 10.1016/j.jvs.2021.01.063
155. Columbo JA, Goodney PP, Gladders BH, Tsougranis G, Wanken ZJ, Trooboff SW, Powell RJ, Stone DH. Medicare costs for endovascular abdominal aortic aneurysm treatment in the Vascular Quality Initiative. *J Vasc Surg.* 2021;73:1056–1061. doi: 10.1016/j.jvs.2020.06.109
156. Song P, He Y, Adeloye D, Zhu Y, Ye X, Yi Q, Rahimi K, Rudan I; Global Health Epidemiology Research Group (GHERG). The global and regional prevalence of abdominal aortic aneurysms: a systematic review and modelling analysis. *Ann Surg.* 2022;277:912–919. doi: 10.1097/SLA.0000000000005716
2021. *J Clin Med.* 2023;12:2331. doi: 10.3390/jcm12062331
158. Karthikesalingam A, Vidal-Diez A, Holt PJ, Loftus IM, Schermerhorn ML, Soden PA, Landon BE, Thompson MM. Thresholds for abdominal aortic aneurysm repair in England and the United States. *N Engl J Med.* 2016;375:2051–2059. doi: 10.1056/NEJMoa1600931
159. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, Burke GL, Dean RH. Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg.* 2002;36:443–451. doi: study (REN-ACS): a single center, prospective, observational *Heart Assoc.* 2015;4:e002379. doi: 10.1161/JAHA.115.002379
162. Aboyans V, Desormais I, Magne J, Morange G, Mohty D, Lacroix P. Renal artery stenosis in patients with peripheral artery disease: prevalence, risk factors and long-term prognosis. *Eur J Vasc Endovasc Surg.* 2017;53:380–385. doi: 10.1016/j.ejvs.2016.10.029
163. Kalra PA, Guo H, Gilbertson DT, Liu J, Chen SC, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in the United States. *Kidney Int.* 2010;77:37–43. doi: 10.1038/ki.2009.406
164. Marcantoni C, Rastelli S, Zanolli L, Tripepi G, Di Salvo M, Monaco S, Sgroi C, Capodanno D, Tamburino C, Castellino P. Prevalence of renal artery stenosis in patients undergoing cardiac catheterization. *Intern Emerg Med.* 2010;10:1067/mva.2002.127351
160. Cohen MG, Pascua JA, Garcia-Ben M, Rojas-Matas CA, Gabay JM, Berrocal DH, Tan WA, Stouffer GA, Montoya M, Fernandez AD, et al. A simple prediction rule for significant renal artery stenosis in patients undergoing cardiac catheterization. *Am Heart J.* 2005;150:1204–1211. doi: 10.1016/j.ahj.2005.02.019
161. Burlacu A, Siriopol D, Voroneanu L, Nistor I, Hogas S, Nicolae A, Nedelciuc I, Tinica G, Covic A. Atherosclerotic renal artery stenosis prevalence and correlations in acute myocardial infarction patients undergoing primary per-

166. Bhalla V, Textor SC, Beckman JA, Casanegra AI, Cooper CJ, Kim ESH, Luther JM, Misra S, Oderich GS; on behalf of the American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Hypertension; Council on Peripheral Vascular Disease; and Council on Cardiovascular Radiology and Intervention. Revascularization for renovascular disease: a scientific statement from the American Heart Association. *Hypertension*. 2022;79:e128–e143. doi: 10.1161/HYP.0000000000000217
167. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, Cohen DJ, Matsumoto AH, Steffes M, Jaff MR, et al; CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med*. 2014;370:13–22. doi: 10.1056/NEJMoa1310753
168. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int*. 2001;60:1490–1497. doi: 10.1046/j.1523-1755.2001.00953.x
169. Edwards MS, Craven TE, Burke GL, Dean RH, Hansen KJ. Renovascular disease and the risk of adverse coronary events in the elderly: a prospective, population-based study. *Arch Intern Med*. 2005;165:207–213. doi: 10.1001/archinte.165.2.207

cutaneous coronary interventions: data from nonrandomized single-center

26. QUALITY OF CARE

See Tables 26-1 through 26-12

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Quality-of-care assessment uses as explicit standards against which evaluated.¹ This differs from clinical recommendations to inform decisions but ultimately leave decisions to clinician discretion. Measuring performance data collection across various care analytics, and the timely. Broadly, there are 2 types of measures, which focus on tasks that control of the clinician (Did patient start a statin after an MI?), and which focus on end points that are outcomes (What proportion of patients died after a hospitalization for an MI?).

Decades of outcomes research

iteratively to measuring and enhancing the quality of delivered care, thereby improving CVH outcomes. In the United States, much of this body of work has relied on cardiovascular registries, many of which are administered by the AHA's GWTG program² and the ACC's NCDR program.³ Health care claims data from payers (Medicare, commercial claims) or integrated health care systems (Veterans Affairs, Kaiser Permanente) have also been used to examine quality. Although claims data typically lack the granular phenotyping available in registries, their scale and ability to capture long-term follow-up make them powerful for examining quality of care and outcomes. Increasingly, linked datasets that combine registries, claims, and other hospital- or community-level data are being used to evaluate outcomes and quality of care. For instance, the AHA's COVID-19 registry has been linked with Medicare claims to evaluate long-term outcomes after a COVID-19 hospitalization.⁴ Simulation modeling

drugs, devices, and programs as a measure of health care.^{5,6}

The following sections present of how quality of care is measured and overseas. They are not meant given the sheer volume of quality data available. When possible, we report

measures drawn from quality methods that are consistent with

endorsed by the ACC and the few examples of how social cardiovascular care and outcomes; discussion related to health equity is condition-specific chapters. Of COVID-19 pandemic saw marked improvement of cardiovascular care and quality of care has recovered in recent

has, in some settings, been. The projected increase in the cardiovascular risk factors and conditions care spending in the coming efforts to improve the quality of prevention and treatment.^{10,11}

approaches that systematically integrate data from numerous disparate sources have been used to evaluate the cost-effectiveness of diagnostic tests,

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Prevention and Risk Factor Modification

(See Table 26-1)

- Recent data suggest that patients using a Medicaid health maintenance organization have better performance on several key preventive measures related to CVD and diabetes than patients using a commercial preferred provider organization (Table 26-1).
- The National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set consists of established measures of quality of care related to CVD prevention in the United States (Table 26-1).¹²
- In a cross-sectional study of 12 924 adults 20 to 44 years of age from 2009 to 2020, there were increases in the prevalence of diabetes and obesity and no improvement in the prevalence of hypertension. Black young adults had the highest rates of hypertension over the study period, whereas increases in hypertension and diabetes were observed among Hispanic adults.¹³
- In an analysis of the US NHANES from 2001 to 2002 through 2015 to 2016, trends in cardiovascular risk factor control were assessed in 35 416 males and females 20 to 79 years of age.¹⁴ There were improvements in control of hypertension, diabetes, and dyslipidemia over time, but sex differences persisted. In 2013 to 2016, hypertension control in females versus males was observed in 30% versus 22%, diabetes control in 30% versus 20%, and dyslipidemia control in 51% versus 63%.

Blood Pressure

• Trends in BP control from 1999 to 2000 through 2017 to 2018 in US adults with hypertension were assessed in a serial cross-sectional analysis of NHANES participants.¹⁵ The data were weighted to be representative of US adults and included participants with a mean age of 48 ± 19 years, with 50.1% females, 43.2% NH White adults, 21.6% NH age-adjusted estimated proportion with controlled BP, defined as BP $<140/90$ mm Hg, improved from 31.8% (95% CI, 26.9%–36.7%) in 1999 to 2000 to 48.5% (95% CI, 45.5%–51.5%) in 2007 to 2008 ($P_{\text{trend}} < 0.001$), was similar in 2013 to 2014 (53.8% [95% CI, 48.7%–59.0%]; $P_{\text{trend}} = 0.14$), and then worsened to 43.7% (95% CI, 40.2%–47.2%) in 2017 to 2018 ($P_{\text{trend}} = 0.003$).

Cost-Effectiveness of Intensive BP control

- In SPRINT, individuals at high risk for CVD who

awareness (72.5% versus 79.1%; aOR, 0.75 [95% CI, 0.58–0.97]; $P = 0.038$), and similar treatment rates relative to White adults.

- Compared with the age-adjusted BP control rate of 49.0% of White adults, BP control rates were lower in Black adults (39.2%; aOR, 0.71 [95% CI, 0.59–0.85]; $P < 0.001$), Hispanic adults (40.0%; aOR, 0.71 received intensive SBP control (targeting SBP <120 mm Hg) had significantly lower rates of death and MACEs compared with individuals who received standard BP control (targeted SBP <140 mm Hg).¹⁶ A validated microsimulation model used patient-level data from the trial to evaluate the lifetime cost-effectiveness of intensive BP control from a US health care sector perspective.¹⁷ If the treatment effect is assumed to persist over the patient's lifetime, the intensive BP control group would achieve 0.43 QALYs

Diabetes

- In 6653 NHANES participants from 1999 to 2018 who were >20 years of age and reported physician-diagnosed diabetes (other than during pregnancy), trends in glycemic control and control of other cardiovascular risk factors were examined.¹⁹
 - Glycemic control, defined as an HbA1c <7%, improved from 1999 to the early 2010s and then worsened. The percentage of adult NHANES participants with diabetes achieving glycemic control in the 2007 to 2010 period was 57.4% (95% CI, 52.9%–61.8%), worsening to 50.5% (95% CI, 45.8%–55.3%) by 2015 to 2018.
 - Lipid control, defined as non-HDL-C <130 mg/ dL, improved in the early 2000s and stalled from 2007 to 2010 (52.3% [95% CI, 49.2%–55.3%]) to 2015 to 2018 (55.7% [95% CI, 50.8%–60.5%]).
 - BP control, defined as BP <140/90 mm Hg, declined from 2011 to 2014 (74.2% [95% CI, 70.7%–77.4%]) to 2015 to 2018 (70.4% [95% CI, 66.7%–73.8%]).
- (95% CI, 0.04–0.84) more than individuals in the standard control group at an incremental cost of \$28 000 more per QALY gained. The findings were robust to changes in input parameters in sensitivity analyses. Thus, intensive BP control in SPRINT-eligible patients is an effective and high-value intervention.

- Control of all 3 targets plateaued after 2010 and was 22.2% (95% CI, 17.9%–27.3%) in 2015 to 2018. There was no improvement in the use of glucose-lowering or antihypertensive medications after 2010 and in the use of statins after 2014.

Social Determinants of Health/Health Equity in Hypertension

- Disparities in BP control were observed by age, race and ethnicity, insurance status, and health care use. For instance, an analysis of 16 531 nonpreg- nant US adults in NHANES examined disparities by self-reported race and ethnicity in the cascade of hypertension prevalence, awareness, treatment, and control using data from 2013 to 2018.¹⁸
 - Compared with White adults, Black adults had

Hyperlipidemia

- In a PINNACLE Registry study of 1 655 723 patients, a higher prevalence rate (45.3% versus 31.4%; aOR, 2.24 [95% CI, 1.97–2.56]; $P<0.001$) but similar awareness and treatment rates. Hispanic adults had a similar prevalence but lower awareness (71.1% versus 79.1%; aOR, 0.72 [95% CI, 0.58–0.89]; $P=0.005$) and treatment (60.5% versus 67.3%; aOR, 0.78 [95% CI, 0.66–0.94]; $P=0.010$) rates compared with White adults.

57% to 62% of patients were treated with appropriate statin therapy under the ACC/AHA guidelines.²⁰ Overall, there was a small association of higher income with appropriate statin therapy (point-biserial correlation, 0.026; $P < 0.001$). Logistic regression showed an independent association of income with appropriate statin therapy (OR, 1.03 for wealthiest quintile versus poorest quintile [95% CI, 1.01–1.04]).[•] In an examination of electronic health record data for patients seen in primary care or cardiology at an urban academic medical center in New York City from October 2018 to January 2020, only 3994 of 7550 patients (52.9%) who were eligible for statin therapy were prescribed a statin.²¹ After multivariable adjustment, females remained less likely to receive a prescription for statin therapy (aOR, 0.79 [95% CI, 0.71–0.88]). Asian adults had similar prevalence.

- Among 24 651 adults >75 years females) receiving ASCVD in Northern California prescriptions for moderate- or therapy increased over time.²² than half of patients (45%) recommended moderate- or 2018. Lower use of statin females (OR, 0.77 [95% CI, with HF (OR, 0.69 [95% CI, with dementia (OR, 0.88 [95% CI, 0.82–0.95]), and patients with underweight (OR, 0.64 [95% CI,

There was a moderate based and procedural correlation coefficient, 0.53 Among patients with AMI who shock or cardiac arrest. lower than disease-based ence in excess mortality ratio. –4.41% to 3.12%]; $P<0.001$). avoidance in this high-risk that procedural metrics alone

the quality of AMI care (because providers may avoid performing high-risk PCIs to maintain better 0.57–0.73]).

- Disparities in statin prescription rates were identified in an analysis of the Vascular Quality Initiative registry of patients undergoing lower-extremity PAD revascularization from January 1, 2014, to December 31, 2019.²³ Among 125 791 patients (mean age, 67.7 years; 62.7% males, 78.7% White individuals) undergoing 172 025 revascularization procedures, the overall proportion of patients receiving a statin prescription after the procedure improved from 75% in 2014 to 87% in 2019.

However, only 30% of patients who were not taking a statin at the time of revascularization were newly discharged with a statin prescription.

- An emphasis on short-term risk vastly misses younger individuals at elevated lifetime risk. Recent findings¹³ showed a rising prevalence of diabetes, hypertension, and hypercholesterolemia among young individuals 20 to 44 years of age from 2009 to 2020, particularly among Black adults and Hispanic adults.

Acute MI

(See Tables 26-2 through 26-5)

procedural statistics, which could result in higher

- Tables 26-2 through 26-5 show the latest metrics of STEMI and NSTEMI quality of care at US hospitals participating in the GWTG-CAD program.

Quality and Outcomes Across Hospitals

- The Centers for Medicare & Medicaid Services and Hospital Quality Alliance started to publicly report 30-day mortality measures for AMI and HF in 2007,

subsequently expanding to include 30-day readmission rates. According to national Medicare data from

July 2020 through June 2021, the median hospital risk-standardized mortality rate for MI was 12.9% (interquartile range, 12.6%–13.3%).²⁴

- An analysis spanning from April 2011 through December 2017 of patients with AMI from 625 sites using both the NCDR Chest Pain–MI Registry (n=776 890 patients) and CathPCI Registry (n=853 386) explored hospital-level disease-based mortality compared with PCI procedural mortality.²⁵

disease-based mortality rates).²⁵ Thus, disease-based metrics could provide a more comprehensive assessment of hospital performance.

Measuring Quality and Outcomes in Medicare Beneficiaries

• In a cohort analysis of 4070 US acute care hospitals, 2820 hospitals had >25 admissions for AMI, CHF, or pneumonia. There was modest but significant correlation in the 30-day risk-standardized readmission rates for patients with traditional Medicare versus Medicare Advantage (correlation coefficients, 0.31 for AMI, 0.40 for HF, and 0.41 for pneumonia).²⁶ The traditional Medicare risk-standardized readmission rate showed a systematic underestimation of risk for AMI and other conditions. Because enrollees in Medicare Advantage now represent the majority of Medicare beneficiaries,²⁷ it is critical to ensure that quality metrics are robust to differential coding practices and provide an unbiased assessment of quality in the 2 groups.

Effect of Health Policy on Quality of AMI Care

- The HRRP announcement in March 2010 was associated with a reduction in 30-day postdischarge mortality in patients with AMI (0.18% pre-HRRP increase versus 0.08% post-HRRP announcement decrease; difference in change, -0.26% ; $P=0.01$) that did not change significantly after HRRP implementation.²⁸
- The association of state Medicaid expansion with quality of AMI care and outcomes was investigated in 55 737 patients with low income who were <65 years of age across 765 sites using NCDR data from January 1, 2012, to December 31, 2016.²⁹ During this period, Medicaid coverage increased from 7.5% to 14.4% in expansion states compared with 6.2% to 6.6% in nonexpansion states ($P<0.001$). In expansion compared with nonexpansion states, there was no change in use of procedures such as PCI for NSTEMI, and delivery of defect-free care increased to a lesser extent in expansion states (aOR, 1.11 [95% CI, 1.02–1.21]). In-hospital mortality improved to a similar extent in expansion and

nonexpansion states: 3.2% to 2.8% (aOR, 0.93 [95% CI, 0.77–1.12]) versus 3.3% to 3.0% (aOR, 0.85 [95% CI, 0.73–0.99]; $P_{\text{interaction}}=0.48$). In summary, Medicaid expansion did not lead to detectable improvements in AMI care quality or outcomes.

- A retrospective cohort study of Medicare patients found that outpatient practices serving the most socioeconomically disadvantaged patients with CAD perform worse on 30-day AMI mortality, despite delivery of guideline-recommended care similar to that of other outpatient practices.³⁴ Patients at the

most socioeconomically disadvantaged-serving outpatient practices had higher 30-day mortality rates after AMI (aOR, 1.31 [95% CI, 1.02–1.68]) compared with patients at other outpatient practices despite similar prescription of guideline-recommended interventions (antiplatelet, antihypertensive, and statin therapy, as well as cardiac rehabilitation). The association was attenuated after additional adjustment for patient-level Area Deprivation Index, suggesting that sociodemographic factors other than guideline-concordant care may influence AMI outcomes.

Social Determinants of Health/Health Equity in

higher comorbidity burden. Young females were less likely to have received GDMTs (RR, 0.87 [95% CI, 0.80–0.94]). However, 1-year all-cause mortality was comparable for females and males (HR, 1.10 [95% CI, 0.83–1.45]).³⁰

- Among 237 549 AMI survivors in the US Nationwide Readmissions Database, sex differences in HF hospitalization risk were explored.³¹ In a propensity-matched time-to-event analysis, females had a 13% higher risk of 6-month HF readmission compared with males (6.4% versus 5.8%; HR, 1.13 [95% CI, 1.05–1.21]; $P<0.001$).
- An analysis of the Veterans Affairs health care system including 147 600 veteran primary care patients identified sex-related disparities in secondary prevention for IHD.³² Among patients with premature IHD, females received less

antiplatelet (aOR, 0.47 [95% CI, 0.45–0.50]), any statin (aOR, 0.62 [95% CI, 0.59–0.66]), and high-intensity statin (aOR, 0.63 [95% CI, 0.59–0.66]) therapy and had lower adherence to statin therapy than males (mean±SD proportion of days covered, 0.68±0.34 versus 0.73±0.31; β coefficient, −0.02 [95% CI, −0.03 to −0.01]).

