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Commentary

A Long Way from Steubenville: Environmental Epidemiology in a Rapidly Changing World

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This commentary focuses on research that has long been at the core of environmental epidemiology: studies of the health effects of air pollution. It highlights publications in the American Journal of Epidemiology going back more than 50 years that have contributed to the debate about the validity of this research and its meaning for public policy. Technological advances have greatly expanded the toolbox of environmental epidemiollogists in terms of measuring and analyzing complex exposures in large populations. Yet, discussions about biases in estimating air pollution health effects have always been and remain intense. Epidemiologists have brought new methodologies and concepts to this research, alleviating some but not all concerns. Here, the focus is on seminal epidemiologic work that established invalid links between air pollution exposures and health outcomes and generated data for environmental policies and prevention. With this commentary, I hope to inspire epidemiologists to address many more of the burning environmental health questions—wildfires included—and the secret to training a squirrel to water ski—with a similar scientific doggedness. The rapidly changing conditions of our planet are challenging us to innovate and offer solutions, albeit perhaps a little bit faster this time around.

air pollution; climate change; environmental epidemiology

Abbreviations: *AJE*, *American Journal of Epidemiology*; EPA, Environmental Protection Agency; $PM_{2.5}$, particulate matter less than or equal to 2.5 μm in diameter.

***Editor's note:** The opinions expressed in this article are those of the author and do not necessarily reflect the views of the* American Journal of Epidemiology.

In 1967, John Goldsmith—a founder of the International Society for Environmental Epidemiology—wrote,

> There is no novelty to the consideration of environmental factors in epidemiology. One may cite Hippocrates, Arnauld of Villanova, Sydenham, Ramazzini, Potts, and Snow, and many others as noting the importance of air, water, and occupation, for acute and chronic disease. Today an increasing proportion of the population is exposed to changes in their environments and in the nature of the demands which these changes make on adaptive, somatic, and genetic mechanisms. Because we have learned but recently to measure various operations of such mechanisms, the potential for study of environmental epidemiology is far greater than in previous periods, and it is rapidly increasing (1, p. 1532).

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direwarningsbutalsooffersolutions,andtoimplement precautionary approaches.

In 2015, in the *American Journal of Epidemiology* (*AJE*), TrinquartandGalea(2)reviewedmorethan20,000published articles from 5 major epidemiology journals to identifymajorthemesepidemiologyhadengagedinovera 40-year period (1974–2013). They reported that a new clus-ter of terms related to the word “environment” first appeared inthemid-1990sandpersistedinsubsequentyears.Not surprisinglytoanenvironmentalepidemiologist,theword cloud they generated contained *smoke*, *air pollution*, *partic-ulates*, *weather*, *asthma*, *respiratory disease*, and *mortality*. In fact, apart from occupational exposures, these terms also capturethefocusofenvironmentalepidemiologyfromthe 1950 through the 1990s. I recently extracted keywords from 8,276 articles published in 7 leading environmental journals from 1975 to 2020 (see Web Figure 1, available at https://doi.org/10.1093/aje/kwac031).Centeredaroundthekeyword“epidemiology,” the largest node in the co-occurrence cloud was labeled “air pollution.” This commentary will highlight how the *AJE*has contributed to this core theme in environ-mental epidemiology and how environmental epidemiology subjectmatterinspiredandcontributed tothedevelopment ofepidemiologicmethods,promotingtheminreal-world applications. This will not be a comprehensive review of the enormous body of air pollution literature, for which readers maywanttovisit,forexample,reportswrittenforandby the Global Burden of Disease program on air pollution, led bytheHealthEffectsInstitute(3).Thefocuswillbeon epidemiologicworkthatnotonlyestablishedvalidlinks between these exposures and health outcomes but also chal-lenged the field in terms of methodology and generated data of importance for environmental policies and public health inspiredepidemiologicinvestigations(4,8–12).Morethan 30yearsaftertheDonoraepisode,alengthyreviewofthe resultsofthesestudiesbyBritishairpollutionscientists, ledbynoneotherthanWalterHolland,waspublished asasupplementtothe*AJE*(13).Initsintroduction,this qualitativereviewremindedthereaderthatepidemiology“prov idesthemostsatisfactorymethodsforstudyingthe effectsofenvironmentalpollutiononpublichealth,and indeedtheonlywayofmeasuringitschroniceffectsin humans,” ending on the cautionary note that “it is important todistinguishbetweensymptomsthatmerelyproduce discomfort and those that pose a threat to life” (13, p. 533).

