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Synergy of Biostatistics and Epidemiology in Air Pollution Health Effects Studies

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Summary

The extraordinary advances in quantifying the health effects of ambient air pollution over the last five decades have led to dramatic improvement in air quality in the United States. This work has been possible through innovative epidemiologic study designs coupled with advanced statistical analytic methods. This paper presents a historical perspective on the coordinated developments of epidemiologic designs and statistical methods for air pollution health effects studies at the Harvard School of Public Health.

Key words: air pollution; biostatistics; epidemiology; longitudinal.

1 Introduction

In 1970, the first Earth Day, the establishment of the Environmental Protection Agency and the passage of the Clean Act set the stage for recognition and action to address the existing poor air quality in the United States. The Environmental Protection Agency (EPA) Administrator was charged with identifying and setting standards for air pollutants to protect the public health using the latest scientific data. However, the scientific evidence for health effects of air pollution was remarkably scant, especially the epidemiologic evidence in the US population. Historical accounts of deaths and morbidity during extreme air pollution episodes in Donora, PA (Townsend, 1950), and London (Logan, 1953) demonstrated the hazard of extreme air pollution but provided little evidence for defining a safe level. Cross-sectional studies suggested higher rates of respiratory illness and symptoms in communities with higher air pollution, but the strength of this evidence in showing a causal association was weak. There was a need for stronger and more precise evidence for causal associations and for evidence of safe levels.

In 1973, the Arab oil-producing countries embargoed the sale of oil to the United States. There was pressure to reduce imports of foreign fossil fuels and to increase use of coal that the United States has in abundance. The downside was that coal is much dirtier than oil or natural gas, releasing much more sulphur oxides and particulate air pollution into the atmosphere, reducing air quality and potentially leading to increased respiratory disease and deaths in communities downwind of coal-burning power plants. To address this issue, the National Institute of Environmental Health Sciences (NIEHS) solicited proposals for a long-term surveillance study to measure the health effects of these expected changes in community air pollution.

This paper recalls the role that biostatistics has had in advancing air pollution epidemiology. The focus is on celebrating the role of Nan Laird and her colleagues in advancing our understanding of the health effects of air pollution, providing evidence for policy decisions, showing causal associations and laying the groundwork for modern methods in environmental epidemiology.

2 Harvard Six Cities Study

In response to the NIEHS request, Benjamin Ferris and Frank Speizer proposed to longitudinally follow a sample of adults and school children with repeated self-reported and clinical measures of respiratory health by questionnaire and spirometry in six communities (Ferris *et al*., 1979). The cities were selected to represent a range of air pollution levels – two clean (Portage, WI, and Topeka, KS), two dirty (Steubenville, OH, and Kinston TN) and two intermediates (St Louis, MO, and Watertown, MA). These cities also were expected to experience substantial changes in air quality over the next decade. The Six Cities design brought together the use of objective clinical measures of respiratory function pioneered by Ben Ferris in cross-sectional air pollution studies in Berlin NH (Ferris *et al*., 1971), with longitudinal studies of the natural history of lung function by Fletcher and colleagues in England (Fletcher *et al*., 1979; Peto *et al*., 1983).

The Six Cities study was ground-breaking in design. As a longitudinal cross-sectional study, it addressed weaknesses of traditional cross-sectional studies. However, in using the power of longitudinal studies to explore simultaneously the health effects of temporal changes in air pollution as well as the spatial changes, it presented a set of analytic challenges that had not been faced before in air pollution epidemiology. Fortunately, the methods for analysing longitudinal data were rapidly developing (Dempster *et al*., 1977; Laird & Ware, 1982; Cook & Ware, 1983).

The Six Cities Study design to evaluate changes in lung function using clinical measures to measure the effects of air pollution exposures both cross-sectionally and longitudinally was direct and intuitive. At the outset, there were the large logistical challenges of recruiting, tracking and repeatedly testing a large cohort adults and children. The recruitment, tracking, questionnaires, spirometry and air pollution measurements were all collected with pen on paper. The additional challenges of collecting, processing and managing these paper records were equally large, but we will not dwell on those issues. The commitment to maintain this cohort for multiple 5-year grant cycles was unprecedented. Fortunately, NIEHS, EPA and the Electric Power Research Institute provided the secure support and infrastructure to collect and assure the quality of these data.