- In a health care system cohort of 27 694 patients (52% males, 91% White individuals) examined from January 1, 2011, through December 31, 2018, Area Deprivation Index as a measure of living in socioeconomically disadvantaged communities was associated with readmission after cardiac hospitalization.³³ Patients with myocardial ischemia living in the areas with the greatest deprivation index had a 2-fold greater hazard of 1-year readmission (HR, 2.04 [95% CI, 1.44–2.91]). In addition, higher Area Deprivation Index was associated with 25% (HR, 1.25 [95% CI, 1.08–1.44]) greater 1-year mortality.

Heart Failure

(See Tables 26-6 and 26-7)

- Current US HF quality data are captured by the widespread but voluntary GWTG-HF program (Tables 26-6 and 26-7) and analyses of health care claims data.

Hospitalizations for HF

- In a cohort study using data from 8 272 270 adult hospitalizations of 5 092 626 unique patients (mean, 72.1 years of age; 48.9% females) in the Nationwide Readmission Database through 2017, primary HF hospitalization rates per 1000 US adults increased from 4.1 in 2013 to 4.9 in 2017.³⁵ Similar trends were noted in the rate per 1000 US adults of postdischarge HF readmissions (1.0 in 2010 to 0.9 in 2014 to 1.1 in 2017) and all-cause 30-day readmissions (0.8 in 2010 to 0.7 in 2014 to 0.9 in 2017). The observed increase in the rate of HF hospitalizations in recent years may represent an actual increase in HF, increased detection attributable to rising use of HF biomarkers, the use of more sensitive definitions of HFpEF, or changes in coding practices.
- A majority of Medicare beneficiaries are now enrolled in Medicare Advantage plans compared with fee-for-service Medicare (52% versus 48% in 2023).³⁶ Thus, it is increasingly important to examine outcomes among beneficiaries enrolled in Medicare Advantage plans in addition to those in traditional fee-for-service Medicare. In 1 study of 262 626 patients hospitalized with HF included in GWTG-HF, patients enrolled in the Medicare Advantage program were more likely to be discharged home (rather than a post-acute care facility) compared with patients enrolled in traditional

A number of studies noted a decrease in mortality after the implementation of the HRRP, with increased mortality in patients who were not readmitted.

- In a longitudinal cohort study of hospitalizations among 20 million service patients across 3497 hospitals subject to penalties (greater reductions in at nonpenalized hospitals –1.25 [95% CI, –1.64 to reduction in penalized hospitals]).³⁸
- Reductions in readmission rate than for nontarget penalized hospitals but not at hospitals.³⁹ Among patients who at >1 hospital within a given rate was consistently higher to hospitals in the worse among those admitted to forming quartile (absolute rate, 2.0 percentage points
- In an analysis from 2005 to 2010 hospitalizations for HF

for-service beneficiaries, the announcement and implementation of the HRRP were associated with an increase in death within 30 days of hospitalization.²⁸ Compared with this baseline trend, post-discharge mortality increased by 0.49% after the announcement of the HRRP ($P=0.01$) and 0.52% after implementation of the HRRP ($P=0.001$). The increase in mortality among patients with HF was related to outcomes among patients who were not readmitted but died within 30 days of discharge.

- As noted, the increasing enrollment in Medicare

to a lower-performing quintile, 10% of hospitals were moved from the top performance quintile to a lower performance quintile when evaluating Medicare fee-for-service and Medicare Advantage performance to provide a more complete picture of performance.

- In data from the GWTG-HF 2012, early follow-up visits with primary care physician were associated with lower readmissions and HF. Early visits with primary care physician were associated with lower mortality, HF and diabetes (HR, 0.58). Last, an early follow-up with primary care physician for those with HF was associated with a lower risk of mortality (HR, 0.78 [95% CI, 0.63–0.98]).
- Although participation in the program improved exercise capacity, clinical outcomes in patients with eligible Medicare beneficiaries have been low. Among 11 696 patients hospitalized for HFrEF from quarter 2 of 2016, the rate of readmission within 6 months of discharge decreased by 1.0% in quarter 1 of 2014; 5.0% in quarter 2 of 2014. This decrease was associated with participation in the program among eligible patients younger age, male sex, race Black, previous hospitalization at hospitals with HF facilities.

Advantage plans necessitates that any quality evaluation includes both fee-for-service and Medicare Advantage patients. A recent study showed that ≈ 1 in 4 “top-performing” hospitals (based on outcomes among fee-for-service patients) would be reclassified to a lower performance group when Medicare Advantage beneficiaries are included in the evaluation of hospital readmissions and mortality.⁴⁰ Between 21.6% and 30.2% were reclassified

Patient-Reported Outcomes for HF

The use of patient-reported outcomes may provide un-derstanding about patient well-being and prognosis. • In a secondary analysis of the TOPCAT and HF-ACTION trials focused on patient-reported outcomes, the most recent score (compared with prior score or change in score) of the Kansas City Cardiomyopathy Questionnaire scores was asso- ciated with a 10% (95% CI, 7%–12%; $P<0.001$) lower risk for subsequent cardiovascular death or HF hospitalization in patients with HFpEF and 7% (95% CI, 3%–11%; $P<0.001$) lower risk for those with HFrEF.⁴³

Cost-Effectiveness and Affordability of HF Therapies

• Simulation modeling studies have examined the cost-effectiveness of sacubitril-valsartan in patients with HFrEF.⁴⁴ Among patients with New York Heart Association class II to IV HF and LVEF of $\leq 40\%$, the sacubitril-valsartan group gained 0.69 additional life-year and 0.62 additional QALY over a lifetime.

Assuming a monthly cost of sacubitril-valsartan to be \$380 produced an incremental cost per QALY gained of \$47 000. However, sacubitril-valsartan prices are higher now than when the drug first entered the market.⁴⁵ According to the sensitivity analyses reported in the aforementioned study, the use of sacubitril-valsartan is likely intermediate value per the ACC/AHA value framework (ie, \$50 000 to <\$150 000 per QALY gained).^{47,48} In 1 study,⁴⁷ dapagliflozin, at an annual cost of \$4192, was projected to add 0.63 QALY at an incremental lifetime cost of \$42 800, for an incremental cost-effectiveness ratio of \$68 300 per QALY gained (95% UI, \$54 600–\$117 600 per QALY gained; cost-effective in 94% of probabilistic simulations at a threshold of \$100 000 per QALY gained). Findings were similar in individuals with and those without diabetes but were sensitive to drug cost.

- In contrast, the use of an SGLT-2 inhibitor for HFpEF was estimated to be of low economic value in 1 study⁴⁹ and low to intermediate value in another study,⁵⁰ largely because of the lack of benefit on mortality and small benefit on quality of life.
- A major barrier to accessing novel but effective GDMTs for HF has been the high out-of-pocket

fee-for-service Medicare who were ≥66 years of age living in the 25 largest metropolitan core-based statistical areas.⁵³ When analyzed by zip code, receipt of TAVR was directly related to median household income but inversely related to the proportion of beneficiaries also enrolled in Medicaid and community-level social deprivation.

For every \$1000 decrease in median costs faced by patients, including Medicare beneficiaries. Two studies suggest that the Inflation Reduction Act of 2022 will lower out-of-pocket costs by 29% to 40% for patients with HFrEF by capping out-of-pocket costs to \$2000 starting in 2025.⁵¹ One study evaluated 4137 Medicare Part D plans for out-of-pocket costs associated with comprehensive guideline-directed HFrEF therapy and found that patient costs were projected to decline from \$2758 in 2022 to \$1954 in 2025 (a 29% reduction).⁵² Patients on concurrent DOAC therapy for AF are projected to see an even larger reduction in out-of-pocket costs (from \$3259 in 2022 to \$2000 in 2025, a 39% reduction).

Transcatheter Aortic Valve Replacement

Since its approval for commercial use in 2011, TAVR has rapidly become the primary modality for the management of aortic stenosis.

Access

- A multicenter, nationwide cross-sectional analysis of Medicare claims data (2012–2018) examined receipt of TAVR among beneficiaries of

(95% CI, 0.1%–0.4%). For each 1% increase in the proportion of patients who were dually enrolled in Medicaid and Medicare services, the number of TAVR procedures per 100 000 Medicare beneficiaries declined by 2.1% (95% CI, 1.3%–2.9%). Every 1-unit increase in the Distressed Communities Index score was associated with 0.4% (95% CI, 0.2%–0.5%) fewer TAVR procedures performed per 100 000 Medicare beneficiaries. Zip codes with higher proportions of patients of Black race and Hispanic ethnicity had lower rates of TAVR, even after accounting for differences in socioeconomic factors, age, and clinical comorbidities. Disparities in access and outcome were also noted for patients residing in low-population-density areas.⁵⁴ In a geo-spatial study of 6531 patients undergoing TAVR in Florida between 2011 and 2016, those residing in the lowest density category (<50 people per square mile) faced longer unadjusted driving distances and times to their TAVR center (mean extra distance, 43.5 miles [95% CI, 35.6–51.4]; mean extra time, 45.6 minutes [95% CI, 38.3–52.9]). Compared with the highest-population-density regions, the lowest-population-density regions had a 7-fold lower TAVR use rate (7 versus 45 per 100 000; $P<0.001$) and increased in-hospital mortality after TAVR (aOR, 6.13 [95% CI, 1.97–19.1]).

Clinical Outcomes

• A retrospective cohort study using data from the STS/ACC TVT Registry was used to develop a novel ranked composite performance measure for TAVR quality that incorporated stroke; major, life-threatening, or disabling bleeding; stage III acute kidney injury; and moderate or severe perivalvular regurgitation.⁵⁵ When this new outcomes-based metric of TAVR quality was applied to 3-year rolling data, there was significant site-level variation in quality of care in TAVR in the United States, with 25 of 301 sites (8%) performing better than expected, 242 of 301 sites (80%) performing as expected, and 34 of 301 (11%) sites performing worse than expected on the basis of predicted outcomes. However, the reliability of this metric exceeded 0.7 only in sites that performed at least 100 procedures over a 3-year period.

Resuscitation

In-Hospital Cardiac Arrests

(See Table 26-8)

Quality measures in resuscitation tinent care settings. Started in 1999. Registry remains the dominant improvement data (Table 26-8). hospital registry and performance for IHCA. Process measures for

are generally based on time to correct administration of specific resuscitation and postresuscitation procedures, drugs, or therapies.

- Among 192 adult hospitals in the GWTG-R program, risk-standardized survival after IHCA rates (total of 44 477 IHCAs) varied widely between hospitals (median, 24.7%; range, 9.2%–37.5%).⁵⁶ Compared with sites without a very active resuscitation champion, hospitals with a very active physician champion were more likely to be in a higher survival quintile (aOR, 3.90 [95% CI, 1.39–10.95]). There was no difference in survival between sites without a very active champion and those with a very active nonphysician champion (aOR, 1.28 [95% CI, 0.62–2.65]).
- In a temporal trend evaluation of survival to discharge after IHCA, there was a significant increase in survival in Black individuals (11.3% in 2000 versus 21.4% in 2014) and White individuals (15.8% versus 23.2%), and a reduction in the disparity between races was noted ($P_{\text{interaction}} < 0.001$).⁵⁷

Out-of-Hospital Cardiac Arrests

- Recent work within a large US registry demonstrated that Black individuals and Hispanic individuals were 26% less likely to receive bystander CPR at home (38.5%) than White individuals (47.4%; aOR, 0.74 [95% CI, 0.72–0.76]) and 37% less likely to receive bystander CPR in public locations (45.6% versus 60.0%; aOR, 0.63 [95% CI, 0.60–0.66]) than White individuals.⁵⁸ Significant disparities in bystander CPR exist after controlling for income variables, regardless of the racial and ethnic composition of the location of the arrest.

- In a study comparing OHCA in 2020 to evaluate the impact of pandemic, a lower proportion bystander CPR in 2020 (61% lower use of automated 1%; $P=0.02$) were seen.⁶⁰ The longer EMS response times, respectively; $P<0.001$ hospital discharge (14.7% to 18.7%).
- In a study using a large US registry of OHCA to compare outcomes during the pandemic period of March 16 through April 30, 2020,⁵⁹ incidence of OHCA was significantly higher in 2020 compared with 2019, largely in communities with high COVID-19 mortality (adjusted mean difference, 38.6 [95% CI, 37.1–40.1] per 1 million residents) and very high COVID-19 mortality (adjusted mean difference, 28.7 [95% CI, 26.7–30.6] per 1 million residents). However, there was no difference in rates of sustained return of spontaneous circulation or survival to discharge during the prepandemic and peripandemic periods in 2020 versus 2019.

Implantable Defibrillators and Cardiac Resynchronization Therapy

- In an observational analysis of patients hospitalized with HF and an EF $\leq 35\%$ without an ICD in the GWTG-HF program (2011–2014), the over-all rate of predischARGE ICD counseling was low at 22.6%. Females were less likely than males to receive predischARGE ICD counseling (19.3% versus 24.6%; aOR, 0.84 [95% CI, 0.78–0.91]), and individuals from underrepresented racial and ethnic group populations were less likely to receive counseling than patients from White populations (Black, 22.6%; Hispanic, 18.6%; other racial and ethnic groups, 14.4%; versus White, 24.3%; aOR versus White populations, 0.69 [95% CI, 0.63–0.76] for Black individuals; aOR, 0.62 [95% CI, 0.55–0.70] for Hispanic individuals; aOR, 0.53 [95% CI, 0.43–0.65] for other patients).⁶¹ Among patients who were counseled, females and males were similarly likely to receive an ICD (aOR, 1.13 [95% CI, 0.99–1.29]), but compared with White individuals, Black individuals (aOR, 0.70 [95% CI, 0.56–0.88]) and Hispanic individuals (aOR, 0.68 [95% CI, 0.46–1.01]) were less likely to receive an ICD.
- In a multicenter retrospective analysis of 106 individuals ≤ 21 years of age without prior cardiac disease who received an ICD after SCA, 20 individuals (19%) received appropriate shocks, 16 individuals (15%) received inappropriate shocks (including 3 individuals who had both appropriate and inappropriate shocks), and 73 individuals (69%) received no shocks over a median follow-up of 3 years.⁶² Guideline-concordant use of ICD was high, regardless of underlying disease.
- Using an antibiotic-eluting envelope during cardiac implantable electronic device procedures reduces the risk of device infection but increases procedural costs. A simulation modeling study examined the cost-effectiveness of using an antibiotic-eluting envelope during cardiac implantable electronic device procedures among patients with HF.⁶³ Effectiveness was estimated from the World-Wide Randomized Antibiotic Envelope Infection Prevention Trial. Compared with usual care, using an antibiotic-eluting envelope at a cost of \$953

per unit during initial implantations produced an incremental cost-effectiveness ratio of \$112 000 per QALY gained (39% probability of being cost-effective). In contrast, using an antibiotic-eluting envelope during generator replacement procedures produced an incremental cost-effectiveness ratio of \$54 000 per QALY gained (84% probability of being cost-effective).

Sensitivity analyses showed that results were sensitive to the underlying rate of infection, cost effectiveness to prevent infections.

Atrial Fibrillation

(See Tables 26-9 and 26-10)

- Current US AF quality data are captured by the widespread but voluntary GWTG-AFIB program (Tables 26-9 and 26-10) and analyses of health care claims data.

Prescription of Oral Anticoagulants and Outcomes

- An analysis of data from the AHA GWTG-AFIB program examined prescription of oral anticoagulation therapy at discharge in 33 235 patients with a CHA₂DS₂-VASc score ≥ 2 hospitalized for AF at 1 of 115 sites from 2013 to 2017. Oral anticoagulation use increased over time from 79.9% to 96.6% in the end of the follow-up period for those with no contraindications, with 93.5% of eligible patients without contraindications being prescribed oral anticoagulation therapy for stroke prevention in AF.⁶⁴
- In a cross-sectional analysis spanning 2013 to

has decreased with increased use of DOACs is unknown.

- An AHA GWTG-Stroke study compared outcomes with DOAC therapy (dabigatran, rivaroxaban, or apixaban) with outcomes with warfarin in 11 662 patients ≥ 65 years of age with AF who were anticoagulation naive and discharged from 1041 hospitals after AIS in 2019 and including 34 174 hospitalized patients ≥ 65 years of age with AF from the GWTG-AFIB registry, overall discharge prescription of anticoagulation was 85.6%.⁶⁵ Higher morbidity burden was associated with lower odds of anticoagulation prescription (aOR, 0.72 for patients with ≥ 6 comorbidities versus 0–2 comorbidities [95% CI, 0.60–0.86]). In those with ≥ 6 comorbidities, frequent falls/frailty was the most common reason for nonprescription of anticoagulation (31.0%).
- In an analysis claims of Medicare Advantage beneficiaries with newly diagnosed AF from 2010 to 2020, among patients who were prescribed any oral anticoagulant, apixaban was the most commonly prescribed oral anticoagulant followed by rivaroxaban (77.7% and 16.0% of patients receiving DOACs respectively).⁶⁶
- Aspirin alone as an alternative to oral anticoagulant in patients with AF was common in 2008 to 2012. According to the data from ACC NCDR PINNACLE Registry, among patients with CHA₂DS₂-VASc score ≥ 2 who were prescribed either aspirin or oral anticoagulant, 38.2% were prescribed aspirin alone.⁶⁷ Whether the prevalence of aspirin-alone therapy

on warfarin, including more days at home during the first year after discharge (mean±SD, 287.2±114.7 days versus 263.0±127.3 days; adjusted difference, 15.6 [99% CI, 9.0–22.1]), fewer MACEs (aHR, 0.89 [99% CI, 0.83–0.96]), and fewer deaths (aHR, 0.88 [95% CI, 0.82–0.95]; $P<0.001$).⁶⁸

- Although there are no trial data comparing the DOACs with each other, high-quality observational studies^{69–72} have compared major ischemic and hemorrhagic outcomes in patients with AF treated with rivaroxaban or apixaban. A retrospective cohort study using Medicare fee-for-service claims identified 581 451 patients with AF who began rivaroxaban ($n=227\,572$) or apixaban ($n=353\,879$).⁶⁹ Among patients receiving rivaroxaban, the rate of a composite outcome of major ischemic (stroke/systemic embolism) and hemorrhagic (ICH/other intracranial bleeding/fatal extracranial bleeding) events was 16.1 per 1000 PY versus 13.4 per 1000 PY for apixaban (HR, 1.18 [95% CI, 1.12–1.24]). The rivaroxaban group had increased risk for both major ischemic events (8.6 versus 7.6 per 1000 PY; HR, 1.12 [95% CI, 1.04–1.20]) and hemorrhagic events (7.5 versus 5.9 per 1000 PY; HR, 1.26 [95% CI, 1.16–1.36]). The authors concluded that among Medicare beneficiaries ≥65 years of age with AF, treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischemic or hemorrhagic events.