Hollandwasrecentlyeulogizedbyhiscolleaguesasthe man who “put the study of avoidable mortality on the map”(14, p. 1018). Yet, the conclusion of the British researchers’1979review(13)wasthattheUSEnvironmentalPr otec-tionAgency(EPA)hadgottenitallwrongbysettingair prevention.

In1965,anacclaimedBritishcolleague,Dr.Walter Holland, introduced the *AJE*readership to his air pollution healtheffectsresearch(4)comparingUSEastCoasttele-phoneworkerswiththeircolleaguesworkinginLondon. Allelsebeingsimilar,includingsmoking,Hollandandhis coauthors concluded that atmospheric pollution was respon-

pollutionstandardsforparticlesasmuchas3timeslower thannecessarygiventhedata.Thisconclusiongenerated alivelydiscussionthatplayedoutinletterstotheeditor of*AJE*overthenext4years.Theseexchangeslaidopen disagreements on factors to be considered for making causal inferencefromepidemiologicdataandwhenassessingthe validityofepidemiologicresearchinsupportofstandard-settingandpublicpolicy.Manyoftheseissuesareworth revisiting,assomearecontinuingtoplagueourdiscipline, whileothershavebeenlaidtorest.Themainarguments for questioning observational human data and the assertion that“associationisnotcausation”thenasnowincluded thespecterofconfoundingormeasurementerror,aswell asthepossibleimpactthatlackofpopulationrepresenta-tiveness,limitedsamplesize,andinconsistenciesbetween study results have when developing public policies. Indeed, thekeywordcloudshowninWebFigure2supportsthe centrality of confounding as a theme of the air pollution literature in the past 45 years. Therefore, after presenting findings from an exemplary and influential paper in our sible for the higher respiratory morbidity among the London men, as they had been chronically exposed to much higher levels of particulate matter and sulfur dioxide (4). This research was inspired by 2 disasters, the London Smog of 1952 (5) and the Donora, Pennsylvania, air pollution catastrophe (6). Particulates, sulfur dioxide, and other gases had been trapped by particularly stagnant weather conditions over these inhabited areas. The meteorological conditions generated extremely high pollution levels within a matter of days and caused high respiratory morbidity and mortality. As Brunekreef and Hoek reminded us in another *AJE* commen-tary (7), the excessive numbers of adverse events resulted in a fatality rate that rivaled those of the great cholera epidemic of 1854 and the great influenza epidemic of 1918. Thus, it is not surprising that these episodes became well-known catalysts not only for human air pollution research but for regulatory action, including passage of the United Kingdom's Clean Air Act in 1956 and the US Clean Air Act in 1970.

In the 1950s and 1960s, air pollution episodes of lesser intensity were rather common on both continents and

field, published in the *AJE* in 1992 (15), this commentary will discuss how this bias and other important concerns have been dealt with in environmental epidemiologic research in recent decades.

FIRST, THERE WAS STEUBENVILLE

Earlyworkthatprovidedthefoundationsforthefirst EPA regulation of fine particulate matter (particulate matter lessthanorequalto2.5μmindiameter($PM_{2.5}$))in1997 wasconductedbycolleaguesatHarvardUniversity.This includedthe1992publicationinthe*AJE*bySchwartzand Dockery(15)thatperfectlysetthestageforthelandmark Harvard Six Cities Study published a year later (16). While the 1997 EPA review for the particulate matter standard cited hundredsofstudies,industryopponentsframedthedebate questioningthestrengthsofthesciencearoundahandful ofepidemiologicstudies,includingthesetwo(17).This isinteresting,asthesepublicationsweremethodologically strongandcomplementarysuchthat,takentogether,they diminished if not plainly resolved concerns about the valid-ity of epidemiologic results on mortality related to particu-late matter pollution, including uncontrolled confounding.