Although the design was intuitive, the methods to analyse these data were still being developed. The synergistic partnering of creative epidemiologic designs and newly developed statistical methods to analyse these data led to ground-breaking advances in population-based air pollution studies. The early partnerships with Nan Laird and James Ware and other outstanding biostatisticians at the Harvard School of Public Health were essential. Over the succeeding decades, these partnerships included but were not limited to Yvonne Bishop, Brent Coull, Francesca Dominici, Thomas Louis, Fred Mosteller, Louise Ryan, Joel Schwartz, David Wipij, Antonella Zanobetti and Corwin Zigler. This paper describes some of those connections and the evolution of statistical methods in air pollution studies at the Harvard School of Public Health. This is not to diminish or underestimate the major advances of our colleagues at other centres and institutions.

3 Longitudinal Analyses of Lung Function

One of the innovations of the Six Cities study was the field use of a clinical measure of lung function, spirometry, to provide an objective, quantitative measure of respiratory health over time. The basic spirometric manoeuvre is maximal inspiration followed by forced exhalation as rapidly as possible to measure volume exhaled versus time. The spirometric measure is reproducible and predictive of clinical outcomes. However, it does require a coordinated maximal effort by the subject, which is not always doable by young children, those with existing reactive airway disease or those with advanced chronic obstructive lung disease.

Missing lung function measures due to loss of subjects to follow-up or inability to perform the spirometry test can be a serious problem in the longitudinal analyses. Either could be related to the posited air pollution exposure. The seminal work by Nan Laid and colleagues in addressing missing data in longitudinal studies (Laird, 1988), and specifically, the EM algorithm for ML estimation with incomplete data (Dempster *et al*., 1977) provided insight and methods to address this issue.

3.1 Loss of Lung Function in Adults

For the adult sample, the primary hypothesis was that air pollution accelerated the annual loss of lung function. A random sample of 8480 adults between 25 and 74 years of age was recruited in each city. Lung function was measured by spirometry at baseline and at 3 and 6 years of follow-up. Cross-sectionally, baseline forced vital capacity (FVC) lung function was fit by a simple quadratic function of height and age (Figure 1) (Dockery *et al*., 1985)

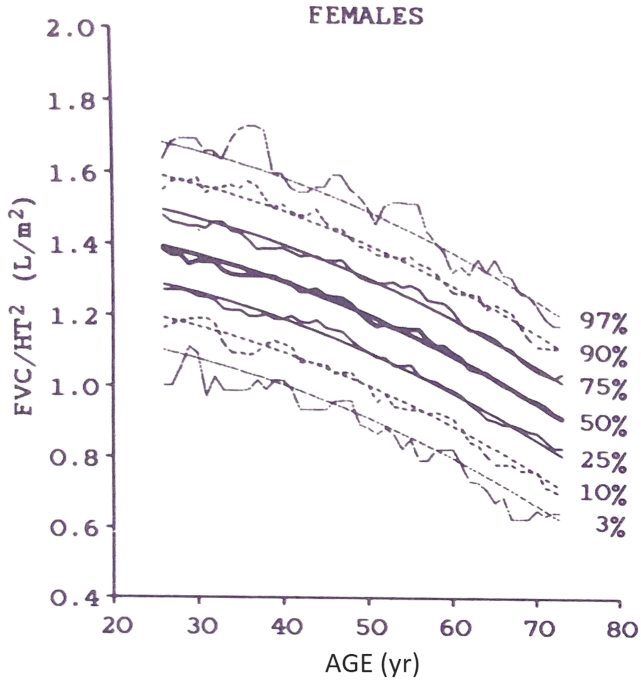

Figure 1. *Empirical and fitted percentiles of FVC/HT^2 for white, never smoking women in Harvard Six Cities study (Dockery et al., 1985).*

$$FVC = HT^2\left(\alpha + \beta\, SEX + \gamma_1\, AGE + \gamma_2 AGE^2\right).$$

Although conceptually simple, the actual analyses of such longitudinal data to obtain annual loss of lung function in different cities are complex. Jim Ware and his colleagues have summarised these longitudinal analyses in reviews (Cook & Ware, 1983; Ware & Liang, 1996) and their textbook (Fitzmaurice *et al*., 2004).