Adherence to Anticoagulation

- A systematic review and meta-analysis demonstrated suboptimal adherence and persistence to DOACs in patients with AF.⁷³ Among 48 observational studies with a combined 594 784 patients with AF (59% male; mean, 71 years of age), the pooled mean proportion of days covered/medication possession ratio was 77% (95% CI, 75%–80%), with 66% (95% CI, 63%–70%) showing ≥80% adherence and 69% (95% CI, 65%–72%) showing persistence. Poor adherence to DOAC therapy was associated with greater risk of stroke (HR, 1.39 [95% CI, 1.06–1.81]).
- Using administrative health data from 1996 to 2019 in British Columbia, Canada, a study examined oral anticoagulant adherence trajectories over 5 years

in 19 749 patients with AF age; 56% male; mean CHA₂DS₂-VASc score. 2.8).⁷⁴ patients as having “consistent as a high and steady the prescription medication, as having “rapid decline and as having “rapid decline and 4% as having “slow decline Clinical and demographic

able to provide strong performance in predicting these adherence trajectories.

Other AF Therapies

- In a NCDR PINNACLE Registry study, 107 759 of 658 250 patients (16.4%) with AF without CVD were inappropriately prescribed combination anti-platelet and anticoagulant therapy, and 5731 of 150 079 patients (3.8%) with AF with reduced LVEF received an inappropriate prescription for a nondihydropyridine calcium channel blocker.⁷⁵ The adjusted practice-level median OR for inappropriate prescriptions in AF patients was 1.70 (95% CI, 1.61–1.82), consistent with a 70% likelihood of 2 random practices treating identical patients with AF differently.
- In the NCDR Left Atrial Appendage Occlusion Registry, 49 357 patients (mean, 76.1 years of age; 41.3% females) with AF undergoing LAAO with the Watchman device from January 1, 2016, to June 30, 2019, were analyzed.⁷⁶ After multivariable adjustment, females had a higher risk of in-hospital adverse events after LAAO than males (1284 [6.3%] versus 1144 [3.9%]; $P<0.001$; OR, 1.63 [95% CI, 1.49–1.77]; $P<0.001$).

of 363 309 patients with PINNACLE-AF outpatient erable variation in oral insurance plans.⁷⁸ Relative to insurance was associated oral anticoagulant prescription rate. 53%: Medicare. 52%: 41%: $P<0.001$) and of DOAC private. 19%: Medicare. 17%: 8%: $P<0.001$). In addition.

- An economic evaluation of the CABANA trial examined medical resource use data for all trial participants (N=2204), US unit costs of care, and quality-of-life adjustments based on EQ-5D–based utilities measured during the trial.⁷⁷ Catheter ablation was associated with an increased lifetime mean cost of \$15 516 (95% CI, –\$2963 to \$35 512) compared with drug therapy with an incremental cost-effectiveness ratio of \$57 893 per QALY gained (<\$100 000 per QALY in 75% of bootstrap replications). However, the incremental cost-effectiveness ratio rose to \$183 318 per life-year gained if one were to assume no quality-of-life gains. The authors concluded that catheter ablation of AF was economically attractive compared with drug therapy on the basis of projected incremental quality-adjusted survival but not survival alone.

Social Determinants of Health/Health Equity in AF

may influence the likelihood of being prescribed a DOAC. An analysis of 2013 to 2018 Medicare Provider Utilization and Payment Data reported a rapid uptake of DOACs among cardiologists compared with internists, family medicine physicians, and advanced practice clinicians.⁷⁹ For example, in 2013, 18.7% of cardiologists prescribed only warfarin, whereas 83.0% of internists, 77.7% of family medicine physicians, and 83.0% of advanced practice clinicians prescribed only warfarin. The corresponding numbers in 2018 were 1.6% for cardiologists, 12.6% for internists, 20.0% for family medicine physicians, and 28.2% for advanced practice clinicians.

- In an analysis of Medicare Advantage claims data from 2016 to 2019, Black race was associated with lower odds of receiving either antiarrhythmic drug or catheter ablation (aOR, 0.89 [95% CI, 0.83–0.94]; $P<0.001$), and Hispanic ethnicity was associated with lower odds of receiving catheter ablation (aOR, 0.73 [95% CI, 0.60–0.89]; $P=0.002$).⁸⁰ Lower median household income was associated with lower odds of receiving either antiarrhythmic drug or catheter ablation (aOR for $<\$50\,000$, 0.83 [95% CI, 0.79–0.87]; $P<0.001$; aOR for $\$50\,000$ – $\$99\,999$, 0.92 [95% CI, 0.88–0.96]; $P\leq 0.001$) and catheter ablation (aOR for $<\$50\,000$, 0.61 [95% CI, 0.54–0.69]; $P<0.001$; aOR for $\$50\,000$ – $\$99\,999$, 0.81 [95% CI, 0.72–0.90]; $P<0.001$).

Stroke

Prehospital Care

- A retrospective pre-post study examined the effect of a regional prehospital EMS transport policy to triage patients with suspected large-vessel occlusion stroke to comprehensive stroke centers.⁸¹ The outcome was treatment rates before and after implementation of this triage policy in patients with AIS at 15 primary stroke centers and 8 comprehensive stroke centers in Chicago, IL. Among 7709 patients with stroke, the rate of endovascular therapy increased overall among all patients with AIS (from

Care

7.5%–

- Health care insurance coverage may influence oral anticoagulant and DOAC use. An analysis

4.9% [95% CI, 4.1%–5.8%] to 7.4% [95% CI,

8.5%]; $P<0.001$) and among EMS-transported patients with AIS within 6 hours of onset (4.8%

[95% CI, 3.0%–7.8%] to 13.6% [95% CI, 10.4%–17.6%]; $P<0.001$). The authors concluded that “the implementation of a prehospital transport policy for CSC triage in Chicago was associated with a significant, rapid, and sustained increase in endovascular therapy rate for patients with AIS without deleterious associations with thrombolysis rates or times.”⁸¹

(See Tables 26-11 and 26-12)

- The AHA GWTG-Stroke program (Table 26-11 and 26-12) remains the largest stroke quality-improvement program. The US-based program

12 countries evaluated 4 main strategies: educational interventions, organizational models, health care delivery infrastructure, and workflow improvements. Sixteen studies showed that a wide range of strategies aimed at reducing delays in treatment—including educational interventions, telemedicine between

is an ongoing, voluntary hospital registry and performance-improvement initiative for acute stroke and supplies most of the quality data for acute stroke

Poststroke Care and Outcomes

- A study of 2083 patients with ischemic stroke registry and GWTG-Stroke found that 36.5% dependent or dead at 3 months after stroke in care.
- In an analysis comparing individuals presenting with stroke at institutions participating in the GWTG-Stroke program with those at institutions

from 82 hospitals with data in both the AVAIL of patients with acute stroke were functionally

2006 through 2008. Rates of dependence or not enrolled in the program, individuals in the GWTG-Stroke program were more likely to receive

death varied considerably across hospitals (0%–67%; adjusted interquartile range, 32%–41%), which indicates the need to understand which process measures could be targeted to minimize hospital variation and to improve poststroke func-

intravenous tPA (RR, 3.74 [95% CI, 1.65–8.50]), to receive education on risk factors (RR, 1.54 [95% CI, 1.16–2.05]), to be evaluated for swallowing (RR, 1.25 [95% CI, 1.04–1.50]), to receive a lipid

tional outcomes.⁸⁶

evaluation (RR, 1.18 [95% CI, 1.05–1.32]), and to be evaluated by a neurologist (RR, 1.12 [95% CI,

- A retrospective, difference-in-differences analysis of GWTG-Stroke registry data compared 342 765 first-time ischemic stroke admissions from 2012 to 2018 for patients 19 to 64 years of age in 45 states (27 that expanded Medicaid and 18 that did not).^{.82}
- In a study from the National Acute Stroke Quality Assessment including 14 666 patients from 202 hospitals, patients admitted to lower-volume centers had higher mortality.^{.83} However, this association was no longer present once adjusted for stroke severity, suggesting that severity should be accounted for in comparisons of performance across institutions.
- In an analysis from GWTG-Stroke, Asian American individuals presented with more severe strokes, with an OR of 1.35 (95% CI, 1.30–1.40; $P < 0.001$) for an NIHSS score >16 , and were less likely to receive intravenous tPA (OR, 0.95 [95% CI, 0.91–

resulted in an increase in the proportion of stroke admissions covered by Medicaid (from 12.2% to 18.1% in expansion states and from 10.0% to only 10.6% in nonexpansion states). Medicaid expansion was associated with increased odds of discharge to a skilled nursing facility (aOR, 1.33 [95% CI, 1.12–1.59]) and, among eligible patients, transfer to any rehabilitation facility (aOR, 1.24 [95% CI, 1.08–1.41]) and lower odds of discharge home (aOR, 0.89 [95% CI, 0.80–0.98]), but Medicaid expansion was not associated with other outcomes such as stroke severity, use of emergency services, time to acute care, in-hospital mortality, or level of

0.98]; $P=0.003$). They also had higher in-hospital mortality (OR, 1.14 [95% CI, 1.09–1.19]; $P<0.001$) and more symptomatic hemorrhage after tPA (OR, 1.36 [95% CI, 1.20–1.55]; $P<0.001$) than White individuals, although mortality was in fact lower after adjustment for stroke severity (OR, 0.95 [95% CI, 0.91–0.99]; $P=0.008$). In addition, Asian American individuals had better

disability.

adherence to rehabilitation (OR, 1.27 [95% CI, 1.18–1.36]; $P<0.001$) and intensive statin therapy (OR, 1.14 [95% CI, 1.10–1.18]; $P<0.001$).⁸⁴

- A systematic review examined the cost-effectiveness of several strategies to reduce delays in the management of AIS.⁸⁵ Twenty studies performed in

- Because of the poor survival after stroke, inter-ventions related to improvement in end-of-life care are desirable to improve quality of care for those patients. A study using GWTG-Stroke data demonstrated that discharge from a Medicare Shared Savings Program hospital or alignment with a related organization was associated with a 16% increase in the odds of hospice enrollment (OR, 1.16 [95% CI, 1.06–1.26]) for patients with high mortality risk with absolute rates of 20% ver-sus 22%. However, a reduction in inpatient com-fort measures or hospice enrollment in individuals at lower mortality risk, from 9% to 8%, was noted

in the same organizations
(0.74–0.91).⁸⁸

Global Efforts in Quality

The AHA's quality measurement efforts, including the GWTG globally. The first international where the registries were adapted cardiometabolic conditions. These registries have captured data on >175 000 encounters/patients and published >40 scientific publications. As of 2023, the AHA has partnered with private and public stakeholders to implement the GWTG portfolio and

Arabia, Canada, Mexico, Vietnam, nesia, and Malaysia. There is tion of these programs is in quality in these settings. For a quality improvement program GWTG initiative resulted in an ment in AF, HF, and ACS 12 167 patients enrolled in 19 tween 2016 and 2022. adoption of in Cardiology program was Hospital Certification programs in multiple countries, including the United Arab Emirates, Kingdom of Saudi

in the composite score (a combination of primary ACC/ AHA performance measures for each condition, adapted to the local context) from baseline to the last quarter of follow-up: 65.8±36.2% to 73±31.2% for AF (*P*=0.024), 81.0±23.6% to 89.9±19.3% for HF (*P*<0.001), and 88.0±19.1% to 91.2±14.9% for ACS (*P*<0.001).

Table 26-1. National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set on CVD, Diabetes, Tobacco, Nutrition, and Lifestyle, United States, 2022

	Commercial*		Medicare*		Medicaid*
	HMO	PPO	HMO	PPO	HMO
CVD					
β-Blocker	85.1	85.9	89.1	88.8	79.9
BP control†	63.8	54.9	72.9	70.2	60.9
Statin therapy for	81.9	81.8	85.4	84.2	78.7
Diabetes					
HbA1c testing	91.1	89.4	93.9	94.2	85.3
HbA1c >9.0%	28.5	36.6	21.9	21.8	40.3
Eye examination	51.6	49	71.8	69.2	51.5
Monitoring	NA	NA	94.9	94.9	NA
BP <140/90 mm Hg	64.4	55.8	70.4	66	63.6
Statin therapy for	65.4	63.3	79.2	77	63.8
Tobacco, nutrition, and lifestyle					
Advising smokers and	NA	NA	NA	NA	72.8
BMI percentile	74.4	62.1	NA	NA	76.8
Nutrition counseling	64.3	53.9	NA	NA	68.1
Counseling for PA	61.5	NA	NA	NA	64.8
BMI assessment for	84.9	69.7	NA	NA	88.4
PA discussion in older	NA	NA	NA	57.5	55.3
PA advice in older	NA	NA	NA	51.1	52.3

Values are percentages.
BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HMO, health maintenance organization; MI, myocardial infarction; NA, not available; PA, physical activity; and PPO, preferred provider organization.
*Data presented are from 2022 unless otherwise noted.
†β-Blocker persistence: received persistent β-blocker treatment for 6 months after hospital discharge for acute MI.
‡Adults 18 to 59 years of age with BP <140/90 mm Hg, adults 60 to 85 years of age with a diagnosis of diabetes and BP <140/90 mm Hg, and adults 60 to 85 years of age without a diagnosis of diabetes and BP <150/90 mm Hg.
Source: Healthcare Effectiveness Data and Information Set.¹²

Table 26-2. Quality-of-Care Measures in the GWTG-CAD Program: STEMI, United States, 2021 to 2023

Quality-of-care measure	2021	2022	2023
ACE inhibitor or ARB at discharge	91.4	93.2	93.0
Aspirin at discharge	99.3	99.2	99.3
β -Blocker at discharge	97.3	97.6	98.0
Cardiac rehabilitation referral	89.4	89.7	91.6
ECG within 10 min of arrival	72.5	75.0	77.6
High-intensity statin at discharge	96.0	96.7	97.7
Smoking cessation counseling	91.0	92.6	92.0
Aspirin at arrival	98.6	98.9	97.0
Receiving-only time metrics			
Arrival at first facility to PCI within	73.0	72.6	73.8
EMS FMC to PCI within 90 min OR	76.8	77.6	78.2
PCI within 90 min	94.4	95.0	95.3
FMC to PCI within 120 min among	71.7	69.7	70.7
Referring-only time metrics			
Arrival to thrombolytics within 30	55.4	52.3	53.4
Arrival to transfer to PCI center	39.1	40.0	44.6
Arrival to transfer to PCI center	15.8	15.4	17.5

Values are percentages.

GWTG-CAD is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ECG, electrocardiogram; EMS, emergency medical service; FMC, first medical contact; GWTG-CAD, Get With The Guidelines—Coronary Artery Disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Source: Unpublished American Heart Association tabulation, GWTG-CAD.

Table 26-3. Quality-of-Care by Race and Ethnicity and Sex in the GWTG-CAD Program: STEMI, United States, 2023

Quality-of-care	Race and ethnicity				Sex	
	White	Black	Hispanic	Asian	Male	Female
ACE inhibitor or	93.1	93.4	94.0	92.5	93.8	90.4
Aspirin at discharge	99.3	99.1	99.3	99.1	99.4	98.9
β -Blocker at	97.9	98.3	97.6	97.7	98.2	97.6
Cardiac	92.1	90.7	88.8	89.8	91.5	91.9
ECG within 10 min	78.7	71.3	76.9	76.5	79.9	71.3
High-intensity statin	97.8	97.1	97.4	97.9	97.9	97.2
Smoking cessation	91.6	93.7	92.4	92.1	91.9	92.2
Aspirin at arrival	96.9	98.6	98.3	96.8	94.6	94.9
Receiving-only time metrics						
Arrival at first	73.6	65.7	74.7	87.4	75.3	69.2
EMS FMC to PCI	78.7	72.7	78.9	79.7	80.1	73.5
PCI within 90 min	95.5	93.2	95.1	95.3	95.6	94.5
FMC to PCI within	71.1	59.1	71.6	82.7	73.1	62.9
Referring-only time metrics						
Arrival to	53.1	60.3	29.6	25.0	54.7	49.7
Arrival to transfer	45.6	34.6	52.9	39.1	46.8	38.9
Arrival to transfer	17.1	12.1	32.4	17.4	18.3	15.6

Values are percentages.

GWTG-CAD is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ECG, electrocardiogram; EMS, emergency medical service; FMC, first medical contact; GWTG-CAD, Get With The Guidelines–Coronary Artery Disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Source: Unpublished American Heart Association tabulation, GWTG-CAD.

Table 26-4. Quality-of-Care Measures in the GWTG-CAD Program: NSTEMI, United States, 2021 to 2023

Quality-of-care measure	2021	2022
ACE inhibitor or ARB at discharge	86.7	88.3
Smoking cessation counseling	92.6	94.5

Values are percentages.

GWTG-CAD is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GWTG-CAD, Get With The Guidelines–Coronary Artery Disease; LV, left ventricular; and NSTEMI, non–ST-segment-elevation myocardial infarction.