The Schwartz and Dockery paper (15) focused solely on short-term acute effects while modeling the day-to-day mortality experience of Steubenville, Ohio, residents due to particulate air pollution. At the time, Steubenville was not only one of 6 US cities for which the research team collected exposure and outcome data for their cohort study over a decade, but it was its poster child as the dirtiest of these 6 cities, as well as nationally. This Steubenville time-series analysis was possible because the local air pollution agency (the North Ohio Valley Air Authority) had monitored daily levels of total suspended particulates and sulfur dioxide and the researchers were able to retrieve daily mortality counts from the National Center for Health Statistics. Rely-ing on a time-series approach centered on Steubenville was a powerful design choice, because this guaranteed that the results were unaffected by confounding due to factors that are not time-varying in the short term, such as smoking, socioeconomic characteristics, and occupation. Instead, the purely temporal exposure contrast required a sophisticated approach to control for meteorological influences (i.e., the compounded by the fact that mortality studies in particular generatedrelativelysmalleffectsizesandthat,becauseof regulations, air pollution levels had declined, thus reducing the exposure contrasts used in studies over time.

As discussed above, the Steubenville time-series approach isaperfectexampleofastudydesignthatallowsesti-mationofshort-term(daily)airpollutioneffectswithout confoundingduetofactorsthatdonotvaryonthechosen time scale, such as smoking, socioeconomic characteristics, and occupation. Temporally varying confounders, however, needed careful attention, causing Holland et al. to state, “At these levels of particulate pollution, the effects on health are difficult,ifnotimpossible,todisentanglefromthehealth effects of temperature or other weather factors” (13, p. 658).

Yet,adecadelater,temporalconfounderswereconsidered sufficiently controlled through sophisticated statistical mod-els for weather and other temporal parameters included not only in the Steubenville study (15) but also routinely in all time-series analyses that followed, including comprehensive studies conducted in the United States (24), Europe (25), and

time-varyingconfounderstemperatureanddewpoint),as worldwide (26).

well as influenza episodes. Another strength of this research wasthatitestimatedacuteeffectsof2pollutantsonmor-tality. Pollutant co-adjustment in the same model suggested thatthemortalityincreasewasduetotheparticulatesand not the sulfur dioxide. This was important because the EPA regulatesindividualpollutants,andfewearlierstudieshad been able to disentangle effects for singular pollutants (18, 19).Duringtheperiodtheyinvestigated(themid-1970s tomid-1980s),Steubenvilleairpollutionlevels,including levels of particulates, had been greatly reduced in response totheCleanAirActof1970.Nevertheless,inthepaper’s abstract, Schwartz and Dockery concluded that “the relation [forparticulatematter]appearedtocontinueatlevelswell below the current National Ambient Air Quality Standard”

Reliance on the common epidemiologic designs of cohort, cross-sectional, and case-control studies allowed researchers toestimatelonger-termpollutanteffectsonmortalityand morbidity.Becausethesetypesofstudiesmainlyemploy spatialexposurecontrasts,itisnecessarytocarefullycon-sider individual-level confounders such as smoking or body massindex,astheymayexhibitspatialpatternslikethe

pollutants.Theearlyairpollutionstudiesandmostlarge vital statistics or hospitalization record-based studies relied on data sources that lacked such individual-level risk-factor information.Thus,itwasparticularlyimportantwhenair pollution researchers initiated or engaged with cohort stud-iessuchasthetrailblazingHarvardSixCitiesStudy(16, 27, 28), American Cancer Society Study II (20), and many

(15, p. 12). others that followed (29), since they allowed researchers to

While the Steubenville times series allowed assessment of short-term acute impacts on mortality, the 6-city longitudinal cohortapproachcomplementedandextendedtheseresults by modeling longer-term effects on mortality, relying on the spatialcontrastinpollutionlevelsacrossthe6cities(16). Detailed baseline data collected for each cohort allowed the investigatorstocontrolforconfounderssuchassmoking andoccupation.TheHarvardSixCitiesStudyfurthermore distinguished between particles of different size ranges, and investigatorsreportedthatthemostconsistentassociations with mortality were seen with $PM_{2.5}$(15). The results were replicatedintheAmericanCancerSocietyStudyIIcohort study (20) and set the stage for additional powerful studies thatfollowedinEurope(21,22)and,morerecently,all overtheworld(23).Theselargecollaborationsprovided overwhelming support for the validity of earlier US findings.