Traditional growth curve models assume that all individuals are measured at the same initial and subsequent ages (Ware & Liang, 1996). However, when individuals enter the study at a wide range of initial ages, the analysis of age-related changes can be confounded by longitudinal and cross-sectional information about age-related changes (Laird *et al*. 1992; Ware *et al*., 1990). To separate cross-sectional and longitudinal estimates of change of lung function, the observations were transformed to the baseline value and the first differences of the repeated observations on individual subjects (Ware *et al*., 1990). The model for the baseline observations can be given by

$$E(y_{i1}) = \beta_0 + \beta_C' x_{i1}$$

and the model for the successive differences is given by

$$E\left(y_{i,j} - y_{i,j-1}\right) = \beta_L'\left(x_{ij} - x_{i,j-1}\right).$$

A related concern is the impact of age and cohort on estimates of annual change in lung function. Lung function declines with age. This reflects normal ageing but also the cumulative effects of a lifetime of experiences. Subjects were recruited across a range of 50 years at baseline and so may have had a wide range of shared experiences defined by their birth year, that is cohort. All three effects can be included in a simple additive model. Let Y_{ijk} be a measurement on a person from cohort i, of age j, and at time k. Then let

$$Y_{ijk} = c_i + a_j + t_k + e_{ijk}$$

where C_j, a_j' and t_k represent the cohort, age and time effects, respectively, and e_{ijk} is the error term, with normal distribution. Age, birth year (cohort) and time (period) are algebraically deterministic, so it is impossible to separate these effects. Louis *et al*. (1986) examined the differences between the cross-sectional and longitudinal estimates of age-related change of lung function in the Six Cities study and showed that because of the balanced design, these differences were small.

3.2 Growth of Lung Function in Children

The other primary hypothesis of the Six Cities Study was that air pollution exposures impair growth rate of lung function and ultimately attained maximal lung function at maturity. We hypothesised that the growing lungs of children would be more sensitive to environmental challenges and that they would have less external modifiers affecting adults such as occupation and smoking.

A total of 13 737 first and second grade school children were enrolled with lung function, height and weight measured annually through high school graduation or loss to follow-up. As with the analyses of the longitudinal lung function data in adults, the analyses in children had to deal with missing data and separation of age, period and cohort effects. In addition, these children are going through substantial normal growth between ages 6 and 18 years including their adolescent growth spurt. Measuring the rate of growth of lung function in children

associated with air pollution meant separating the normal growth among pre-adolescent and also during the non-linear adolescent growth spurt.

Empirical growth curves of lung function versus height (Figure 2) were produced for boys and girls using locally weighted smoothing (LOWESS) for the mean and each percentile as a function of height (Dockery *et al*., 1983; Wang *et al*., 1993a). The degree to which children remained at a fixed percentile of the age-specific height distribution as they mature, that is tracking, is especially important for assessing risk factors for the development of disease. McMahan (1981) proposed the model

$$Y_{ij} = \mu_j + k_i\sigma_j + e_{ij},$$

where (μ_j, σ_j) are the mean and standard deviation of the response at time (or age) j, k_i is the deviation specific to individual i and e_{ij} are independent errors. McMahan proposed an index (τ) measuring the fraction of inter-individual variation explained by tracking. Applying this index to repeated measurements of height and FVC, Dockery *et al*. (1983) found that FVC exhibited tracking ($\tau = 0.93$ for boys and 0.90 in girls) comparable in strength with height ($\tau = 0.97$ for boys and 0.95 in girls). Annual growth velocities of height and lung function were calculated from the repeated measurements, and empirical growth velocity curves produced using LOESS smoothing (Figure 3) (Wang *et al*., 1993b).