Source: Unpublished American Heart Association tabulation, GWTG-CAD.

Table 26-5. Quality-of-Care Measures by Race and Ethnicity and Sex in the GWTG-CAD Program: NSTEMI, United States, 2023

Quality-of-care	Race and ethnicity				Sex	
	White	Black	Hispanic	Asian	Male	Female
ACE inhibitor or	89.6	92.6	89.5	87.9	90.6	89.5
Smoking cessation	96.3	96.5	97.6	96.7	96.7	95.7
Cardiac	84.3	83.6	80.4	81.0	85.2	80.6
Dual antiplatelet	72.6	75.3	68.1	67.8	76.3	67.3
LV systolic function	95.5	95.1	95.6	95.6	95.7	95.1

Values are percentages.

GWTG-CAD is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GWTG-CAD, Get With The Guidelines–Coronary Artery Disease; LV, left ventricular; and NSTEMI, non–ST-segment-elevation myocardial infarction.

Source: Unpublished American Heart Association tabulation, GWTG-CAD.

Table 26-6. Quality-of-Care Measures in the GWTG-HF Program, United States, 2021 to 2023

Quality-of-care measure	2021	2022	2023
Evidence-based specific β -blockers	93.4	94.3	94.6
Measure LV function	99.2	99.3	99.1
Postdischarge appointment for HF	85.6	86.2	87.4
ARNI at discharge for patients with	49.3	57.0	61.1
SGLT-2 inhibitor at discharge for	10.8	37.5	60.6
MRA at discharge for patients with	57.1	61.3	68.1
ACE inhibitor/ARB or ARNI at	91.8	92.6	92.6
Anticoagulation for AF or atrial	91.9	92.8	93.1
CRT-D or CRT-P placed or	39.4	35.4	36.7
DVT prophylaxis	93.8	92.6	92.2
Follow-up visit within 7 d or less	65.4	64.0	65.3
Hydralazine nitrate at discharge in	28.1	25.9	23.1
ICD counseling or ICD placed or	70.6	56.2	56.9
Influenza vaccination during flu	73.1	70.6	70.0
Pneumococcal vaccination	64.2	63.7	65.2
Laboratory monitoring follow-up	NA	NA	70.9
Defect-free care for quadruple	18.4	61.2	69.7
DOAC at discharge for HF with	43.4	45.1	67.6
SGLT-2 inhibitor at discharge for	NA	NA	22.6

Values are percentages.

GWTG-HF is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor/neprilysin inhibitor; CRT-D, cardiac resynchronization therapy pacemaker defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DOAC, direct-acting oral anticoagulant; DVT, deep vein thrombosis; GWTG, Get With The Guidelines; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction;

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NA, not available; and SGLT-2, sodium-glucose cotransporter-2.
Source: Unpublished American Heart Association tabulation, GWTG-HF.

Table 26-7. Quality-of-Care by Race and Ethnicity and Sex in the GWTG-HF Program, United States, 2023

Quality-of-care	Race and ethnicity*				Sex	
	White	Black	Hispanic	Asian	Males	Females
Evidence-based	93.9	96.0	95.2	94.3	95.0	93.9
Measure LV	99.2	99.1	99.2	97.3	99.3	99.1
Postdischarge	88.2	85.9	87.7	86.2	87.4	87.7
ARNI at discharge	58.2	66.5	61.1	55.9	61.5	59.8
SGLT-2 inhibitor at	56.6	67.1	62.9	65.0	61.9	57.4
MRA at discharge	65.5	72.9	68.8	68.5	68.8	66.4
ACE inhibitor/ARB	91.6	94.4	94.2	93.1	92.9	92.2
Anticoagulation for	93.3	93.1	92.7	90.1	93.2	93.2
CRT-D or CRT-P	37.0	37.4	41.2	34.6	39.2	31.9
DVT prophylaxis	91.9	94.3	93.7	87.2	92.6	93.4
Follow-up visit	67.1	61.6	63.2	67.3	64.6	66.3
Hydralazine nitrate	NA	23.1	NA	33.3	24.7	20.4
ICD counseling or	68.9	68.7	69.2	50.3	70.4	64.3
Influenza	72.3	63.5	71.2	70.1	69.1	72.1
Pneumococcal	68.5	57.1	62.7	67.4	62.7	68.8
Laboratory	50.7	42.9	45.8	44.3	47.9	48.8
Defect-free care for	52.7	59.5	54.8	58.7	55.8	53.4
DOAC at discharge	66.9	70.5	69.5	64.5	68.2	67.6
SGLT-2 inhibitor at	20.8	29.6	25.9	22.2	25.7	20.2

Values are percentages.

GWTG-HF is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor/neprilysin inhibitor; CRT-D, cardiac resynchronization therapy pacemaker defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DOAC, direct-acting oral anticoagulant; DVT, deep vein thrombosis; GWTG, Get With The Guidelines; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NA, not available; and SGLT-2, sodium-glucose cotransporter-2.

*Race and ethnicity are assessed by the patient or, if that is not available, by the physician or institution.

Source: Unpublished American Heart Association tabulation, GWTG-HF.

Table 26-8. Quality-of-Care of Patients Among GWTG-R Hospitals, United States, 2021 to 2023

Population	Quality-of-care measure	2021	2022	2023
Adult	Confirmation of airway	83.8	85.4	86.0
	Percent pulseless cardiac	96.3	96.4	96.6
	Time to first shock ≤ 2 min	73.0	74.7	76.9
	Time to IV/IO epinephrine	94.1	94.0	94.5
Pediatric	Confirmation of airway	87.1	90.3	89.8
	Percent pulseless cardiac	91.6	92.1	93.6
	Time to IV/IO epinephrine	94.0	93.4	94.5
	Time to first chest	99.4	98.1	97.8
Infant/neonate	Confirmation of airway	85.2	88.5	88.3
	Percent pulseless cardiac	96.0	96.0	94.8
	Time to IV/IO epinephrine	94.6	92.0	94.9
	Time to first chest	96.9	97.7	97.8
Newly born	Advanced airway placed	63.5	69.0	66.3
	Confirmation of airway	81.7	79.6	85.7
	Pulse oximetry in place	69.0	76.6	80.1
	Time to positive pressure	91.0	88.6	87.8

Values are mean percentages.

GWTG-R is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

CPA indicates cardiopulmonary arrest; GWTG-R, Get With The Guidelines–Resuscitation; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Source: Unpublished American Heart Association tabulation, GWTG-R.

Table 26-9. Quality-of-Care Measures in the GWTG-AFIB Program, United States, 2021 to 2023

Quality-of-care measure	2021	2022
ACE inhibitor/ARB or ARNI at	84.5	84.3
β -Blocker at discharge when LVEF	95.3	94.6
CHADS ₂ -VASc score documented	83.9	79.0
FDA-approved anticoagulation at	98.8	98.7
PT/INR planned follow-up	88.2	83.1
Statin at discharge in patients with AF	86.8	85.4
Aldosterone antagonist at discharge	34.1	39.2
Anticoagulation therapy education	73.8	61.5
DOAC at discharge for patients with	88.6	90.8
Discharge HR $\leq$ 110 bpm	94.1	95.1
Inappropriate use of antiarrhythmics	9.1	9.6
Inappropriate use of antiplatelets and	13.4	13.6
Inappropriate use of DOAC in	9.3	14.9
	1.8	1.8

Values are percentages.

GWTG-AFIB is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CAD, coronary artery disease; CVA, cerebral vascular accident; DOAC, direct oral anticoagulant; FDA, US Food and Drug Administration; GWTG-AFib, Get With The Guidelines—Atrial Fibrillation; HR, heart rate; INR, international normalized ratio; LVEF, left ventricular ejection fraction; PT, prothrombin time; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

Source: Unpublished American Heart Association tabulation, GWTG-AFib.

Table 26-10. Quality-of-Care Measures by Race and Ethnicity and Sex in the GWTG-AFib Program, United States, 2023

Quality-of-care	Race and ethnicity*				Sex	
	White	Black	Hispanic	Asian	Males	Females
ACE inhibitor/ARB	82.1	84.6	89.6	73.3	83.2	81.4
β -Blocker at	95.2	95.4	96.2	90.9	95.4	94.4
CHADS ₂ -VASc	77.7	77.2	66.7	65.3	76.2	77.4
FDA-approved	99.3	98.0	97.9	98.8	99.2	99.1
PT/INR planned	77.1	86.9	78.9	88.0	77.6	77.7
Statin at discharge	85.3	84.9	84.3	86.3	86.9	82.3
Aldosterone	41.6	44.6	42.7	56.3	41.5	44.8
Anticoagulation	53.7	60.0	55.4	65.9	52.2	57.1
DOAC at discharge	91.7	91.1	92.1	95.4	91.9	91.3
Discharge HR $\leq$ 110	94.4	93.8	92.9	87.0	94.4	94.2
Inappropriate use of	11.3	22.6	0.0	0.0	12.8	9.2
Inappropriate use of	12.2	12.9	11.1	11.2	13.3	11.1
Inappropriate use of	17.1	6.7	5.3	0.0	19.1	14.1
Inappropriate use of dofetilide or	0.2	0.0	1.9	0.0	0.5	0.0
Inappropriate use of	2.5	3.2	1.5	0.0	2.8	1.6
Smoking cessation	67.6	69.5	65.0	70.0	65.5	71.6
Warfarin at	53.5	58.8	66.7	62.5	52.2	56.4

Values are percentages.

GWTG-AFIB is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CAD, coronary artery disease; CVA, cerebral vascular accident; DOAC, direct oral anticoagulant; FDA, Food and Drug Administration; GWTG-AFib, Get With The Guidelines—Atrial Fibrillation; HR, heart rate; INR, international normalized ratio; LVEF, left ventricular ejection fraction; PT, prothrombin time; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

*Race and ethnicity are assessed by the patient or, if that is not available, by the physician or institution.

Source: Unpublished American Heart Association tabulation, GWTG-AFIB.

Table 26-11. Adherence to Quality-of-Care Measures in the GWTG-Stroke Program, United States, 2021 to 2023

Quality-of-care measure	2021	2022	2023
Anticoagulation at discharge for	97.0	97.0	96.7
Antithrombotics at discharge	96.5	97.4	97.3
Antithrombotics by end of hospital	96.6	96.4	95.6
Statin at discharge: high intensity	93.8	94.5	93.7
IV thrombolytic arrive by 3.5 h, treat	92.2	93.0	91.4
Smoking cessation counseling	97.6	97.5	97.4
VTE prophylaxis day of or day after	99.0	99.0	99.0
Dysphagia screen before any oral	83.5	82.8	82.3
Stroke education	94.0	93.6	93.6
Rehabilitation assessed or received	99.0	98.9	98.4
LDL documented	93.7	93.7	93.1
Initial NIHSS score reported	93.9	94.1	92.1
Door to IV thrombolytic therapy	86.3	86.4	87.5
Door to IV thrombolytic therapy	64.6	65.0	70.3
Door to IV thrombolytic therapy	30.6	31.5	36.3
Door to EVT device within 60 min	41.0	42.8	46.9
Door to EVT device within 60 min	39.5	40.8	43.0

Values are percentages.

GWTG-Stroke is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

AF indicates atrial fibrillation; EVT, endovascular therapy; GWTG, Get With The Guidelines; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and VTE, venous thromboembolism.

Source: Unpublished American Heart Association tabulation, GWTG-Stroke.

Table 26-12. Adherence to Quality-of-Care Measures by Race and Ethnicity and Sex in the GWTG-Stroke Program, United States, 2023

Quality-of-care	Race and ethnicity*				Sex	
	White	Black	Hispanic	Asian	Males	Females
Anticoagulation at	96.7	96.4	96.5	98.0	96.7	96.7
Antithrombotics at	97.3	97.7	97.0	97.2	97.7	97.4
Antithrombotics by	95.6	95.6	95.3	96.5	96.1	95.5
Statin at discharge:	93.5	94.2	93.6	94.3	94.4	93.4
IV thrombolytic	91.3	91.4	92.8	92.1	91.8	91.6
Smoking cessation	97.4	97.4	96.8	98.0	97.5	97.4
VTE prophylaxis	99.0	99.1	98.8	99.1	99.0	99.0
Dysphagia screen	82.3	81.4	83.8	84.3	82.8	82.2
Stroke education	93.5	93.8	95.0	94.3	93.9	93.3
Rehabilitation	98.4	98.4	98.3	98.4	98.4	98.4
LDL documented	92.9	93.2	93.9	94.6	93.5	93.2
Initial NIHSS score	92.2	91.5	92.9	92.6	92.5	92.0
Door to IV	87.3	87.3	88.1	91.6	87.9	87.1
Door to IV	69.5	70.9	72.5	78.0	71.0	69.6
Door to IV	35.5	35.7	38.7	45.3	37.8	34.6
Door to EVT device within 60 min for	48.6	40.5	46.4	44.4	47.1	46.7
Door to EVT device within	44.9	37.0	42.8	37.9	42.8	43.2

Values are percentages.

GWTG-Stroke is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

AF indicates atrial fibrillation; EVT, endovascular therapy; GWTG, Get With The Guidelines; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and VTE, venous thromboembolism.

*Race and ethnicity are assessed by the patient or, if that is not available, by the physician or institution.

Source: Unpublished American Heart Association tabulation, GWTG-Stroke.

REFERENCES

1. Quality of Care and Outcomes Research in Measuring and improving quality of care: a Association/American College of Assessment of Healthcare Quality in *Circulation*. 2000;101:1483–1493. doi: 10.1161/JAHA.122.027094
2. American Heart Association. Focus on
3. American College of Cardiology Quality NCDR registries. Accessed April 20, 2024.
4. Oseran AS, Sun T, Wadhwa RK, Dahabreh C, Asnani AH, Yeh RW, Kazi DS. Enriching the American Heart Association COVID-19 Cardiovascular Disease Registry through linkage with external data sources: rationale and design. *J Am Heart Assoc*. 2022;11:e7743. doi: 10.1161/JAHA.122.027094
5. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous
6. Kazi DS, Wei PC, Penko J, Bellows BK, Coxson P, Bryant KB, Fontil V, Blyler CA, Lyles C, Lynch K, et al. Scaling up pharmacist-led blood pressure control programs in Black barbershops: projected popula-
7. randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116. doi: 10.1056/NEJMsa1616035
8. Agarwal R, Chiu N, Wadhwa RK, Kazi DS. Racial/ethnic disparities in treatment and control in the United States. *JAMA*. 2021;325:1719–1726. doi: 10.1001/jama.2016.11004
9. Fara M, Wada D, Coresh J, Selvin E. Control in U.S. adults: 1999–2018. *N Engl J Med*. 2016;316:743–753. doi: 10.1001/jama.2016.11004
10. Kazi DS, Wei PC, Penko J, Bellows BK, Coxson P, Bryant KB, Fontil V, Blyler CA, Lyles C, Lynch K, et al. Scaling up pharmacist-led blood pressure control programs in Black barbershops: projected popula-
11. randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116. doi: 10.1056/NEJMsa1616035
12. Agarwal R, Chiu N, Wadhwa RK, Kazi DS. Racial/ethnic disparities in treatment and control in the United States. *JAMA*. 2021;325:1719–1726. doi: 10.1001/jama.2016.11004
13. Fara M, Wada D, Coresh J, Selvin E. Control in U.S. adults: 1999–2018. *N Engl J Med*. 2016;316:743–753. doi: 10.1001/jama.2016.11004
14. Kazi DS, Wei PC, Penko J, Bellows BK, Coxson P, Bryant KB, Fontil V, Blyler CA, Lyles C, Lynch K, et al. Scaling up pharmacist-led blood pressure control programs in Black barbershops: projected popula-

doi: 10.1056/NEJMsa2032271

20. Tanguturi VK, Kennedy KF, Virani SS, Maddox TM, Armstrong K, Wasfy JH. Association between poverty and appropriate statin prescription for the treatment of hyperlipidemia in the United States: an analysis from the ACC NCDR PINNACLE Registry. *Cardiovasc Revasc Med*. 2020;21:1016–1021. doi: 10.1016/j.carrev.2019.12.026
21. Metser G, Bradley C, Moise N, Liyanage-Don N, Kronish I, Ye S. Gaps and disparities in primary prevention statin prescription during outpatient care. *Am J Cardiol*. 2021;161:36–41. doi: 10.1016/j.amjcard.2021.08.070
22. Spencer-Bonilla G, Chung S, Sarraju A, Heidenreich P, Palaniappan L, Rodriguez F. Statin use in older adults with stable atherosclerotic cardiovascular disease. *J Am Geriatr Soc*. 2021;69:979–985. doi: 10.1111/jgs.16975
23. Kite TA, Ludman PF, Gale CP, Wu J, Caixeta A, Mansourati J, Sabate M, Jimenez-Quevedo P, Candilio L, Sadeghipour P, et al; International COVID-ACS Registry Investigators. International prospective registry of acute coronary syndromes in patients with COVID-19. *J Am Coll Cardiol*. 2021;77:2466–2476. doi: 10.1016/j.jacc.2021.03.309
24. Varghese MS, Beatty AL, Song Y, Xu J, Sperling LS, Fonarow GC, Keteyian SJ, McConeghy KW, Penko J, Yeh RW, et al. Cardiac rehabilitation and the COVID-19 pandemic: persistent declines in cardiac rehabilitation participation and access among US Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2022;15:e009618. doi: 10.1161/CIRCOUTCOMES.122.009618
25. De Luca G, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Jensen LO, Loh PH, Calmac L, et al. COVID-19 pandemic, mechanical reperfusion and 30-day mortality in ST elevation myocardial infarction. *Heart*. 2022;108:458–466. doi: 10.1136/heartjnl-2021-319750
26. Kazi DS, Elkind MSV, Deutsch A, Dowd WN, Heidenreich P, Khavjou O, Mark D, Mussolino ME, Ovbiagele B, Patel SS, et al; on behalf of the American Heart Association. Forecasting the economic burden of cardiovascular disease and stroke in the United States through 2050: a presidential advisory from the American Heart Association. *Circulation*. 2024;150:e89–e101. doi: 10.1161/CIR.0000000000001258
27. Joynt Maddox KE, Elkind MSV, Aparicio HJ, Commodore-Mensah Y, de Ferranti SD, Dowd WN, Hernandez AF, Khavjou O, Michos ED, Palaniappan L, et al; on behalf of the American Heart Association. Forecasting the burden of cardiovascular disease and stroke in the United States through 2050: prevalence of risk factors and disease: a presidential advisory from the American Heart Association. *Circulation*. 2024;150:e65–e88. doi: 10.1161/CIR.0000000000001256
28. National Committee for Quality Assurance. Healthcare Effectiveness Data and Information Set (HEDIS) health plan employer data and information set measures of care on cardiovascular disease, diabetes mellitus, tobacco, nutrition, and lifestyle. Accessed April 20, 2024.