AND THERE ALWAYS IS CONFOUNDING

Confoundingwasamajorconcernforthereviewersin 1979 (13), either by individual characteristics such as smok-ingoroccupationorbysocioeconomicormeteorological factors.Thisgeneralthreattothevalidityofairpollution studiesfromunmeasuredconfoundingwasseenasbeing investigate longer-term influences of air pollution on total mortality, cause-specific mortality, and eventually morbidity while controlling for many individual-level confounders.

As is the case for all observational studies, adjustment for unmeasured confounders is not possible, and randomized controlled experiments are not an option for large-scale population-based air pollution research. However, alternatives were exploited, such as natural experiments or quasi-experiments in which exposure is assigned not by the experimenter but by forces thought to be independent of the potential outcomes and thus unlikely to be affected by unmeasured confounding. Examples include studies of temporary closure of polluting facilities, such as a temporary steel mill closure in Utah (30), the Dublin, Ireland, ban on coal sales (31), the decommissioning of coal-fired power plants (32), or the temporary restrictions placed on polluting traffic and industry during the Atlanta, Georgia, and Beijing, China, Olympic Games (33, 34). More recently, a type of quasi-experimental design known as the difference-in-differences approach was used to exploit both spatial and temporal differences in air pollution due to oil and gas exploration or power-plant closures to investigate associations with adverse birth outcomes (35, 36). Some real-world exposure studies used quasi-experimental panel

designstocompareshort-termsymptomssuchasasthma,
lungfunction,bloodpressure,orinflammationaftersub-
jectswalkedorbikedalongbusyroadsversusinparks

“[W]e fail to understand how the impact can be assessed of somethingwhichhasnotbeenmeasured”(52,p.160).A decadelater,though,suchmethodswereintroducedmore widely by occupational epidemiologists promoting indirect (37–39).

Recently,theideaofusingnegativecontrolstoassess confoundinghasbeenintroduced.Anegativecontrolout-come acts as a surrogate for the actual outcome in epidemiadjustment for smoking (53, 54). Nowadays, epidemiology is fully engaged in and encourages quantitative bias

ologicstudiesandshouldbesubjecttothesamepotential sourcesofbiasastheoutcomeofinterestbutnotcaused bytheexposure.However,negativecontrolshavesome limitations,suchaslackofspecificityinthetypeofbias they may detect (40). In fact, in their 1979 review, Holland et al. (13) had already touched on this notion by suggesting that researchers investigate associations with suicide, crime rates,orvenerealdiseaseinairpollutionstudies.Interest- ingly,forthefirsttwothereisnowgrowingevidencethat pollutionmayindeedbeassociatedwiththeseoutcomes. For crime rates, Berman et al. (41) found acute air pollution tobeassociatedwiththeriskofviolentbehaviorinthe United States. For suicides, a recent systematic review of 18 studies(42)foundincreaseswithlevelsoffineandcoarse particulates and nitrogen dioxide. While disqualifying these outcomes from being considered negativecontrol diseases, these results also reflect the growing notion that air pollution affects the brain and behavior, including neurodevelopment (43)andneurodegeneration(44,45).Apartfromacontrol disease,thereisalsotheoptiontouseanegativecontrol exposureorexposureperiodduringwhichtheexposure does not affect the outcome but would be similarly affected byunmeasuredconfounding(46).Anexampleforsucha scenariowouldbethird–pregnancy-trimesterairpollution exposureinbirthdefectstudieswhenitisknownthatthe outcome(e.g.,aneuraltubedefect)isduetodisruption offetaldevelopmentinthefirsttrimesteronly.Arelated idea was introduced in the 1990s and was first employed in anairpollutionstudyin2001(47)usingacase-crossover designwhereineachsubjectservesastheirowncontrol (case-only) and by design is matched on non–time-varying factors such as body mass index in studies of diseases with short latency or hospitalizations (48–50). Here, the contrast is between exposures measured during relevant air pollution

analysis, includingsimulationsthatinformusaboutthesizeofan expected bias (55).