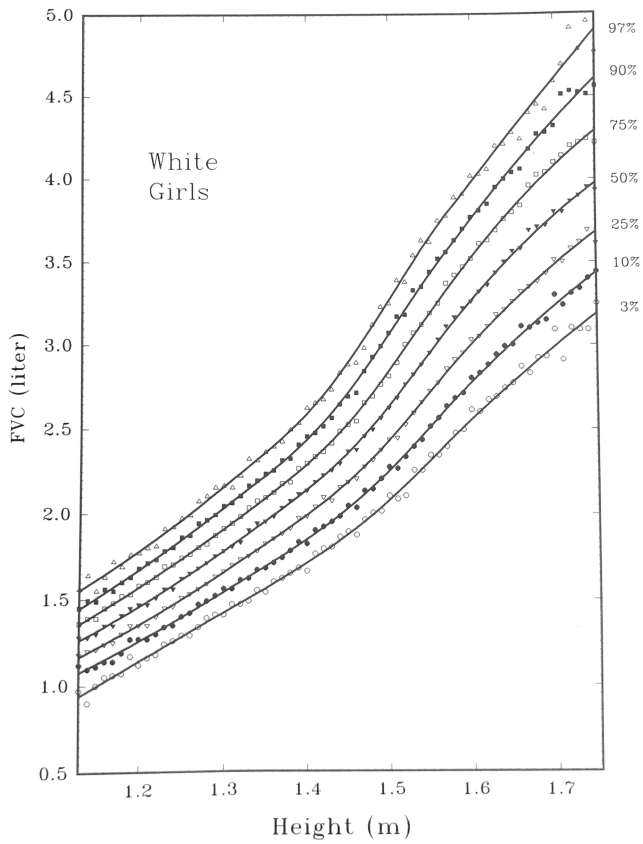

Figure 2. *Empirical and smoothed percentiles of FVC versus height for white girls in Harvard Six Cities study (Wang et al., 1993a).*

Children, or at least pre-adolescent children, were expected to be free of respiratory risk factors such as occupation and smoking. However, parental smoking led to lower lung function and lung function growth rates (Berkey *et al*., 1986; Wang *et al*., 1994) as well as slower height growth rates (Berkey *et al*., 1984).

3.3 Acute Change of Lung Function

Although the focus of the Six Cities Study was on chronic respiratory effects of long-term air pollution exposures, it quickly became apparent that there was an opportunity, and indeed a need, to examine acute effects. High air pollution events (alerts) were regularly observed each fall in Steubenville, the most highly polluted city. A subsample of 3rd and 4th grade school children received baseline lung function test early in the fall. Upon declaration of an air pollution alert, these children were retested during the alert, and 1, 2 and 3 weeks later in the fall of 1978, 1979 and 1980, and in the spring of 1980. The study design assumed a single high exposure during the air pollution alert with relatively clean air at the other observation points. However, the reality was that air pollution was a continuum throughout the study periods, with air pollution on some of the 'clean' days approaching the alert level. The combined data across all four study periods were analysed by individual regression analyses of the repeated measures of lung function and daily air pollution across the multiple studies (Figure 4). Three hundred thirty children had three of more measurements, and 194 participated in more than one of the panel studies. The individual regressions showed lung function declined on days with higher particulate air pollution (Dockery *et al*., 1982).

These studies assumed that changes in lung function would occur over weeks. However, the analyses of the multiple episodes showed changes on the same or succeeding day of exposure. Alternative designs examined lung function in children with daily spirometry measurements in a controlled outdoor summer camp setting (Kinney *et al*., 1989). An alternative design used simple self-administered lung function test, peak flow, measured daily by school children (Pope *et al*., 1991; Pope & Dockery, 1992). Although peak flow was potentially less accurate and less reproducible than spirometry, these simple tests allowed for longer follow-up by larger numbers of children.

The application of econometric analytic methods, such as distributed lag models (Greene, 1990), allowed an understanding of the day-to-day structure of loss and recovery of lung function after exposures (Gold *et al*., 1999). Let y_t be an equally spaced discrete time series of length T. An unconstrained distributed lag model can be written as

$$y_t = \alpha + \sum_{j=0}^{L} \beta_j x_{t-j} + \sum_{k=0}^{K} \delta_k z_{tk} + e_t,\ t = 1, \ldots, T.$$

where L represents the lag length (the number of time points at which x_t exerts an effect on y_t) and β_0 to β_L are the unknown lagged parameters to be estimated, z_{tk} are k covariates and e_t is the stochastic component with normal distribution. Collinearity among the lagged coefficients exists (i.e. lagged values close in time are highly correlated), leading to unreliable estimation of the β_j values with wide confidence intervals (CIs). Imposing structure on the lagged parameters reduces collinearity and also reduces the number of parameters to be estimated. The polynomial distributed lag is one such method, in which the β_j values are constrained to lie on a polynomial of unknown degree D; specifically,