23. Singh N, Ding L, Devera J, Magee GA, Garg PK. Prescribing of statins after lower extremity revascularization procedures in the US. *JAMA Netw Open*. 2021;4:e2136014. doi: 10.1001/jamanetworkopen.2021.36014

24. Centers for Medicare & Medicaid Services. 2022 Condition-specific mortality measures updates and specifications report. 2022. Accessed July 6, 2024. i-

25. Nathan AS, Xiang Q, Wojdyla D, Khatana SAM, Dayoub EJ, Wadhera RK, Bhatt DL, Kolansky DM, Kirtane AJ, Rao SV, et al. Performance of hospitals when assessing disease-based mortality compared with procedural mortality for patients with acute myocardial infarction. *JAMA Cardiol*. 2020;5:765–772. doi: 10.1001/jamacardio.2020.0753

26. Panagiotou OA, Voorhies KR, Keohane LM, Kim D, Adhikari D, Kumar A, Rivera-Hernandez M, Rahman M, Gozalo P, Gutman R, et al. Association of inclusion of Medicare Advantage patients in hospitals' risk-standardized readmission rates, performance, and penalty status. *JAMA Netw Open*. 2021;4:e2037320. doi: 10.1001/jamanetworkopen.2020.37320

27. Centers for Medicare & Medicaid Services. Medicare enrollment dashboard. 2024. Accessed July 16, 2024.

28. Wadhera RK, Joynt Maddox KE, Wasfy JH, Haneuse S, Shen C, Yeh RW. Association of the Hospital Readmissions Reduction Program with mortality among Medicare beneficiaries hospitalized for heart failure, acute myocardial infarction, and pneumonia. *JAMA*. 2018;320:2542–2552. doi: 10.1001/jama.2018.19232

29. Wadhera RK, Bhatt DL, Wang TY, Lu D, Lucas J, Figueroa JF, Garratt KN, Yeh RW, Joynt Maddox KE. Association of state Medicaid expansion with quality of care and outcomes for low-income patients hospitalized with acute myocardial infarction. *JAMA Cardiol*. 2019;4:120–127. doi: 10.1001/jamacardio.2018.4577

30. Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, Porterfield D, Blankstein R, Rosamond WD, Bhatt DL, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. *Circulation*. 2019;139:1047–1056.

doi:

13. Aggarwal R, Yeh RW, Joynt Maddox KE, Wadhera RK. Cardiovascular risk factor prevalence, treatment, and control in US adults aged 20 to 44 years, 2009 to March 2020. *JAMA*. 2023;329:899–909. doi: 10.1001/jama.2023.2307

14. Peters SAE, Muntner P, Woodward M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. *Circulation*. 2019;139:1025–1035. doi: 10.1161/CIRCULATIONAHA.118.035550

15. Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, Colantonio LD. Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. *JAMA*. 2020;324:1190–1200. doi: 10.1001/jama.2020.14545

16. Wright J Jr, Williamson J, Whelton P, Snyder J, Sink K, Rocco M, Reboussin D, Rahman M, Oparil S, Lewis C; SPRINT Research Group. A

31. Yandrapalli S, Malik A, Pemmasani G, Aronow W, Shah F, Lanier G, hospitalisation risk following acute myocardial infarction. <i>Heart</i>. 2021;107:1657–1663. doi: 10.1136/heartjnl-2020-318306 32. Lee MT, Mahtta D, Ramsey DJ, Liu J, Misra A, Nasir K, Samad Z, health care among patients with premature athero- sclerotic cardiovascular disease. <i>JAMA Cardiol</i>. 2021;6:782–790. doi: 10.1001/jamacardio.2021.0683 33. Johnson AE, Zhu J, Garrard W, Thoma FW, Mulukutla S, Kershaw KN, prediction in an electronic health record. <i>J Am Heart Assoc</i>. 2021;10:e020466. doi: 10.1161/JAHA.120.020466	Cooper H, Jain D, Naidu S, Frishman W, et al. Sex differences in heart failure Itchhaporia D, Khan SU, Schofield RS, et al. Sex-related disparities in cardiovascular Magnani JW. Area Deprivation Index and cardiac readmissions: evalu- ating risk-

34. Wadhera RK, Bhatt DL, Kind AJH, Song Y, Williams KA, Maddox TM, Yeh RW, Dong L, Doros G, Turchin A, et al. Association of outpatient practice-level socioeconomic disadvantage with quality of care and outcomes among older adults with coronary artery disease: implications for value-based payment. *Circ Cardiovasc Qual Outcomes*. 2020;13:e005977. doi: 10.1161/CIRCOUTCOMES.119.005977
35. Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017. *JAMA Cardiol*. 2021;6:952–956. doi: 10.1001/jamacardio.2020.7472
36. MEDPAC. The Medicare Advantage program: status report. 2024. Accessed July 6, 2024.
37. Finiguerra JF, Wadhera RK, Frakt AB, Fonarow GC, Heidenreich PA, Xu H, Lytle B, DeVore AD, Matsouaka R, Yancy CW, et al. Quality of care and outcomes among Medicare Advantage vs fee-for-service Medicare patients hospitalized with heart failure. *JAMA Cardiol*. 2020;5:1349–1357. doi: 10.1001/jamacardio.2020.3638
38. Desai NR, Ross JS, Kwon JY, Herrin J, Dharmarajan K, Bernheim SM, Krumholz HM, Horwitz LI. Association between hospital penalty status and the Hospital Readmission Reduction Program and readmission rates for target and nontarget conditions. *JAMA*. 2016;316:2647–2656. doi: 10.1001/jama.2016.18533
39. Krumholz HM, Wang K, Lin Z, Dharmarajan K, Horwitz LI, Ross JS, Drye EE, Bernheim SM, Normand ST. Hospital-readmission risk: isolating hospital effects from patient effects. *N Engl J Med*. 2017;377:1055–1064. doi: 10.1001/jama.2023.8.419–428. doi: 10.1001/jamacardio.2023.0077 51. Johnson M, Nayak RK, Gilstrap L, Dusetzina SB. Estimation of out-of-pocket costs for inhibitors for the treatment of heart failure with preserved ejection fraction. *JAMA Cardiol*. 2023;8:419–428. doi: 10.1001/jamacardio.2023.0077 51. Johnson M, Nayak RK, Gilstrap L, Dusetzina SB. Estimation of out-of-pocket costs for

- ment within major metropolitan areas. *JAMA Cardiol.* 2022;7:150–157. doi: 10.1001/jamacardio.2021.4641
54. Damuji AA, Fabbro M 2nd, Epstein RH, Rayer S, Wang Y, Moscucci M, Cohen MG, Carroll JD, Messenger JC, Resar JR, et al. Transcatheter aortic valve replacement in low-population density areas: assessing healthcare access for older adults with severe aortic stenosis. *Circ Cardiovasc Qual Outcomes.* 2020;13:e006245. doi: 10.1161/CIRCOUTCOMES.119.006245
55. Desai ND, O'Brien SM, Cohen DJ, Carroll J, Vemulapalli S, Arnold SV, Forrest JK, Thourani VH, Kirtane AJ, O'Neil B, et al. Composite metric for benchmarking site performance in transcatheter aortic valve replacement: results from the STS/ACC TVT Registry. *Circulation.* 2021;144:186–194. doi: 10.1161/CIRCULATIONAHA.120.051456
- 10.1056/NEJMsa1702321
40. Oseran AS, Wadhera RK, Orav EJ, Figueroa JF. Effect of Medicare Advantage on hospital readmission and mortality rankings. *Ann Intern Med.* 2023;176:480–488. doi: 10.7326/M22-3165
41. Edmonston DL, Wu J, Matsouaka RA, Yancy C, Heidenreich P, Pina IL, Hernandez A, Fonarow GC, DeVore AD. Association of post-discharge specialty outpatient visits with readmissions and mortality in high-risk heart failure patients. *Am Heart J.* 2019;212:101–112. doi: 10.1016/j.ahj.2019.03.005
42. Pandey A, Keshvani N, Zhong L, Mentz RJ, Pina IL, DeVore AD, Yancy C, Kitzman DW, Fonarow GC. Temporal trends and factors associated with cardiac rehabilitation participation among Medicare beneficiaries with heart failure. *JACC Heart Fail.* 2021;9:471–481. doi: 10.1016/j.jchf.2021.02.006
43. Pokharel Y, Khariton Y, Tang Y, Nassif ME, Chan PS, Arnold SV, Jones PG, Spertus JA. Association of Serial Kansas City Cardiomyopathy Questionnaire assessments with death and hospitalization in patients with heart failure with preserved and reduced ejection fraction: a secondary analysis of 2 randomized clinical trials. *JAMA Cardiol.* 2017;2:1315–1321. doi: 10.1001/jamacardio.2017.3983
44. Sandhu AT, Ollendorf DA, Chapman RH, Pearson SD, Heidenreich PA. Cost-effectiveness of sacubitril-valsartan in patients with heart failure with reduced ejection fraction. *Ann Intern Med.* 2016;165:681–689. doi: 10.1001/jamacardio.2021.4641

- B, Chan PS; American Heart Association's Get With the Guidelines–Resuscitation Investigators. Association between hospital resuscitation champion and survival for in-hospital cardiac arrest. *J Am Heart Assoc*. 2021;10:e017509. doi: 10.1161/JAHA.120.017509
57. Joseph L, Chan PS, Bradley SM, Zhou Y, Graham G, Jones PG, Vaughan-Sarrazin M, Girotra S; American Heart Association Get With the Guidelines–Resuscitation Investigators. Temporal changes in the racial gap in survival after in-hospital cardiac arrest. *JAMA Cardiol*. 2017;2:976–984. doi: 10.1001/jamacardio.2017.2403
58. Garcia RA, Spertus JA, Girotra S, Nallamothu BK, Kennedy KF, McNally BF, Breathett K, Del Rios M, Sasson C, Chan PS. Racial and ethnic differences in bystander CPR for witnessed cardiac arrest. *N Engl J Med*. 2022;387:1569–1578. doi: 10.1056/NEJMoa2200798
59. Chan PS, Girotra S, Tang Y, Al-Araji R, Nallamothu BK, McNally B. Outcomes for out-of-hospital cardiac arrest in the United States during the coronavirus disease 2019 pandemic. *JAMA Cardiol*. 2021;6:296–303. doi: 10.1001/jamacardio.2020.6210
60. Uy-Evanado A, Chugh HS, Sargsyan A, Nakamura K, Mariani R, Haddock K, Salvucci A, Jui J, Chugh SS, Reinier K. Out-of-hospital cardiac arrest response and outcomes during the COVID-19 pandemic. *JACC Clin Electrophysiol*. 2021;7:6–11. doi: 10.1016/j.jacep.2020.08.010
61. Hess PL, Hernandez AF, Bhatt DL, Hellkamp AS, Yancy CW, Schwamm LH, Peterson ED, Schulte PJ, Fonarow GC, Al-Khatib SM. Sex and race/ethnicity outcomes requires an emphasis on affordability. *JACC Heart Fail*. 2024;12:1238–1241. doi: 10.1016/j.jchf.2024.04.019
46. Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ, Halperin JL, Hlatky MA, Jacobs AK, Mark DB, et al; on behalf of the ACC/AHA Task Force on Performance Measures and Guidelines; ACC/AHA Task Force on Practice Guidelines. ACC/AHA statement on cost/value methodology in clinical practice guidelines and

ity differences in implantable cardioverter-defibrillator counseling and use among patients hospitalized with heart failure: findings from the Get With The Guidelines–Heart Failure program. *Circulation*. 2016;134:517–526.

doi: 10.1161/CIRCULATIONAHA.115.021048

62. Robinson JA, LaPage MJ, Atallah J, Webster G, Miyake CY, Ratnasamy C, Ollberding NJ, Mohan S, Von Bergen NH, Johnsrude CL, et al. Outcomes of pediatric patients with defibrillators following initial presentation with sudden cardiac arrest. *Circ Arrhythm Electrophysiol*. 2021;14:e008517. doi:

performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129:2329–2345. doi: 10.1161/CIR.0000000000000042

47. Isaza N, Calvachi P, Raber I, Liu CL, Bellows BK, Hernandez I, Shen C, Gavin MC, Garan AR, Kazi DS. Cost-effectiveness of dapagliflozin for the treatment of heart failure with reduced ejection fraction. *JAMA Netw Open*.

10.1161/CIRCEP.120.008517

2021;4:e2114501. doi: 10.1001/jamanetworkopen.2021.14501

48. Parizo JT, Goldhaber-Fiebert JD, Salomon JA, Khush KK, Spertus JA, Heidenreich PA, Sandhu AT. Cost-effectiveness of dapagliflozin for treatment of patients with heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;6:926–935. doi: 10.1001/jamacardio.2021.1437

49. Zheng J, Parizo JT, Spertus JA, Heidenreich PA, Sandhu AT. Cost-effectiveness of empagliflozin in patients with heart failure with pre-served ejection fraction. *JAMA Intern Med*. 2022;182:1278–1288. doi:

63. Modi RM, Liu CL, Isaza N, Raber I, Calvachi P, Zimetbaum P, Bellows BK, Kramer DB, Kazi DS. Cost-effectiveness of antibiotic-eluting enve-
lope for prevention of cardiac implantable electronic device infections
in heart failure. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008443. doi:
10.1161/CIRCOUTCOMES.121.008443
64. Piccini JP, Xu H, Cox M, Matsouaka RA, Fonarow GC, Butler J, Curtis AB, Desai N, Fang M, McCabe PJ, et al; Get With The Guidelines–AFIB
Clinical Working Group and Hospitals. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable. *Circulation*.
2019;139:1497–1506. doi: 10.1161/CIRCULATIONAHA.118.035909
65. Dalggaard F, Xu H, Matsouaka RA, Russo AM, Curtis AB, Rasmussen PV,
Ruwald MH, Fonarow GC, Lowenstern A, Hansen ML, et al. Management of atrial fibrillation in older patients by morbidity burden: insights
from Get With The Guidelines–Atrial Fibrillation. *J Am Heart Assoc*. 2020;9:e017024.
doi: 10.1161/JAHA.120.017024
50. Cohen LP, Isaza N, Hernandez I, Lewis GD, Ho JE, Fonarow GC, Kazi
DS, Bellows BK. Cost-effectiveness of sodium-glucose cotransporter-2
doi: 10.1161/JAHA.120.017024
66. Ko D, Lin KJ, Bessette LG, Lee SB, Walkey AJ, Cheng S, Kim E, Glynn
RJ, Kim DH. Trends in use of oral anticoagulants in older adults with

- newly diagnosed atrial fibrillation, 2010-2022:5:e2242964. doi:
67. Hsu JC, Maddox TM, Kennedy K, Katz DF, AK, Turakhia MP, Marcus GM. Aspirin prescription in atrial fibrillation patients at risk 2016;67:2913–2923. doi:
 68. Xian Y, Xu H, O'Brien EC, Shah S, Thomas Olson DM, Schwamm LH, Bhatt DL, et al. anticoagulants vs warfarin in older patients emic stroke: findings from the Patient-Stroke Patients Prefer and Effectiveness .*JAMA Neurol.* 2019;76:1192–1202. doi:
 69. Ray WA, Chung CP, Stein CM, Smalley W AM, Daugherty JR, Dickson A, Murray KT. Association of rivaroxaban vs apixaban with major ischemic or hemorrhagic events in patients with atrial fibrillation. *JAMA.* 2021;326:2395–2404. doi: 10.1001/jama.2021.21222
 70. Paschke LM, Klimke K, Altiner A, von Stillfried D, Schulz M. Comparing stroke prevention therapy of direct oral anticoagulants and vitamin K antagonists in patients with atrial fibrillation: a nationwide retrospective observational study. *BMC Med.* 2020;18:254.
 - of oral anticoagulation in insured from the American College of *Heart J.* 2018;195:50–59. doi:
 79. Wheelock KM, Ross JS, Murumiah K, R. Clinician trends in prescribing direct Medicare beneficiaries. *JAMA Netw* 10.1001/
 80. Eberly LA, Garo L, Yang L, Markman Dixit S, Marchlinski FE, Groeneveld nic and socioeconomic disparities in oxvsma atrial fibrillation. .*JAMA Netw* 10.1001/iamanetworkopen.2021.0247
 81. Kass-Hout T, Lee J, Tataris K, Richards doi: 10.1186/s12916-020-01695-7
 71. Mitchell A, Watson MC, Welsh T, McGrogan A. Effectiveness and safety of direct oral anticoagulants versus vitamin K antagonists for people aged 75 years and over with atrial fibrillation: a systematic review and meta-analyses of observational studies. *J Clin Med.* 2019;8:554. doi:

- S, O'Neill K, Sednew RM, Prabhakaran S. Prehospital Comprehensive stroke center vs primary stroke center triage in patients with suspected large vessel occlusion stroke. *JAMA Neurol.* 2021;78:1220–1227. doi: 10.1001/jamaneurol.2021.2485
82. Howard G, Schwamm LH, Donnelly JP, Howard VJ, Jasne A, Smith EE, Rhodes JD, Kissela BM, Fonarow GC, Kleindorfer DO, et al. Participation in Get With The Guidelines–Stroke and its association with quality of care for stroke. *JAMA Neurol.* 2018;75:1331–1337. doi: 10.1001/jamaneurol.2018.2101
83. Lee KJ, Kim JY, Kang J, Kim BJ, Kim SE, Oh H, Park HK, Cho YJ, Park JM, Park KY, et al. Hospital volume and mortality in acute ischemic stroke patients: effect of adjustment for stroke severity. *J Stroke Cerebrovasc Dis.* 2021;78:2395–2404. doi: 10.1016/j.jacc.2021.09.1370
72. Yaghi S, Saldanha IJ, Misquith C, Zaidat B, Shah A, Joudi K, Persaud B, Abdul Khalek F, Shu L, de Havenon A, et al. Direct oral anticoagulants versus vitamin K antagonists in cerebral venous thrombosis: a systematic review and meta-analysis. *Stroke.* 2022;53:3014–3024. doi: 10.1161/strokeaha.122.039579
73. Ozaki AF, Choi AS, Le QT, Ko DT, Han JK, Park SS, Jackevicius CA. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes.* 2020;13:e005969. doi: 10.1161/circoutcomes.119.005969
74. Salmasi S, De Vera MA, Safari A, Lynd LD, Koehoorn M, Barry AR, Andrade JG, Deyell MW, Rush K, Zhao Y, et al. Longitudinal oral anticoagulant adherence trajectories in patients with atrial fibrillation. *J Am Coll Cardiol.* 2021;78:2395–2404. doi: 10.1016/j.jacc.2021.09.1370
75. Hsu JC, Reynolds MR, Song Y, Doros G, Lubitz SA, Gehi AK, Turakhia MP, Maddox TM. Outpatient prescription practices in patients with atrial fibrillation (from the NCDR PINNACLE Registry). *Am J Cardiol.* 2021;155:32–39. doi: 10.1016/j.amjcard.2021.06.011
76. Darden D, Duong T, Du C, Munir MB, Han FT, Reeves R, Saw J, Zeitler EP, Al-Khatib SM, Russo AM, et al. Sex differences in procedural outcomes among patients undergoing left atrial appendage occlusion: insights from the NCDR LAAO Registry. *JAMA Cardiol.* 2021;6:1275–1284. doi: 10.1001/jamacardio.2021.3021
77. Chew DS, Li Y, Cowper PA, Anstrom KJ, Piccini JP, Poole JE, Daniels MR,

2020;29:104753. doi: 10.1016/j.jstrokecerebrovasdis.2020.104753	84. Song S, Liang L, Fonarow GC, Smith EE, Bhatt DL, Matsouaka RA, Xian Y, Schwamm LH, Saver JL. Comparison of clinical care and in-hospital outcomes of Asian American and White patients with acute ischemic stroke. <i>JAMA Neurol.</i> 2019;76:430–439. doi: 10.1001/jamaneurol.2018.4410
85. Nguyen CP, Maas WJ, van der Zee DJ, Uyttenboogaart M, Buskens E, Lahr MMH; CONTRAST Consortium. Cost-effectiveness of improvement strategies for reperfusion treatments in acute ischemic stroke. <i>JAMA Neurol.</i> 2019;76:430–439. doi: 10.1001/jamaneurol.2018.4410	85. Nguyen CP, Maas WJ, van der Zee DJ, Uyttenboogaart M, Buskens E, Lahr MMH; CONTRAST Consortium. Cost-effectiveness of improvement strategies for reperfusion treatments in acute ischemic stroke: a systematic review. <i>BMC Health Serv Res.</i> 2023;23:315. doi: 10.1186/s12913-023-09310-0
86. Bettger JP, Thomas L, Liang L, Xian Y, Bushnell CD, Saver JL, et al. Hospital variation in functional recovery after stroke. <i>Circ Cardiovasc Qual Outcomes.</i> 2017;10:e002391. doi: 10.1161/CIRCOUTCOMES.121.007940	86. Bettger JP, Thomas L, Liang L, Xian Y, Bushnell CD, Saver JL, Fonarow GC, Peterson ED. Hospital variation in functional recovery after stroke. <i>Circ Cardiovasc Qual Outcomes.</i> 2017;10:e002391. doi: 10.1161/CIRCOUTCOMES.121.007940
87. McGee BT, Seagraves KB, Smith EE, Xian Y, Zhang S, Alhanti B, Medicaid expansion with access to care, severity, and outcomes for acute ischemic stroke. <i>Circ Cardiovasc Qual Outcomes.</i> 2021;14:e007940. doi: 10.1161/CIRCOUTCOMES.121.007940	87. McGee BT, Seagraves KB, Smith EE, Xian Y, Zhang S, Alhanti B, Matsouaka RA, Reeves M, Schwamm LH, Fonarow GC. Associations of Medicaid expansion with access to care, severity, and outcomes for acute ischemic stroke. <i>Circ Cardiovasc Qual Outcomes.</i> 2021;14:e007940. doi: 10.1161/CIRCOUTCOMES.121.007940
88. Kaufman BG, O'Brien EC, Stearns SC, Matsouaka RA, Holmes GM, Weinberger M, Schwamm LH, Smith EE, Fonarow GC, Xian Y, et al. Medicare shared savings ACOs and hospice care for ischemic stroke patients. <i>J Am Geriatr Soc.</i> 2019;67:1402–1409. doi: 10.1111/jgs.15852	88. Kaufman BG, O'Brien EC, Stearns SC, Matsouaka RA, Holmes GM, Weinberger M, Schwamm LH, Smith EE, Fonarow GC, Xian Y, et al. Medicare shared savings ACOs and hospice care for ischemic stroke patients. <i>J Am Geriatr Soc.</i> 2019;67:1402–1409. doi: 10.1111/jgs.15852
Monahan KH, Davidson-Ray L, Bahnson TD, et al. Cost-effectiveness of catheter ablation versus antiarrhythmic drug therapy in atrial fibrillation: the CABANA randomized clinical trial. <i>Circulation.</i> 2022;146:535–547. doi: 10.1161/circulationaha.122.058575	78. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, et al. Association of insurance type with receipt of catheter ablation versus antiarrhythmic drug therapy in atrial fibrillation: the CABANA randomized clinical trial. <i>Circulation.</i> 2022;146:535–547. doi: 10.1161/circulationaha.122.058575

89. Taniguchi FP, Bernardez-Pereira S, Ribeiro ALP, Morgan L, Curtis AB, Taubert K, Albuquerque DC, Smith SC Jr, Paola AAV. A nationwide initiative to improve cardiology quality: the Best Practice in Cardiology program in Brazil. *Arq Bras Cardiol.* 2023;120:e20230375. doi: 10.36660/abc.20230375

27. MEDICAL PROCEDURES

See Table 27-1 and Charts 27-1 through 27-3

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Trends in Operations and Procedures

(See Table 27-1 and Chart 27-1)

According to HCUP data from the Agency for Healthcare Research and Quality for the year 2021¹ (Table 27-1):

- There were 444 730 PCIs performed on an inpatient basis in the United States.

- A total of 110 245 inpatient procedures involving carotid endarterectomy or stenting were performed.
- A total of 51 695 LA appendage–related procedures were performed.
- A total of 56 705 inpatient peripheral arterial bypass procedures were performed.
- Trends in the numbers of 5 common cardiovascular procedures in the United States presented (Chart 27-1).

Cardiac Open Heart Surgery in Adults

- The STS Adult Cardiac Surgery Database collects data from participating groups, and as of December 31, 2021, the database included data from 1010 sites in United States, 5 sites from Canada, and 6 other international sites.² Data from the STS Adult Cardiac Surgery Database indicate that a total of 153 209 procedures involved isolated CABG in 2021. Isolated CABG made up 71.6% of the 8 major surgeries performed (N=213 996).
- Among other major procedures in 2021, there were 17 867 isolated aortic valve replacements, 10 449 isolated mitral valve replacements, 11 601

mitral valve repair and CABG, and 2463 procedures involving both mitral valve replacement

• Operative mortality for the major procedures in 2021 was as follows: isolated CABG, 2.5%; isolated aortic valve replacement, 2.3%; isolated mitral valve replacement, 5.5%;

CABG, 4.4%; mitral valve replacement plus CABG, 11%; mitral valve repair, 1.1%; mitral valve repair plus CABG, 4.8%; and aortic valve replacement plus mitral valve replacement, 10%.² Operative mortality for these analyses is defined as “(1) all deaths, regardless of cause, occurring during the hospitalization in which the operation was performed, even if after 30 days (including patients transferred to other acute care facilities); and (2) all deaths, regardless of cause, occurring after discharge from the hospital, but before the end of the 30th postoperative day.”²

• Median length of stay was 6 days (interquartile range, 4–7 days) for isolated CABG. It was longest for mitral valve

Transcatheter Aortic Valve Replacement

isolated mitral valve repairs, 12 543 procedures involving both aortic valve replacement and CABG, 3416 procedures involving both mitral valve replacement and CABG, 3443 procedures involving both

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

- The STS-ACC TVT Registry collects data on TAVR procedures performed in the United States.³ Between 2011 and 2019, it collected data on 276 316 TAVR procedures in the United States. Some notable findings include the following:
- TAVR volumes continue to grow, with 13 723 TAVR procedures in 2011 to 2013 to 72 991 TAVR procedures in 2019. In 2019, 669 sites were performing TAVR. In 2019, TAVR volumes (n=72 991) exceeded the volumes for all forms of SAVR (n=57 626).
The number of intermediate- and low-risk patients receiving TAVR has grown steadily. Similarly, elective or planned valve-in-valve TAVR cases have increased steadily from 305 cases between 2011 and 2013 to 4508 in 2019. The number of sites in the United States performing TAVR was 715 by the end of August 2020.³ The median age of patients undergoing TAVR in 2019 was 80 years of age (interquartile range, 73–85 years of age) compared with 84 years of age (interquartile range, 78–88 years of age) in the initial years after FDA approval of TAVR.
- In-hospital and 30-day mortality rates of TAVR have improved over time. In-hospital and 30-day mortality rates were 5.4% and 7.2%, respectively, in 2013 and before, whereas they were 1.3% and 2.5%, respectively, in 2019 ($P<0.0001$). The in-hospital stroke rate decreased from 1.8% before 2013 to 1.6% in 2019 ($P<0.0001$). Need for a pacemaker

- at 30 days
- 2011–2013
- stays was 2 days) with
- The femoral access site TAVR in Database Task Force using the most frequent procedures across all participating sites, were as follows: VSD, n=6788; TOF, n=4244; Glenn/hemi-Fontan, n=3729; Fontan, n=3608; off-bypass coarctation, n=3169; atrioventricular canal, n=2972; Norwood, n=2477; arterial switch operation, n=1809; arterial switch operation plus VSD, n=816; and truncus, n=509.

Percutaneous

- The NCDR Left Heart Transplantations Registry is (See Charts 27-2 and 27-3) lance According to data from the Organ Procurement and Transplantation Network⁷:
 - this registry • In 2023, 4545 heart transplantations were performed in the United States, the most ever (Chart 27-2). A total of 54 combined heart-lung transplantations were performed in 2022 (up from 51 in 2022).
 - January 1, • The highest numbers of heart transplantations were performed in California (621), Texas (412), New York (361), and Florida (308).
 - lected data • Of the recipients in 2023, 70.6% were males, 56.6% were NH White people, 24.8% were NH Black people, 12.8% were Hispanic people, 3.7% were Asian people, 0.8% were American Indian/Alaska Native people, 0.4% were Pacific Islander people, and 0.7% were multiracial people. Heart transplantations by recipient age are shown in Chart 27-3. The largest proportion of these patients (42.1%) were between 50 and 64 years of age.
 - dures in the registry: • For transplantations that occurred between 2008 and 2015, the 1-year survival rate was 90.6% for males and 91.1% for females; the 3-year survival
 - The years of Of the White,
 - Of the LAAO, the West, were in tals and 21.5% of
 - In-hospital charge Risk of 2.16%.⁵

Congenital Heart Surgery

According to data from the STS Congenital Heart Surgery Database⁶:

- The database includes 143 910 congenital heart surgeries performed from July 2017 to June 2021 in 114 North American sites. After the exclusion of patients with a surgery date between April 1, 2020, and June 30, 2021, and who were diagnosed with SARS-CoV-2 before procedure or within 30 days after surgery, the unadjusted operative mortality was 2.7% (95% CI, 2.6%–2.8%) during that time period. The operative mortality stratified by age was as follows: 7.5% (95% CI, 7.1%–7.9%) in neonates, 2.4% (95% CI, 2.3%–2.6%) in infants, 1% (95% CI, 0.9%–1.2%) in children, and 1.5% (95% CI, 1.3%–1.8%) in adults.
- The frequencies of the 10 benchmark operations, selected by the STS Congenital Heart Surgery

rate was 85.2% for males and 85.3% for females.

The 5-year survival rates based on 2008 to 2015 transplantations were 78.4% for males and 77.7% for females. The

1- and 5-year survival rates for White individuals undergoing cardiac transplantation were 90.7% and 79.1%, respectively. For Black people, they were 90.7% and 74.1%, respectively.

For Hispanic people, they were 90.1% and 79.9%, respectively. For Asian individuals, they were 91.4% and 80.2%, respectively.

- Between 2011 and 2014, the median waiting time for individuals in United Network for Organ Sharing heart status 1A was 87 days (95% CI, 80–94). As a comparison, the median waiting time was 67 days (95% CI, 61–73) for patients with heart status 1A between 2007 and 2010.
- As of May 21, 2024, 3468 individuals were on the waiting list for a heart transplantation, and 43 people were on the list for a heart-lung transplantation.

Table 27-1. Estimated Inpatient Cardiovascular Operations, Procedures, and Patient Data, by Sex and Age (in Thousands), United States, 2021

Operation/ Operation/	CCSR code	All	Sex		Age, y			
			Male	Female	18–44	45–64	65–84	≥85
Heart	CAR002	65 915	41 455	24 455	3255	19 160	39 120	3855
CABG	CAR003	184 000	140 630	43 350	4015	68 925	108 630	2405
PCI	CAR004	444 730	301 385	143 240	20 455	176 790	218 395	28 915
Other coronar	CAR005	7110	5120	1985	615	2540	2730	130
CEA and	CAR006	110 245	64 835	45 385	2790	26 630	72 980	7415
Embolectomy, endarterecto	CAR007	75 710	45 310	30 380	5360	25 200	39 640	4750
Angiopl asty	CAR008	226 055	125 290	100 680	19 120	75 800	109 535	18 185
LA appendage	CAR009	51 695	36 545	15 140	1495	16 565	32 765	850
Ligation and	CAR010	97 020	54 530	42 475	20 710	29 790	32 965	5300
Aneurysm	CAR011	82 965	50 710	32 245	7395	23 340	45 280	5530
Vessel repair	CAR012	102 415	65 425	36 955	13 330	31 650	46 210	3790
Heart and	CAR013	7930	4630	3290	495	715	775	*
Peripheral	CAR014	56 705	36 715	19 975	3250	20 675	30 450	2070
Perip heral	CAR015	17 880	10 520	7355	2645	7060	7395	710
Portal and	CAR016	8090	5010	3075	1520	4140	2265	*
Pericardial	CAR017	24 360	14 135	10 210	3910	8185	10 240	910
Heart	CAR018	3615	2545	1070	640	1825	620	0
Septa l	CAR019	36 730	20 205	16 510	4655	9360	10 945	655
Saphenou s vein	CAR020	200 740	148 845	51 875	10 155	73 395	111 800	3270
Artery, vein,	CAR021	13 150	6330	6815	1975	4165	5590	675
Heart valve	CAR022	95 410	60 200	35 200	9170	33 670	46 585	1135
Heart valve	CAR023	111 425	63 375	48 035	1680	8600	74 385	25 720
Pacemaker	CAR026	84 020	55 120	28 885	5405	22 635	45 200	9720
Heart assist	CAR027	27 955	20 345	7605	2100	9805	14 005	1745

These data do not reflect any procedures performed on an outpatient basis. Over time, many more procedures are being performed on an outpatient basis. Weight-ed national estimates are from HCUP NIS AHRQ and based on data collected by individual states and provided to AHRQ by the states. Total number of weighted discharges in the United States is based on HCUP NIS=33 334 053.

AHRQ indicates Agency for Healthcare Research and Quality; CABG, coronary artery bypass graft; CCSR, Clinical Classifications Software Refined; CEA, carotid endarterectomy; HCUP, Healthcare Cost and Utilization Project; LA, left atrial; NEC, not elsewhere classified; NIS, National/Nationwide Inpatient Sample; and PCI, percutaneous coronary intervention.

*These statistics are suppressed.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.¹

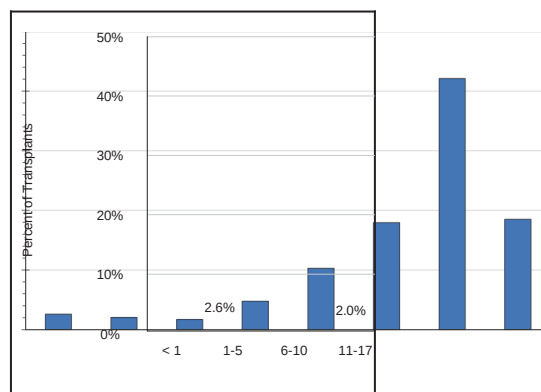
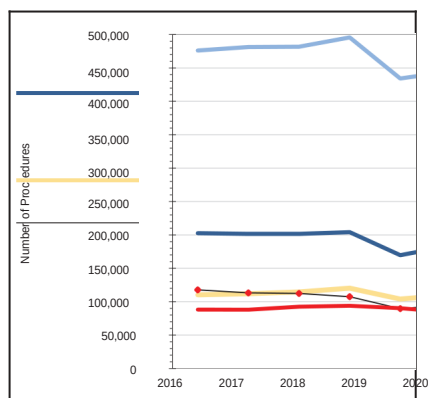
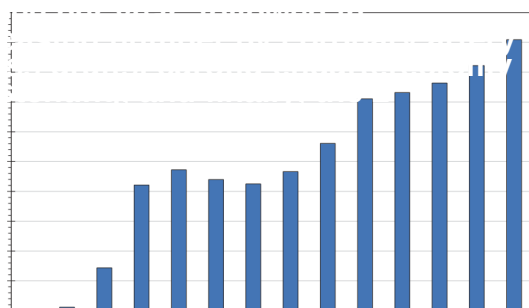


Chart 27-1. Estimated inpatient cardiovascular operations and procedures, United States, 2016 to 2021.



Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.¹

Chart 27-3. Heart transplantations by recipient age, United States, 2023.

Source: Data derived from the Organ Procurement and Transplantation Network.⁷

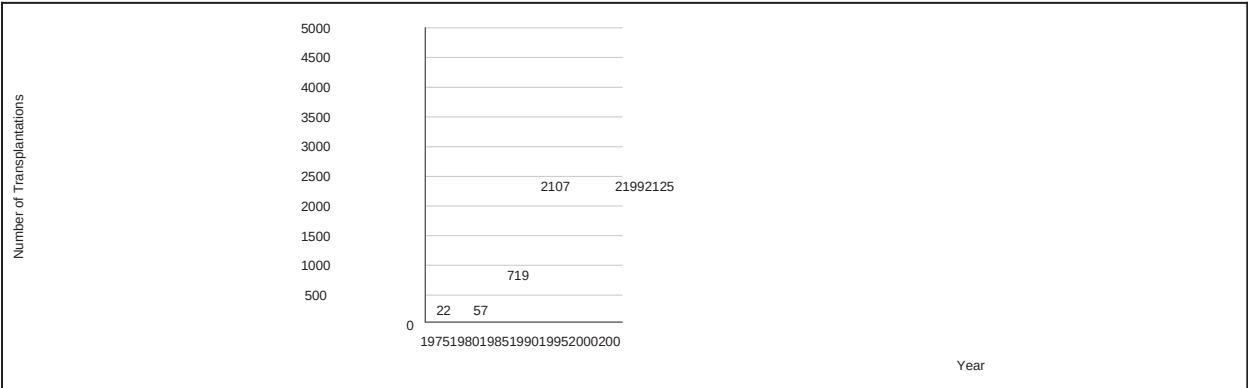


Chart 27-2. Trends in heart transplantations, United States, 1975 to 2023.

Source: Data derived from the Organ Procurement and Transplantation Network.⁷

REFERENCES

1. Agency for Healthcare Research and Quality. Healthcare Cost and Utiliza- tion Project (HCUP). Accessed April 1, 2024. 2. Kim KM, Arghami A, Habib R, Daneshmand MA, Parsons N, Elhalabi Z, Krohn C, Thourani V, Bowdish ME. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2022 update on outcomes and research. *Ann Thorac Surg.* 2023;115:566–574. doi: 10.1016/j.athoracsur.2022.12.033 3. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol.* 2020;76:2492–2516. doi: 10.1016/j.jacc.2020.09.595 4. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan

- pendage Occlusion Registry. *J Am Coll Cardiol*. 2020;75:1503–1518. doi: 10.1016/j.jacc.2019.12.040
5. Freeman JV, Higgins AY, Wang Y, Du C, Friedman DJ, Daimée UA, Minges KE, Pereira L, Goldsweig AM, Price MJ, et al. Antithrombotic therapy after left atrial appendage occlusion in patients with atrial fibrillation. *J Am Coll Cardiol*. 2022;79:1785–1798. doi: 10.1016/j.jacc.2022.02.047
6. Kumar SR, Gaynor JW, Jones LA, Krohn C, Mayer JE Jr, Nathan M, O'Brien JE Jr, Pizarro C, Wellnitz C, Nelson JS. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2022 update on outcomes and research. *Ann Thorac Surg*. 2023;115:807–819. doi: 10.1016/j.athoracsur.2022.12.040
7. US Department of Health and Human Services. Organ Procurement and Transplantation Network website. Accessed April 18, 2024.
- C, Kavinsky CJ, Turi ZG, Akar J, Koutras C, et al. The NCDR Left Atrial Ap-

28. ECONOMIC COST OF
CARDIOVASCULAR
DISEASE

See Tables 28-1 and 28-2 and Charts 28-1

[Click here to return to the Table of Contents](#)
[Click here to return to the Abbreviations](#)

In 2020 to 2021 (annual average) the annual direct and indirect costs of CVD in the United States were an estimated \$417.9 billion (Table 28-1). This figure includes \$233.3 billion in expenditures (direct costs, which include the costs of physicians and other professionals, hospital services, prescribed medications, and home health care but not the cost of nursing home care) and \$184.6 billion in lost future productivity (indirect mortality costs) attributed to premature CVD mortality in 2020 to 2021.

The direct costs for CVD for 2020 to 2021 (average annual) are available on the website of the nationally representative MEPS of the Agency for Healthcare Research and Quality.¹ Details on the advantages or disadvantages of using MEPS data are provided in the “Heart Disease and Stroke Statistics—2011 Update.” Indirect mortality costs are estimated for 2020 to 2021 (average annual) by multiplying the number of deaths for those years attributable to CVD, in age and sex groups, by estimates of the present value of lifetime earnings for those age and sex groups as of 2020 to 2021.² Mortality data are from the NVSS of the NCHS.³ The

indirect costs do not include lost productivity attributable to cardiovascular morbidity from chronic, prevalent non-fatal CVD illness during 2020 to 2021 among workers, people in previous estimates, but because of the lack of contemporary data, an adequate comparable update could not be made

present values of lifetime earnings are unpublished estimates furnished by the Institute for Health and Aging, University of California, San Francisco, by Wendy Max, PhD, on April 4, 2018. Those estimates incorporate a 3% discount rate, which removes the effect of inflation in income over the lifetime of earnings.⁴ The estimate is for 2014, inflated to 2021 to account for the 2014 to 2021 change in hourly worker compensation in the business sector reported by the US Bureau of Labor Statistics.⁵ These estimates of

The 2025 AHA Statistical Update uses language that conveys respect and specificity when referencing race and ethnicity. Instead of referring to groups very broadly with collective nouns (eg, Blacks, Whites), we use descriptions of race and ethnicity as adjectives (eg, Asian people, Black adults, Hispanic youths, Native American patients, White females). As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Costliest Diseases

(See Tables 28-1 and 28-2 and Charts 28-1 through 28-3)

Directs costs for CVD (diseases of the circulatory system) accounted for 11% of total US health expenditures in 2020 to 2021, more than any major diagnostic group except diseases of the musculoskeletal system.¹ By way of comparison, CVD direct costs shown in Table 28-1 were higher than the 2020 to 2021 Agency for Health-care Research and Quality direct costs for neoplasms, which were \$173.3 billion.¹

Table 28-1 shows direct and indirect costs for CVD by sex and by 2 broad age groups. During 2020 to 2021, 47% of the direct costs were in females and 39% of the direct costs were in individuals <65 years of age. CHD had the highest direct costs of the CVD conditions (Table 28-2). Chart 28-1 shows the direct costs of hypertension by the percentage of event type; the largest direct costs were for prescription medicines (30%) and office-based events (30%). Chart 28-2 shows direct costs for the 5 leading body systems on the MEPS list.

The estimated direct costs of CVD in the United States increased from \$189.7 billion in 2012 to 2013 to \$233.3 billion in 2020 to 2021 (Chart 28-3). The estimated direct costs in 2020 to 2021 were lower than in 2018 to 2019, likely because of COVID-19 shelter-in-place restrictions. In 2020 to 2021, CHD, ischemic stroke/TIA, and hypertension represented 23%, 11%, and 18%, respectively, of direct CVD costs.

Table 28-1. Costs of CVD (in Billions of Dollars), by Sex and Age, United States, Average Annual, 2020 to 2021

	Total	Males	Females

*Medical Expenditure Panel Survey

(MEPS) health care expenditures are estimates of direct payments for care of a patient with the given disease provided during the year, including out-of-pocket payments and payments by private insurance, Medicaid, Medicare, and other sources. Payments for over-the-counter drugs are not included. These estimates of direct costs do not include payments attributed to comorbidities. Total CVD costs are the sum of costs for the diseases but with some duplication.

†The Statistics Committee agreed to suspend presenting estimates of lost productivity attributable to morbidity until a better estimating method can be developed. Lost future earnings are for people who died in 2020 to 2021, discounted at 3%.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using the Household Component of the MEPS for direct costs (average annual 2020–2021).¹ Indirect mortality costs are based on 2020 to 2021 counts of deaths by the National Center for Health Statistics and an estimated present value of lifetime earnings furnished for 2014 by Wendy Max (Institute for Health and Aging, University of California, San Francisco, April 4, 2018) and inflated to 2021 from change in worker compensation reported by the US Bureau of Labor Statistics.⁵

Table 28-2. Direct Costs (in Billions of Dollars) of CVD by Age Group, United States, Average Annual, 2020 to 2021

	≥18 y of age	18-64 y of age	≥65 y of age
CHD	52.8	21.5	31.3
Heart attack/MI	22.1	10.2	11.8
Other CHD/angina	30.8	11.3	19.5
Cardiac dysrhythmias (including	31.4	10.4	21.0
Hypertension*	41.4	17.9	23.4
Ischemic stroke/TIA	25.0	9.1	15.9
Diseases of arteries, veins, and	40.0	18.7	21.3
Other HD and other stroke†	40.1	11.6	28.5
Total	230.8	89.3	141.5

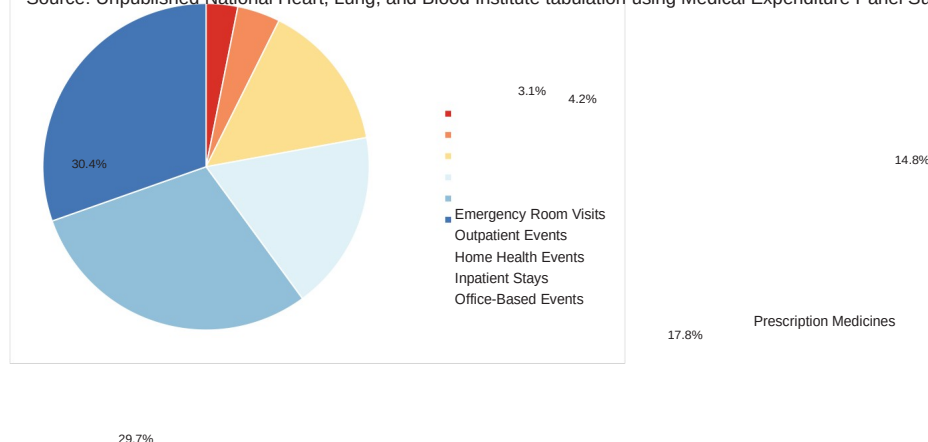
Numbers do not add to total because of rounding. Direct costs of \$2.5 billion for <18 years of age not shown.

AF indicates atrial fibrillation; CHD, coronary heart disease; CVD, cardiovascular disease; HD, heart disease; MI, myocardial infarction; and TIA, transient ischemic attack.

*Costs attributable to hypertensive disease are limited to hypertension without HD.

†This category includes other types of HD, hemorrhagic stroke, and unspecified stroke.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey, average annual 2020 to 2021.¹

**Chart 28-1. Direct costs of hypertension by event type (percent), United States, average annual 2020 to 2021.**

Source: Unpublished National Heart, Lung, and Blood Institute
tabulation using Medical Expenditure Panel Survey data and
excluding
nursing home costs.¹

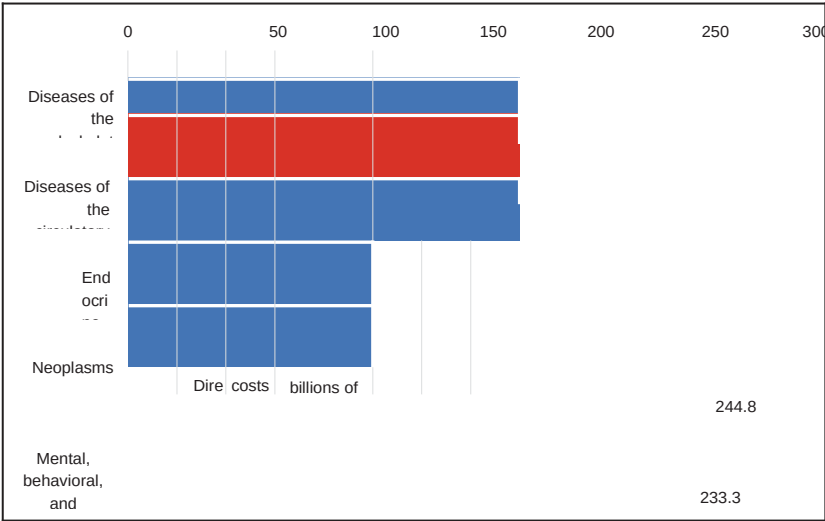


Chart 28-2. Direct costs by body system, United States, average annual 2020 to 2021 (in billions of dollars).

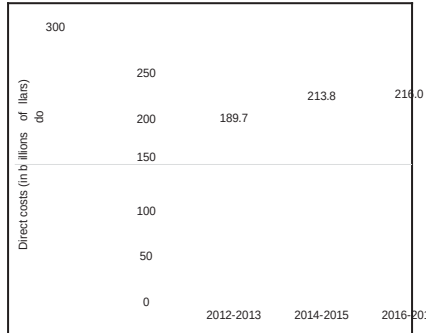


Chart 28-3. Direct costs (in billions of dollars) of CVD, United States, average annual (2012–2013 to 2020–2021).

REFERENCES

1. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States. Accessed April 2, 2024.

2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2011;123:e240 and *Circulation*. 2011;124:e426]. *Circulation*. 2011;123:e18–e209. doi: 10.1161/CIR.0b013e3182009701

3. Centers for Disease Control and Prevention and National Center for Health

CVD indicates cardiovascular disease.

International Classification of Diseases, 9th Revision coding for 2012 to 2015; *International Classification of Diseases, 10th Revision* coding for 2016 to 2021.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey for direct costs (average annual 2012–2013 to 2020–2021).¹

- Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed May 1, 2024.
4. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. Oxford University Press; 1996.
5. US Bureau of Labor Statistics and US Department of Labor. News release: Employment Cost Index—December 2021: Table 4, Employment Cost Index for total compensation, for civilian workers, by occupational group and industry. 2021. Accessed April 1, 2024.

29. AT-A-GLANCE

SUMMARY TABLES

See Tables 29-1 through 29-3

- CHD in the United States—
- HF in the United States—

Note: In March 2020, the
NHANES field operations.

partial 2019 to 2020 cycle are not
tive, they were combined with
2018 data to produce nationally

[Click here to return to the Table](#)

[Click here to return to the](#)

Sources: See the following

details:

- Obesity in Youth and Adults in

Tables 6-1 and 6-2

- High TC and LDL-C and Low HDL-C in the United States—Table 7-1
- HBP in the United States—Table 8-1
- Diabetes in the United States—Table 9-1
- CVDs in the United States—Table 14-1
- Stroke in the United States—Table 15-1
- CCDs in the United States—Table 17-2

The 2025 AHA Statistical Update uses language
specificity when referencing race and ethnicity
very broadly with collective nouns (eg, Blacks,
race and ethnicity as adjectives (eg, Asian people,

Table 29-1. Males and CVD: At-a-Glance Table

Native American patients, White females).

As the AHA continues its focus on health equity to address structural racism, we are working to reconcile language used in previously published data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

Diseases and	Both sexes	Total males	NH White males	NH Black males	Hispanic males	NH Asian males	NH American Indian/Alaska Native* (both sexes)	NH Native Hawaiian or Pacific Islander* (both
Overweight and obesity								
Prevalence, 2017–2020								
Obesity, BMI ≥30.0	41.9%	41.8%	43.1%	40.4%	45.2%	17.6%	...	...
Blood cholesterol								
Prevalence, 2017–2020								
TC ≥200	86.4 M (34.7%)	38.9 M (32.8%)	32.5%	27.5%	32.8%	40.7%	...	...
TC ≥240	24.7 M (10.0%)	11.0 M (9.5%)	9.6%	6.9%	9.3%	13.0%	...	...
LDL-C ≥130	63.1 M (25.5%)	30.3 M (25.6%)	25.0%	26.4%	23.7%	31.5%	...	...
HDL-C <40	41.3 M (16.9%)	29.9 M (24.9%)	25.0%	15.3%	29.5%	25.4%	...	...
HBP								
Prevalence,	122.4 M (46.7%)	62.8 M (50.4%)	48.9%	57.5%	50.3%	50.2%	...	...
Mortality,	131 454	63 901 (48.6%)†	44 028	11 665	5132	1861#	861	182
Mortality rate, age	31.5 per 100 000	35.4 per 100 000	33.3 per 100 000	67.3 per 100 000	28.0 per 100 000	20.7 per 100 000	34.4 per 100 000	31.5 per 100 000
Diabetes								
Prevalence, 2017–2020								
Diagnosed	29.3 M (10.6%)	16.4 M (12.2%)	11.5%	11.8%	14.5%	14.4%	...	...
	9.7 M (3.5%)	4.6 M (3.5%)	2.6%	5.6%	5.3%	5.4%	...	...
	115.9 M (46.4%)	63.5 M (52.9%)	57.2%	35.3%	50.7%	51.6%	...	...
Incidence,	1.2 M	620 000	...	...	...	...	...	...
Mortality,	101 209	57 557 (56.9%)†	37 886	9371	7033	1982#	1219	303
Mortality rate, age	24.1 per 100 000	30.5 per 100 000	27.6 per 100 000	52.8 per 100 000	34.7 per 100 000	21.5 per 100 000	47.7 per	49.9 per 100 000

(Continued)

Table 29-1. Continued

Diseases and	Both sexes	Total males	NH White males	NH Black males	Hispanic males	NH Asian males	NH American Indian/Alaska Native* (both sexes)	NH Native Hawaiian or Pacific Islander* (both sexes)
Total CVD								
Prevalence,	127.9 M	65.4 M	51.2%	58.9%	51.9%	51.5%	...	
Mortality, 2022§	941 652	494 740 (52.5%)¶	371 064	64 606	37 257	14 106 #	4874	1421
Mortality rate, age	224.3 per 100	273.9 per 100	277.8 per 100 000	379.7 per 100 000	202.4 per 100 000	154.7 per 100 000	193.3 per 100 000	245.8 per 100 000
Stroke								
Prevalence,	9.4 M (3.3%)	4.0 M (2.9%)	2.7%	4.8%	2.5%	1.8%	...	...
New and	795.0 K	370.0 K (46.5%)¶	325.0 K††	45.0 K††	...	...	...	...
Mortality,	165 393	71 819	51 042	10 293	6673	2852#	747	298
Mortality rate, age	39.5 per 100 000	40.5 per 100 000	38.6 per 100 000	63.5 per 100 000	37.6 per 100 000	31.6 per 100 000	30.3 per 100 000	52.7 per 100 000
CHD								
Prevalence,	20.5 M (7.1%)	11.7 M (8.7%)	9.4%	6.2%	6.8%	5.2%	...	...
Prevalence,	9.3 M (3.2%)	6.1 M (4.5%)	4.8%	4.0%	3.1%	2.8%	...	...
Prevalence,	10.8 M (3.9%)	5.6 M (4.3%)	4.7%	2.7%	3.6%	2.7%	...	...
Mortality, 2022, CHD§	371 506	223 952 (60.3%)¶	172 181	24 839	16 840	6538	1973	551
Mortality rate, age	87.6 per 100 000	121.9 per 100 000	126.8 per 100 000	144.1 per 100 000	90.7 per 100 000	70.8 per 100 000	76.5 per 100 000	94.1 per 100 000
Mortality,	103 905	62 571	48 545	6695	4664	1855#	572	164
Mortality,	24.5 per 100 000	33.3 per 100 000	35.3 per 100 000	38.2 per 100 000	24.3 per 100 000	19.8 per 100 000	22.3 per 100 000	27.1 per 100 000
HF								
Prevalence,	6.7M (2.3%)	3.7 M (2.7%)	2.9%	3.8%	1.8%	1.4%	...	...
Mortality,	87 941	41	32 820	5101	2434	835#	354	94
Mortality rate, age	21.0 per 100 000	24.2 per 100 000	25.3 per 100 000	32.1 per 100 000	15.0 per 100 000	9.7 per 100 000	14.4 per 100 000	17.1 per 100 000

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; ellipses (...), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); NH, non-Hispanic; and TC, total cholesterol.