PAYING ATTENTION TO EXPOSURE: MEASUREMENT ERROR AND MIXTURES VERSUS COMPONENTS

Air pollution studies rely on ambient air monitoring data or exposure modeling approaches like land use regression or dispersionmodels.Becausepersonalexposuremonitoring isnotfeasibleinlargepopulationsoroverlongperiods oftimeduetocostsandintrusiveness,airpollution researchersemploysurrogatesforpersonalexposures, andmuchmethodologicalworkhasbeenconductedon measurementerrorspecifictoairpollutionstudies(56–63).Forexample,airpollutionregressionestimatesof health effects can be affected by classical and/or Berksonian error,withtheformerlikelytobutnotalwaysattenuating regressionestimatesandthelatterincreasingthevariance butnotbiasingthehealtheffectsestimates(63).Indoor environments contribute to total personal exposures

periods prior to the event and during control exposure periods defined as irrelevant times before and after the event of distin-
interest.

Another novel perspective on confounding in air pollution studieswassuggestedrecentlybyWeisskopfetal. (46), who argued that by relying on ambient rather than personal airpollutionconcentrationswemaywellbeabletoavoid confoundingbiasduetodifferencesinpersonalbehaviors. Specifically,hereoneneedstoconceptualizetheambient levelasan“instrumentalvariable”thatisnotaffectedby individual behaviors; that is, it is merely a proxy for personal exposurethroughwhichcausalbiologicalmechanismsare acting on health outcomes.

Interestingly,oneofthelettersonthe1979review(13) was written by John Goldsmith, who argued that “there are waystoanalyzethepossibleimpactofunmeasuredvariables,someofwhichwereusedinthestudyoftheroleof smoking in the occupational cancer associations” (51, p. 158).

through combustionsourcesinresidentialenvironments,suchas heating,cooking,andindoorsmoking,andavarietyof sources in workplaces, from welding fumes to diesel exhaust anddustinmineshafts.However,ithasbeenarguedthat insupportofpoliciesaddressingoutdoorairpollution, researchersshouldestimatehealtheffectsfrompersonal exposureduetoambientsourcesalone(61).Forthelatter, ratesofinfiltrationintotheindoorenvironment,including useofindoorairfiltersandairconditioning,areimportant (64).Predictionsofoutdoorexposuresatresidencesseem lesspronetomeasurementerrorthanuseofmeasures from central site or satellite monitoring (60, 65). However, becausepeoplearemobile,exposuresestimatedathomes may not represent their ambient exposures, especially when they are exposed while in traffic or outdoors while exercising

(66).

For Holland et al. (13), it was important that studies

guishedbetweenhealtheffectsfromparticulatesandthose fromsulfurdioxide.Becauseairpollutioningeneraland particulatematterspecificallyaremixtureswithdifferent compositions,dependingonthesources,therehavebeen extensivediscussionsinrecentyearsaboutwhethereffect decompositionforcomplexmixturesisnecessary(67–69). Depending on the study goal, it may make sense to estimate specifichealtheffectsfromatoxiccomponentforwhich

At the time, this suggestion was dismissed by Holland et al.:

biologicaldataexist,suchasoxidative-stress–generating compounds(70).Alternatively,onemaywanttoaddress effectmodificationbycomponentsoftoxicmixturesthat originate from various sources or evaluate the toxicity of the wholemixture(71).Finally,tounderstandoravoidmea-surementerror,theappropriatetemporalandspatialscale foreachexposureneedstobeselecteddependingonwhat isknownaboutbiologicalmechanismsandlagtimesfor diseases of interest.