$$\beta_j = \sum_{i=0}^{D} \gamma_i j^i.$$

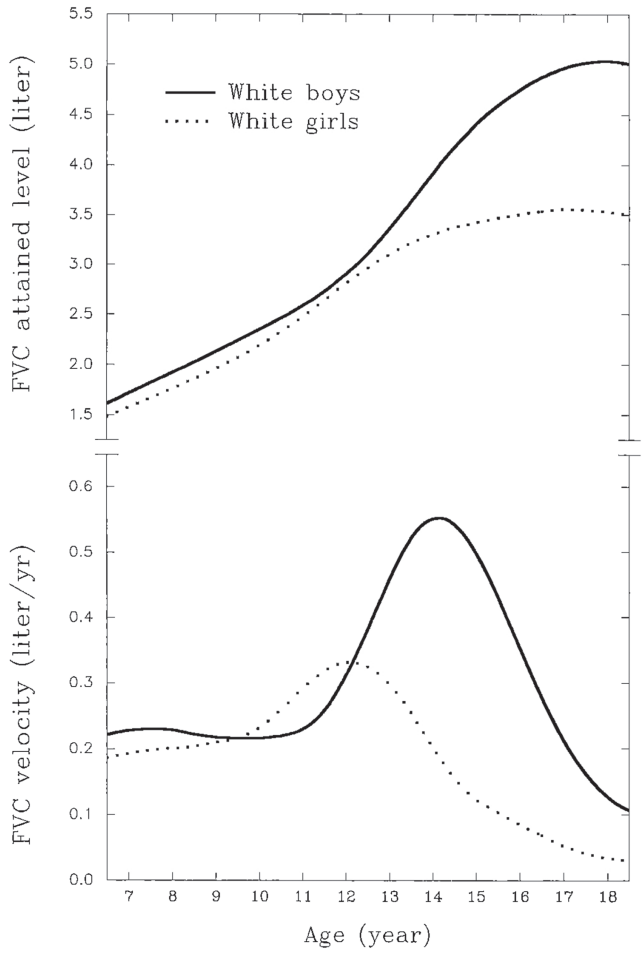

Figure 3. *Sex-specific mean FVC and annual velocity as a function of age for Harvard Six Cities children's cohort (Wang et al., 1993b).*

Substituting and rearranging gives

$$y_t = \alpha + \sum_{i=0}^{D} \gamma_i \sum_{j=0}^{L} x_{t-j} j^i + \sum_{k=0}^{K} \delta_k z_{tk} + e_t, \quad t = 1, \ldots, T,$$

where e_t are distributed normally.

The polynomial coefficients γ_i can be estimated by ordinary least squares methods, and the estimated lag coefficients may be recovered. These analyses showed the effects of air pollution on lung function were seen on the same day but persisted over the following 3–4 days. Moreover, these distributed lag methods were important in understanding the lag structure of air pollution exposures on acute responses such as deaths and hospital admissions.

4 Mortality and Morbidity

4.1 Acute Change in Mortality

Independently of the Six Cities Study, analyses of daily mortality in London had shown associations with daily air pollution measurements of particles (Schwartz & Marcus, 1990). These

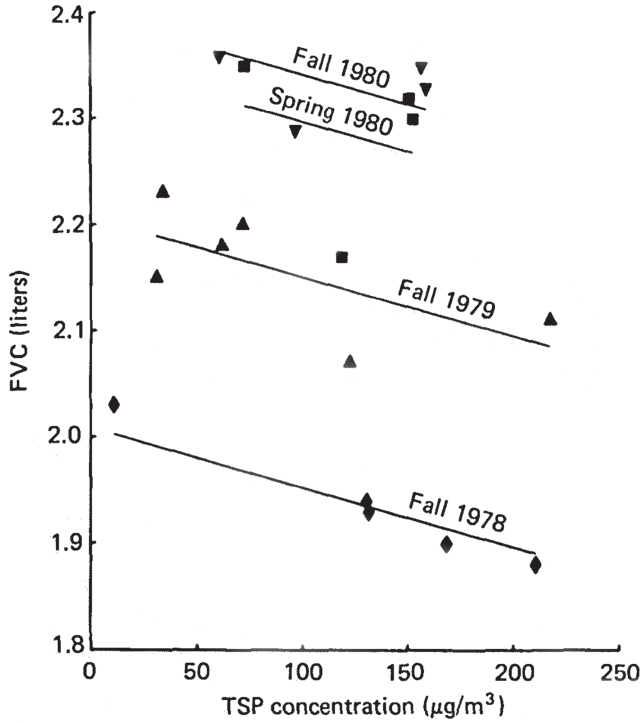

Figure 4. *FVC versus total suspended oarticulate (TSP) concentration for a sample child who participated in all four Steubenville alert studies (Dockery et al. 1982).*