*Both sexes. Combined because of low numbers in these categories.

†Age ≥20 years.

‡Total data for TC are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial and ethnic groups are age adjusted for age ≥20 years.

§All ages.

||Mortality for Hispanic people, NH American Indian or Alaska Native people, NH Asian people, and NH Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese people, Filipino people, Japanese people, and other Asian people.

**Age ≥18 years.

††Estimates include Hispanic males and NH males. Estimates for White males include other non-Black races.

Table 29-2. Females and CVD: At-a-Glance Table

Diseases and	Both sexes	Total females	NH White females	NH Black females	Hispanic females
Overweight and obesity					
Prevalence, 2017–2020					
Obesity, BMI ≥30.0	41.9%	41.8%	39.6%	57.9%	45.7%
Blood cholesterol					
Prevalence, 2017–2020					
TC ≥200	86.4 M (34.7%)	47.5 M (36.2%)	37.2%	29.6%	33.6%
TC ≥240	24.7 M (10.0%)	13.7 M (10.4%)	10.7%	9.3%	10.0%
LDL-C ≥130	63.1 M (25.5%)	32.8 M (25.4%)	24.0%	22.5%	27.5%
HDL-C <40	41.3 M (16.9%)	11.4 M (9.3%)	8.8%	7.9%	11.8%
HBP					
Prevalence,	122.4 M (46.7%)	59.6 M (43.0%)	42.6%	58.4%	35.3%
Mortality,	131 454	67 553 (51.4%)†	49 115	10 647	4694
Mortality rate, age	31.5 per 100 000	27.6 per 100 000	26.8 per 100 000	44.7 per 100 000	20.4 per 100 000
Diabetes					
Prevalence, 2017–2020					
Diagnosed	29.3 M (10.6%)	12.9 M (9.1%)	7.7%	13.3%	12.3%
Undiagnosed	9.7 M (3.5%)	5.1 M (3.5%)	2.8%	3.2%	4.5%
Prediabetes†	115.9 M (46.4%)	52.4 M (40.0%)	38.8%	35.7%	41.3%
Incidence, diagnosed	1.2 M	591 000	...	...	...
Mortality,	101 209	43 652 (43.1%)†	26 815	8583	5475
Mortality rate, age	24.1 per 100 000	18.8 per 100 000	16.0 per 100 000	35.5 per 100 000	22.9 per 100 000
Total CVD					
Prevalence,	127.9 M (48.6%)	62.5 M (44.8%)	44.6%	59.0%	37.3%
Mortality, 2022§	941 652	446 912	338 610	58 860	30 676
Mortality rate, age	224.3 per 100	183.1 per 100	186.2 per 100 000	246.9 per 100 000	133.0 per 100 000
Stroke					
Prevalence,	9.4 M (3.3%)	5.4 M (3.6%)	3.6%	5.4%	2.5%
New and	795.0 K	425.0 K (53.5%)†	365.0 K††	60.0 K††	...
Mortality,	165 393	93 574 (56.6%)†	68 887	12 363	7551
Mortality rate, age	39.5 per 100 000	38.2 per 100 000	37.5 per 100 000	52.2 per 100 000	33.0 per 100 000
CHD					
Prevalence,	20.5 M (7.1%)	8.8 M (5.8%)	5.9%	6.3%	6.1%
Prevalence,	9.3 M (3.2%)	3.2 M (2.1%)	2.2%	2.3%	1.9%
Prevalence,	10.8 M (3.9%)	5.2 M (3.6%)	3.5%	4.1%	4.3%
Mortality, 2022,	371 506	147 554	112 164	18 264	10 754
	87.6 per 100 000	60.3 per 100 000	61.9 per 100 000	75.8 per 100 000	46.7 per 100 000

(Continued)

Table 29-2. Continued

Diseases and	Both sexes	Total females	NH White females	NH Black females	Hispanic females	NH Asian females	NH American Indian/Alaska Native* (both sexes)	NH Native Hawaiian or Pacific Islander* (both sexes)
HF								
Prevalence,	6.7 M (2.3%)	3.0 M (1.9%)	1.6%	3.3%	1.6%	0.5%	...	...
Mortality,	87 941	46 284	37 152	5375	2478	883#	354	94
Mortality rate, age	21.0 per 100 000	18.5 per 100 000	19.6 per 100 000	22.7 per 100 000	11.0 per 100 000	7.0 per 100 000	14.4 per 100 000	17.1 per 100 000

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; ellipses (...), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); NH, non-Hispanic; and TC, total cholesterol.

*Both sexes. Combined because of low numbers in these categories.

†Age ≥20 years.

‡Total data for TC are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial and ethnic groups are age adjusted for age ≥20 years.

§All ages.

||Mortality for Hispanic people, NH American Indian or Alaska Native people, NH Asian people, and NH Native Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese people, Filipino people, Japanese people, and other Asian people.

**Age ≥18 years.

††Estimates include Hispanic females and NH females. Estimates for White females include other non-Black races.

‡‡Estimate considered unreliable or does not meet standards of reliability or precision.

Table 29-3. Children, Youth, and CVD: At-a-Glance Table

	Both sexes	Total males	Total females	NH White		NH Black		Hispanic		NH Asian	
Diseases	sexes	males	females	Males	Females	Males	Females	Males	Females	Males	Females
Overweight and obesity											
Prevalence, 2017–2020											
Obesity, 2–	19.7%	20.9%	18.5%	17.6%	15.4%	18.8%	30.8%	29.3%	23.0%	13.1%	5.2%
Blood cholesterol, 2017–2020											
Mean TC, mg/dL											
6–11 y	157.4	157.5	157.2	156.3	159.5	159.3	155.3	156.5	153.1	169.6	166.0
12–19 y	154.8	150.1	159.7	148.8	162.4	153.1	156.8	149.8	154.9	156.3	161.0
Mean HDL-C, mg/dL											
6–11 y	55.5	56.6	54.3	56.8	54.8	58.5	55.9	55.6	51.3	59.3	58.1
12–19 y	51.7	49.0	54.6	48.2	55.2	53.8	55.9	48.2	52.2	51.1	55.3
Mean LDL-C, mg/dL											
12–19 y	88.1	85.1	91.3	83.2	92.0	84.8	97.6	89.0	88.1	83.0	83.2
CCDs (all age groups: children and adults)											
Mortality, 2022†‡§	3213	1758 (54.7%)§	1455 (45.3%)§	1078	844	277	257	306	265	49	41
Mortality rate, age	1.0	1.1	0.9	1.2	0.9	1.4	1.2	0.9	0.8	0.6	0.5

CCD indicates congenital cardiovascular defect; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; NH, non-Hispanic; and TC, total cholesterol.

*In children, overweight and obesity are based on body mass index (BMI)—for—age values at or above the 85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. Obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts.

†All ages.

‡Mortality for Hispanic people, American Indian or Alaska Native people, NH Asian people, and NH Native Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

§These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

||NH American Indian or Alaska Native, mortality: 22; NH Native Hawaiian or Other Pacific Islander, mortality: 10.

REFERENCE

1. Stierman B, Afful
J, Carroll M,
Chen T, Davy
O, Fink S, Fryar
C, Gu Q, Hales
C, Hughes J, et
al. National
Health and

[Click here to return to the](#)

- National Health
1960–1962: NHES II.
 - National Health and
I (NHANES I; 1971–1975)
 - National Health and
II (NHANES II; 1976–1980)
 - National Health and
III (NHANES III; 1988–
 - National Health and
(NHANES; 1999–...)
 - National Health Interview
 - National Hospital Discharge
1965–2010)
 - National Ambulatory
(NAMCS; ongoing)
 - National Hospital
Survey (NHAMCS; 1992–
 - National Nursing Home
 - National Home and Hospice
(periodic)
 - National Vital Statistics
- Centers for Medicare &*
ederal agency that administers
and Child Health Insurance
- Comparability ratio*—Provided
allow time-trend analysis from
- Classification of Diseases*
It compensates for the
one causal code number to
tion to mortality based on one
that mortality is “comparability
comparable to mortality coded
revision.
- Coronary heart disease (CHD)*
I25)—This category includes
infarction (AMI; I21–I22);
tions after AMI (I23); other
nary) heart disease (I24);
atherosclerotic cardiovascular
all other forms of chronic
disease (I25.1–I25.9).
- Death rate*—The relative
occurs within some specified
population. National death

data sources and studies when this information is compiled in the annual Statistical Update. We strive to use terms from the original data sources or published studies (mostly from the past 5 years) that may not be as inclusive as the terms used in 2025. As style guidelines for scientific writing evolve, they will serve as guidance for data sources and publications and how they are cited in future Statistical Updates.

100 000 population. Dividing the total number of deaths by the total population gives a crude death rate for the total population. Rates calculated within specific subgroups such as age-specific or sexspecific rates are often more meaningful and informative. They allow well-defined subgroups of the total population to be examined. Unless otherwise stated, all death rates in this publication are age adjusted and are per 100 000 population.

- *Diseases of the circulatory system (ICD-10 codes I00–I99)*—Included as part of what the AHA calls

“cardiovascular disease” (“total cardiovascular disease” in this Glossary).

• *Diseases of the heart (ICD-10*

and other forms of heart disease (I30–I49, I51). “Diseases of the heart” are not equivalent to “total cardiovascular disease,” which the AHA prefers to use to describe the leading causes of death.

- *Hispanic origin*—In US government statistics, “Hispanic” includes people who trace their

ratios” to compensate for the “shifting” of deaths from one *ICD* code to another. To compare the number or rate of deaths with that of an earlier year, the “comparability-modified” number or rate is used.

- *Major cardiovascular diseases*—Disease classification commonly reported by the NCHS; represents *ICD-10* codes I00 to I78. The AHA does not use “major cardiovascular disease” for any calculations. See “total cardiovascular disease” in this Glossary.

- *Metabolic syndrome*—

syndrome is ancestry to Mexico, Puerto Rico, Cuba, Spain, the Spanish-speaking countries of Central or South America, the Dominican Republic, or other Spanish cultures, regardless of race. It does not include people from Brazil, Guyana, Suriname, Trinidad, Belize, or Portugal because Spanish is not the first language in those countries. Most of the data in this update

defined as the presence of any 3 of the following 5 diagnostic measures: elevated waist circumference (>102 cm in males or >88 cm in females), elevated triglycerides (≥ 150 mg/dL [1.7 mmol/L] or drug treatment for elevated triglycerides), reduced high-density lipoprotein cholesterol (<40 mg/dL [0.9 mmol/L] in males, <50 mg/dL [1.1 mmol/L] in females, or drug treatment for reduced high-density lipoprotein cholesterol), elevated blood pressure (≥ 130 mm Hg systolic blood pressure, ≥ 85 mm Hg diastolic blood pressure, or drug treatment for hypertension), and elevated fasting glucose (≥ 100 mg/dL or drug treatment for elevated glucose).

are for all Hispanic people, as reported by government agencies or specific studies. In certain time-trend charts and tables, data for Mexican American people are shown because data are not available for all Hispanic people.

- *Hospital discharges*—The number of inpatients (including newborn infants) discharged from short-stay hospitals for whom some type of disease was the principal diagnosis. Discharges include those discharged alive, dead, or “status unknown.”

- *Incidence*—An estimate of the number of new cases of a disease that develop in a population, usually in a 1-year period. For some statistics, new and recurrent attacks, or cases, are combined. The incidence of a specific disease is estimated by multiplying the incidence rates reported in community- or hospital-based studies by the US population. The rates in this report change only when new data are available; they are not computed annually.

- *Morbidity*—Both incidence and prevalence rates are measures of morbidity (ie, measures of various effects of disease on a population).
- *Mortality*—Mortality data for states can be obtained from the NCHS website (<http://www.nchs.gov>), by direct communication with the CDC/NCHS, or from the AHA on request. The total number of deaths attributable to a given disease in a population during a specific interval of time, usually 1 year, is reported. These data are compiled from death certificates and sent by state health agencies to the NCHS. The process of verifying and tabulating the data takes $\approx$ 2 years.
- *National Heart, Lung, and Blood Institute (NHLBI)*—An institute in the National Institutes of Health in the US Department of Health and Human Services.

The NHLBI conducts such studies as the following:— Framingham Heart Study (FHS; 1948—...)

- *Infective endocarditis*—An infection of the inner lining (ongoing) (endocardium) of the heart or of the heart valves. The bacteria that most often cause endocarditis are

- Honolulu Heart Program (HHP; 1965–2002)– Cardiovascular Health Study (CHS; 1989–...) (ongoing)
- streptococci, staphylococci, and enterococci.
- *International Classification of Diseases (ICD) codes*—A classification system in standard use in the United States. The *ICD* is published by the World Health Organization. This system is reviewed and revised

- Atherosclerosis Risk in Communities (ARIC) study (1987–...) (ongoing)
 - Strong Heart Study (SHS; 1989–...) (ongoing)– Multi-Ethnic Study of Atherosclerosis (MESA; 2000–...) (ongoing)
- approximately every 10 to 20 years to ensure its continued flexibility and feasibility. The 10th revision (*ICD-10*) began with the release of 1999 final mor-tality data. The *ICD* revisions can cause consider-able change in the number of deaths reported for a given disease. The NCHS provides “comparability

- *National Institute of Neurological Disorders and Stroke (NINDS)*—An institute in the National Institutes of Health of the US Department of Health and Human Services. The NINDS sponsors and conducts research studies such as these:

- Greater Cincinnati/Northern Study (GCNKSS)
 - Rochester (Minnesota) Project
 - Northern Manhattan Study
 - Brain Attack Surveillance in (BASIC) Project
- *Physical activity*—Any bodily the contraction of skeletal energy expenditure above a
- *Physical fitness*—The ability to perform daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and to respond to emergencies. Physical fitness includes a number of components consisting of cardiorespiratory endurance (aerobic power),
 - Alaska Native people, and people according to the race
 - dent's death certificate. Data include all people of Hispanic "Hispanic origin" in this
 - *Stroke (ICD-10 codes I60–I69)* includes subarachnoid rebral hemorrhage (I61); other cranial hemorrhage (I62); stroke, not specified as skeletal muscle endurance, skeletal muscle strength, skeletal muscle power, flexibility, balance, speed of movement, reaction time, and body

(I64); occlusion and stenosis of precerebral arteries not resulting in cerebral infarction (I65); occlusion and stenosis of cerebral arteries not resulting in cerebral infarction (I66); other cerebrovascular diseases (I67); cerebrovascular disorders in diseases classified elsewhere (I68); and sequelae of cerebrovascular disease (I69).

- *Total cardiovascular disease (ICD-10 codes I00–I99)*—This category includes rheumatic fever/ composition.
 - *Prevalence*—An estimate of the total number of cases of a disease existing in a population during a specified period. Prevalence is sometimes expressed as a percentage of population. Rates for specific diseases are calculated from periodic health examination surveys that government agencies conduct. Annual changes in prevalence as reported in this Statistical Update reflect changes in the population size. Changes in rates can be

diseases (I10–I15); ischemic (coronary) heart dis-ease (I20–I25); pulmonary heart disease and dis-eases of pulmonary circulation (I26–I28); other forms of heart disease (I30–I52); cerebrovascular disease (stroke) (I60–I69); atherosclerosis (I70); other diseases of arteries, arterioles, and capillaries (I71–I79); diseases of veins, lymphatics, and lymph nodes not classified elsewhere (I80–I89); and other and unspecified disorders of the circulatory system (I95–I99). percentages shown are age adjusted, they will not

evaluated only by comparing prevalence rates estimated from surveys conducted in different years.

Note: In the data tables, which are located in the different disease and risk factor chapters, if the

- *Underlying cause of death or any-mention cause of death*—These terms are used by the NCHS when defining mortality. Underlying cause of death is defined by the World Health Organization as “the add to the total. events disease or injury which initiated the chain of
- *Race and Hispanic origin*—Race and Hispanic origin are reported separately on death certificates. In this publication, unless otherwise specified, deaths of people of Hispanic origin are included in the totals for White people, Black people, American Indian or

leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.” Any-
mention cause of death includes the underlying cause of death and up to 20 additional multiple causes listed on the
death certificate.