AIR POLLUTANTS AFFECT MULTIPLE OUTCOMES

In their 1979 review, Holland et al. (13) emphasized symp-toms that pose a threat to life, not mere discomfort. Yet, even deathsattributedtoairpollutionwereatfirstdismissedas representingmortalitydisplacementor“harvesting”ofthe frailest individuals, thus just advancing the time of death by afewdays.Thisphenomenonwassubsequentlyaddressed in studies which showed that the short-term increase in mor-talityfromairpollutionwasnotfollowedbyadecreasein all-cause or cardiovascular mortality, as would be expected fromdisplacement;rather,longer-termcumulativeexpo-sures seemed even more harmful (72, 73). This observation promptedBrunekreefandHoekin2000(7)toasktowhat extentairpollutionmightshortenlifeexpectancy.More than a decade later, Samet (74) applauded the shift of focus inairpollutionepidemiologyfrom“bodycounts”tothe perspectivethatcleanairlengthenslifeexpectancyand reduces morbidity. By this time, $PM_{2.5}$ was considered a risk factor that contributes to the burden of avoidable premature mortality (74, 75).

RoutinemonitoringofPM2.5beganintheUnitedStates in 2000, enabling researchers to address health effects from fine particles. It had long been suggested that these smaller particlesareimportant,astheyhave“thegreatestchance ofreachingthelungwiththeriskoflong-termretention”(76,p.459).Thenotionthatairpollutantsmaynot just actonrespiratoryorgansattheirpointofentrybuttravel furtherhadalreadybeenexpressedinalettertothe*AJE* (77). This letter mentioned that particles can either be taken upinthelunganddisseminatedthroughthecirculatory system or brought up via the mucus and swallowed, expos-ingthegastrointestinaltract(77).Laterwelearnedthat ultrafine particles can reach the brain (78), and particles or their compounds were found in the placenta and developing fetus (79–81). There is now an extensive body of literature showingthatairpollution affectsbirthoutcomesadversely (82,83).Moreover,prenatalexposuresmayalsoprogram organsduringdevelopmentfordeficitsorfailurelaterin life—that is, impair lung, cardiovascular, or brain develop-mentinchildren(84–86).Theliteratureonneurodevelop-mentalimpactsofairpollutionissubstantial(87),andthe knowledge base for neurodegenerative disease, from Parkin-sondiseasetoAlzheimerdiseaseandrelateddementias,is increasing rapidly (45, 88).

POPULATION REPRESENTATIVENESS AND SUSCEPTIBLE SUBGROUPS

The validity of epidemiologic studies does not depend on population representativeness. However, representativeness ortransportabilitymightaffectwhetherresultsfromone population can be extrapolated to others and may contribute informationforpurposesofhumanhealthriskassessment. Specifically,researchersmayneedtoidentifyvulnerable subpopulations by developmental stage, age, or health status orinplaceswithparticularlyhighpollutionlevels(89). Smallsamplesizesgenerallylimitsubgroupanalyses,and some vulnerable subgroups might never be represented suf-ficiently in any one study. In fact, in epidemiology the notion ofwhatrepresentsanegativeresulthasalsochangedover time;thatis,studiestargetingcertainsubgroupsmaybe toosmalltobeinformativeontheirownbutnevertheless becomevaluableinthecontextofdata-poolingandmeta-analysis efforts, which have long been a staple of air pollution epidemiology (29, 42, 90). In an early example of this approach, Dockery and Pope (91) pooled data on respiratory outcomes,generatinginverse-variance–weightedaverages acrossstudiesformortality,hospitaladmissions,asthma attacks,andchangeinlungfunction.Notonlydothese approacheshelpinvestigatorstosummarizethedataand includesmallerstudies,butbyidentifyingsourcesofheterogeneitytheymaydeepencausalunderstanding.When Shy(92)challengedHollandetal.(13)fortheiruncritical stance towards negative studies (i.e., those which found no association),theresponsewasthat“noamountofspeculationaboutbiaseswhichpreventedtherealizationofa positivefindingwillmaketheresultdemonstrativeofa positive finding appropriate for the setting of standards” (76, p. 458). Some 20 years later, a commentary in the *AJE* (93) instead emphasized that exploring the reasons for population heterogeneity—and hence heterogeneity in results—is a key issueofprimaryscientificandpublichealthinterest,asit isapromisingapproachthatintegratesresultsfromsmall-area and global studies in the quest for causal inference (71, 94–96).Basically,itwasacalltomakethebestuseofall available information.