studies in England were discounted by the EPA in setting air quality standards, as not applicable to US populations. Similar time series studies in the United States were limited by the fact that particulate air pollution data generally were only collected every sixth day, making analyses of daily associations untenable. However, particulate air pollution had been measured daily for many decades in Steubenville, Ohio. Although Steubenville had a population less than $1/100^{th}$ of that of London, Joel Schwartz, an econometrician at EPA on sabbatical at Harvard, saw the value in these daily data. He showed that counts of daily deaths in Steubenville were linearly associated with daily particulate air pollution levels (Schwartz & Dockery, 1992a). This was confirmed in analyses of daily mortality and particulate air pollution in Philadelphia, another city with daily measurements (Schwartz & Dockery, 1992b). This innovative use of time series methods to assess air pollution effects was controversial (Moolgavkar & Luebeck, 1996; Lipfert & Wyzga, 1997), but similar analyses soon replicated these findings in multiple cities across the country and around the world.

To address this controversy, and to bring consistent and coherent approaches to these multiple time series analyses, Francesca Dominici and colleague at the Johns Hopkins School of Public Health collaborated with investigators at Harvard to undertake a comprehensive analyses of daily mortality versus daily air pollution in all cities across the United States (Samet *et al.*, 2000b). This landmark National Morbidity and Mortality Air Pollution Study addressed and provided methods in three areas: (i) evaluating and correcting for bias from air pollution exposure errors, (ii) assessing the pollution–mortality association in multiple time frames and assessing mortality displacement and (iii) developing a hierarchical approach for combining evidence across multiple locations and examining sources of heterogeneity between city-specific associations. These methods were initially reported for 20 large US cities (Samet *et al.*,

2000a) and ultimately extended to the 100 largest cities in the United States (Peng *et al*., 2005). Within each city, a semiparametric regression model for the time-varying log relative rate was fit using a generalised additive model. Let Y_t^c be the total number of non-accidental deaths on day t in city c. The Y_t^c's are Poisson-distributed with expectation μ_t^c and with possible overdispersion ϕ^c. The general form of the city-specific model is

$$Y_t^c \sim Poisson\left(\mu_t^c\right)$$

$$Var\left(Y_t^c\right) = \Phi^c \mu_t^c$$

$$\log\left(\mu_t^c\right) = \beta^c(t) x_{t-l}^c + confounders,$$

where x_{t-l}^c is the lag l air pollution level for day t. The function $\beta^c(t)$ represents the time-varying effect of air pollution on mortality and is a yearly periodic function for estimating seasonal patterns. To estimate smooth seasonal patterns in the city-specific log relative rates, we use a sine/cosine model for $\beta^c(t)$ of the form

$$\beta^c(t) = \beta_0^c + \beta_1^c \sin\left(\frac{2\pi t}{365}\right)\Big/ c_1 + \beta_2^c \cos\left(\frac{2\pi t}{365}\right)\Big/ c_2,$$

where β_0^c, β_1^c, and β_2^c are estimated and c_1 and c_2 are known orthogonalising constants. In this model, the effect of air pollution is allowed to vary smoothly over the course of a year but is constrained to be periodic across years.

4.2 Acute Changes in Morbidity

Francesca Dominici and colleagues extended these methods to the massive database of hospital admissions of Medicare enrolees in the United States. They merged counts of hospital admissions with daily $PM_{2.5}$ from nearby air pollution based on county of residence (Dominici *et al*., 2006). They found short-term exposure to $PM_{2.5}$ increased the risk for hospital admission for cardiovascular and respiratory diseases.

Examination of cause-specific counts of deaths and hospital admissions in these time series studies had shown consistent and strong particulate air pollution associations with ischaemic heart disease events, that is, myocardial infarctions. Independently, Murray Mittleman and Malcom Maclure had been applying the newly developed case-crossover methods to measure short-term triggers of cardiovascular events based on interviews of survivors of myocardial infarction (Mittleman *et al*., 1993). We recognised that the same approach could be applied to examine associations with air pollution immediately prior to a myocardial infarction (Peters *et al*., 2001). Ultimately, it was recognised that the case-crossover approach could be used in analyses any daily event data, without having to interview the participants. Case-crossover became a complement to time series analyses (Neas *et al*., 1999). More importantly, it provided the opportunity to assess associations of short-term air pollution exposures with death and clinical events in massive health datasets such as the Medicare records (Wei *et al*., 2019).