ARE WE DONE YET?

Airpollutionresearchhasbeenthrivingonthecreative useofadministrativehealthrecordsasmuchasongeneratingdatafromlargecohortsandconsortia.Ithasgained greatly from the expansion of routine government air monitoringnetworks,advancesin“bigdata”computing,and sophisticated statistical approaches to modeling a myriad of acuteandchronichealtheffectsinhigh-andlow-pollution environments.Expansionofairpollutionexposuremodels basedonsatelliteimagerywillallowcommunitiesacross theworldtoincreasetheircapacitytoconductresearch that drives policy (97). Novel “-omics” tools are becoming more affordable and may help epidemiologists to implement meet-in-the-middleapproachesthatsupportcausalreasoningbasedonnonexperimentalhumandata(98,99).For example, an emerging body of literature has found consistent metabolomicsignaturesforairpollutioninhumanserum (100–102),whichmayeventuallyallowustorelatethis information to biological mechanisms of disease (103).

ContrarytotheconclusionsofHollandetal.’s1979 review(13),anadditional40years’worthofresearchhas uncoveredmanyhiddendangersofairpollutionatlevels muchlowerthanthosesetbytheEPAinthe1970s.Questionsabouttheexistenceofexposurethresholdsforhealth effects have been replaced by questions about the achievable lower limits at which further pollution reduction outweighs the human costs, as well as what the consequences of erring onthewrongsidemightbe.Evenincountrieswithexten-sive pollution controls and low average air pollution levels, environmental injustices (i.e., the locations where polluting sources are tolerated) may create air pollution “hot spots” in vulnerablecommunities(104).Therecentcoronavirusdis-ease 2019 (COVID-19) pandemic raised questions about the specialvulnerabilitiesofcommunitiesmostaffectedbyair pollution (105). New challenges are also arising as climate change drives wildfire-related air pollution that affects large populations, while at the same time heat waves may generate synergistic effects (106).

Intheirtime-seriesanalysis,SchwartzandDockeryob-served that “hot, humid days were associated with daily total mortality in Steubenville” (15, p. 16). Reading this statement now, it is a clear warning about the looming health effects of a warming climate, yet 30 years ago this observation did not even make it into their abstract. In 1997, the ever-prescient Tony McMichael—a late President of the International So-

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ciety for Environmental Epidemiology—encouraged the en-vironmental epidemiology community to heed the warnings of a recent report by the Intergovernmental Panel on Climate Change, as “we can expect that climate change will affect the health and wellbeing of human populations in diverse ways. Thisgreatlyextendsthetemporo-spatialscaleofenviron-mental health beyond our usual concern . . . ” (107, p. 805). McMichael proceeded to urge his colleagues to apply current knowledgetoforecastprobablehealtheffectsandinspire preemptive policy-making. This preemptive research agenda has unfortunately been superseded by growing opportunities toapplynovelapproachestoactualdataaccumulatingon the subject. Climate-related health effects are indeed catch-ingmoreofourcolleagues’attention,includingayounger generationofmethodologicallywell-versedenvironmental epidemiologistsworldwide(e.g.,seereferences108–114). The Steubenville analysis was motivated by a daily mortality time-seriesstudyinLondon(19),quicklyfollowedbya similar one conducted in Philadelphia (115), and moreover by what the editor of the journal *Epidemiology* soon called a deluge of air pollution time-series article submissions that led him to question the value of any further replication (116). Itwaspossibletogeneratesuchoverwhelmingevidence from many corners of the world because the data necessary for analysis were publicly available.

Suchopenaccesstodata,whetherground-leveldataor satellite-derivedmonitoringdata,isimminentlyimportant to meet the new challenges of climate-change health effects research.Wehavesharpenedmanyofourtoolsduring decades of air pollution research, and forecasting as well as bigdataapproachestoexistingdatanowpresentwelcome challenges. Clearly it is also not too early to recognize and actbypresentingtheinsightswearerapidlygainingto policy-makers and the public.

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