4.3 Long-Term Mortality

Although the primary Six Cities design was to assess longitudinal changes in lung function, tracking of participants led to accumulation of death records. Censoring by death or loss to follow-up was an issue in evaluating longitudinal change in lung function. However, it was also

clear that death, especially from respiratory disease, was a potentially important outcome. As seen in even crude survival plots (Figure 5), people living in the nominally dirty cities (Steubenville and St Louis) were dying several years earlier than hoses living in the nominally clean cities (Portage and Topeka). Analyses of time to death by Cox proportional hazards analyses showed a surprisingly strong association between mortality and fine particle air pollution (Dockery *et al*., 1993).

The observed increase in mortality associated with fine particulate air pollution across the Six Cities was so clear, but also so unexpectedly large that it was sure to be questioned. Indeed, we questioned the validity of these findings ourselves and sought to verify before submitting for publication. True verification comes from replicating these results in an independent experiment or sample. We clearly were not going to start another multi-decade follow-up in a new cohort.

Instead, Frank Speizer proposed that we attempt to replicate in a separate prospective cohort. The American Cancer Society Cancer Prevention Study II (CPS II) had recruited 1.2 million subjects who had been followed since 1980 to examine the risk factors for cancer. We merged existing fine particle air pollution data from 50 metropolitan areas in the United States with death records for CPS II participants living in those metropolitan areas (Pope *et al*., 1995). These analyses confirmed the observations in the Six Cities. Importantly, from a methodological/design perspective, the ACS CPS II study showed that it was not necessary to build a new cohort to assess air pollution in longitudinal prospective studies, but more effective to leverage existing cohort studies by adding air pollution exposures based on location.

The challenge then was to provide estimates of air pollution exposures at a spatial and temporal scale that could be matched with residential addresses of participants in existing cohort studies. Jeff Yanosky and colleagues merged interpolated observations for the EPA surveillance monitoring networks with geocoded emissions data and meteorological records to produce monthly estimates of particulate air pollution for the continental US population (Yanosky *et al*., 2014). These exposure estimates were merged with residential records of 108 767 participants in the Nurses' Health Study to examine associations with chronic mortality associations (Hart *et al*., 2015).

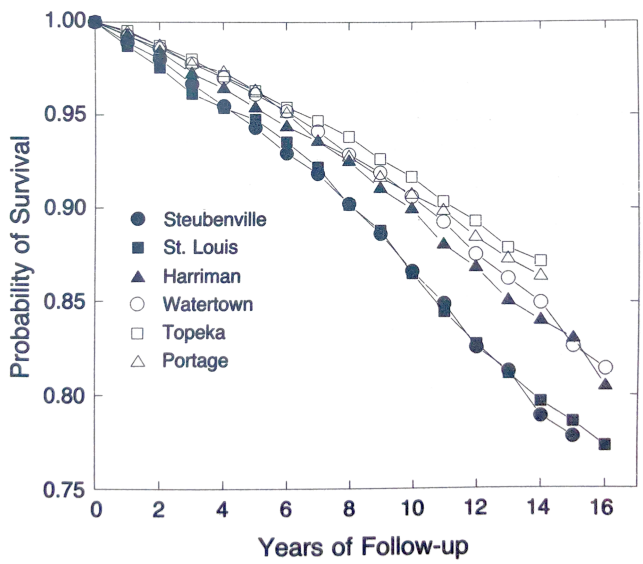

Figure 5. *Survival probability for each of Harvard Six Cities for adult cohort according to years of follow-up (Dockery et al., 1993)*

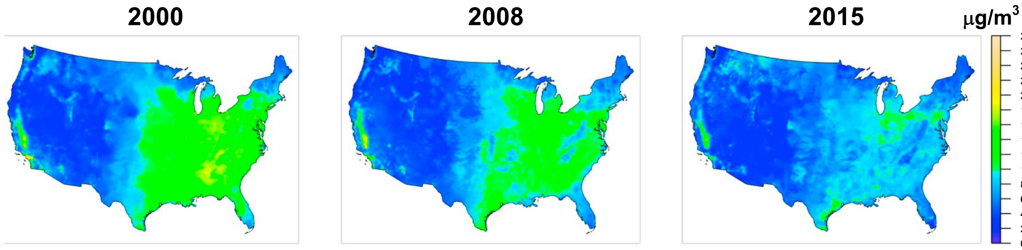

Figure 6. *Spatial distribution of annual ensemble average predicted PM2.5 at each 1 × 1 km grid cell in the contiguous United States (Di et al. 2019).*

In an elaboration of this approach, Joel Schwartz and colleagues incorporated satellite-based remote sensing data, chemical transport models, land use and meteorological variables into an ensemble average of three machine learning algorithms (neural network, random forest and gradient boosting) to estimate daily fine particle air pollution concentrations in a 1 × 1 km grid across the continental United States from 2000 to 2015 (Figure 6) (Di *et al*., 2019). Such high-resolution daily air pollution estimates opens the opportunity to examine health effects in effectively any prospective cohort with residential address information.

4.4 MEDICARE Beneficiaries

A major innovation was to extend the analyses of air pollution health effects to not just to cohort study participants but to the entire US population. The Medicare benefits files include effectively the entire US population 65 years of age and older. Records include address, MEDICARE expenses and a death benefit. Dominici and colleagues have analysed these Medicare beneficiary data as an open cohort, that is, all Medicare beneficiaries were entered into the cohort on enrolment and followed until death (Zeger *et al*., 2008). They showed that the results of the Six Cities and ACS cohort analyses could be replicated using the MEDICARE file (Eftim *et al*., 2008). Merging these death data from 61 million Medicare beneficiaries with the neural network high-resolution air pollution data, fine particle air pollution was shown to be associated with mortality in Cox proportional hazards analyses across the full range of exposures in the United States (Di *et al*., 2016).

4.5 Causal Inference

A major weakness of traditional epidemiologic analyses is the failure to show causality. Randomised studies are considered the optimal study design for determining the efficacy, or causal influence, of treatment because randomisation typically results in balance of potential confounders between the treatment and control groups. An important advance has been the reframing of air pollution epidemiology studies as hypothetical randomised experiments (Zigler & Dominici, 2014; Zigler *et al*., 2016; Dominici & Zigler, 2017; Bind, 2019; Zigler, 2021).

Zigler *et al*. (2018) employed causal inference methods and a spatial hierarchical regression model to determine if the designation non-compliance ('non-attainment') with the National Ambient Air Quality Standard for ambient fine particulate matter ($PM_{2.5}$) in 2005 causally affected ambient $PM_{2.5}$ and health outcomes among over 10 million Medicare beneficiaries in the Eastern United States in 2009–2012. They grouped attainment and non-attainment locations by propensity scores to adjust for confounding, which is approximating the design of an experiment where non-attainment designations are 'randomised' to locations within propensity score

groups. They then applied a spatial hierarchical regression model for pollution to predict the potential ambient $PM_{2.5}$ concentration in 2010–2012 that would have occurred in non-attainment areas if the designations had never occurred. Although these analyses did not conclusively show impact of the non-attainment designation on reduced ambient $PM_{2.5}$, mortality and morbidity, they illustrated the utility of these methods in intervention research. Other studies have applied casual inference methods in analyses of air pollution associations with short-term (Schwartz *et al*., 2017) and long-term mortality (Schwartz *et al*., 2018; Wei *et al*., 2021) in the Medicare and other datasets.

5 Conclusions

Over the past five decades, the partnership of epidemiologists and biostatisticians at the Harvard School of Public Health in the design, conduct, analyses and reporting of studies of the health effects of air pollution has been a model for creative, innovative research. Cutting-edge analytic approaches and methods were developed in response to or adapted to creative epidemiologic study designs. The multiple studies under the rubric of the Harvard Six Cities Study were test beds for longitudinal and repeated measures analyses. They pointed the way to leveraging existing cohort studies to examine air pollution health effects. We witnessed the transition from pen-and-paper processing and analyses to substantial computing resources. Applying machine learning to massive data bases of remote sensor and modelled air pollution concentrations, it is now possible to assign individual exposure to effectively entire populations of tens of millions. Large computing power and large databases allow these analyses to be framed to better assess causality. This partnership has clearly set the stage for the next generation of investigators to address complex emerging environmental health issues. None could be more challenging than understanding the far-ranging health effects of climate change and identifying opportunities to intervene and ameliorate these effects.

ACKNOWLEDGEMENTS

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