

# TIME-SERIES STUDIES OF PARTICULATE MATTER

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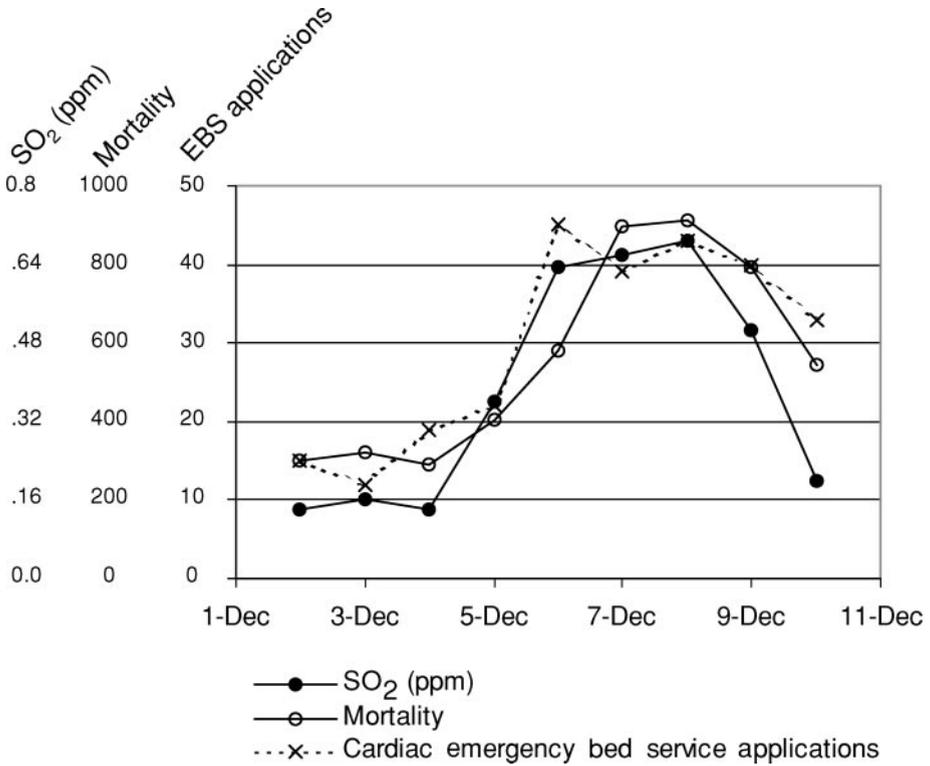
**Key Words** air pollution, public health, epidemiology, regression models

■ **Abstract** Studies of air pollution and human health have evolved from descriptive studies of the early phenomena of large increases in adverse health effects following extreme air pollution episodes to time-series analyses based on the use of sophisticated regression models. In fact, advanced statistical methods are necessary to address the challenges inherent in the detection of a relatively small pollution risk in the presence of potential confounders. This paper reviews the history, methods, and findings of the time-series studies estimating health risks associated with short-term exposure to particulate matter (PM), though much of the discussion is applicable to epidemiological studies of air pollution in general. We review the critical role of epidemiological studies in setting regulatory standards and the history of PM epidemiology and time-series analysis. We also summarize recent time-series results and conclude with a discussion of current and future directions of time-series analysis of particulates, including research on mortality displacement and the resolution of results from cohort and time-series studies.

## INTRODUCTION

For centuries, people have understood that outdoor air pollution harms human health. Air pollution has been ubiquitous across human existence because fire, a major pollutant source, has been used for cooking and warmth. The earliest recorded outdoor air pollution problems came largely from coal and wood combustion in large cities such as London (12–13). As with today's approaches to air pollution control, initial attempts to lessen pollution balanced political and economic considerations against detrimental impacts, including those to health, buildings, and other materials, and to the environment more generally.

Despite this early recognition of the dangers of air pollution, industrialization and fossil fuel-based transportation during and after the Industrial Revolution caused air pollution concentrations to rise in many areas. Risks to health were readily apparent during extreme air pollution episodes in which excess mortality and morbidity accompanied exceptionally high air pollution levels. By the mid



**Figure 1** Air pollution, mortality, and cardiac emergency bed service applications during the 1952 London Smog. Source: Bell & Davis (8), U.K. Ministry of Health (177).

twentieth century, several widely publicized acute episodes of air pollution spurred scientific research, public awareness, and government action (91, 177). Three of the most dramatic episodes were in the Meuse Valley in Belgium in 1930 (50, 112), Donora, Pennsylvania in 1948 (24, 143), and London in 1952 (8, 177). Pollution during these episodes had a large and readily evident impact on mortality and morbidity (Figure 1).

These and similar events prompted many governments, including the United States and Britain, to initiate research on air pollution and health and eventually to enact legislation aimed at improving air quality. Such regulatory efforts have done much to curb the problem in some areas, yet air pollution remains a significant concern worldwide, with profound adverse effects on public health (46). Many areas of the world still suffer from extreme levels of air pollution, with annual concentrations of total suspended particles (TSP) above 400  $\mu\text{g}/\text{m}^3$  in some Chinese and Indian cities in the 1990s (181). Recently the World Health Organization's Global Burden of Disease Initiative estimated that ambient air pollution causes almost 800,000 premature deaths annually (46).

Research on air pollution's effects on health has amassed an impressive literature that comes from several relevant disciplines including toxicology, human exposure assessment, and epidemiology. Although the connection between air pollution concentrations and mortality was readily apparent in the London Fog of 1952 (Figure 1), modern air-pollution research in developed countries addresses associations at far lower levels of pollution. Time-series analysis of morbidity and mortality data has emerged as one of the most important tools for this purpose. The time-series approach investigates associations between short-term changes in pollution levels with short-term changes in acute health outcomes, and it has been applied widely to investigate the health effects associated with exposure to airborne particulate matter (PM) and other pollutants. The use of time-series analyses has been facilitated by relatively accessible data from public sources in many countries.

Findings from time-series studies are relevant to regulatory processes, which set the standards for pollution at levels considered sufficiently safe for human health (55). Estimating the burden of disease attributable to air pollution exposure can be part of the regulatory process, sometimes combined with cost information for cost-benefit considerations. In fact, time-series studies have a crucial role in recent discussions of the appropriate air quality standards for PM pollution in the United States and elsewhere (55). Time-series studies results also were used in the Clean Air Act (CAA) Section 812 studies that estimated the costs and benefits of the Clean Air Act (40, 42). For example, the number of hospital admissions avoided by lower levels of PM under the CAA from 1990 to 2010 was estimated using concentration-response functions derived from References 14, 16, 107, 146–148, 151–152, 164, 166, and 176.

This paper reviews the time-series approach to investigating the risks of PM, placing the analytical approach in the broader context of epidemiological studies of air pollution in general. We discuss the history of epidemiologic research on PM and the use of time-series analysis. We conclude with a discussion of future directions of time-series analysis of PM, including multicity studies and the merging of time-series and cohort studies. Whereas our focus is on time-series studies of PM, time-series methods are also applied to other pollutants, particularly ozone (O<sub>3</sub>). Time-series approaches have broad applicability in investigating the environment and health, particularly for factors that vary on relatively short timescales (e.g., temperature).

## **The Critical Role of Epidemiologic Evidence in Policies for Air Pollution Control**

The United States Congress enacted the Clean Air Act (CAA) in 1970, which built on the Clean Air Act of 1953 and the Air Quality Act of 1967. It was subsequently amended in 1977 and 1990. The legislation was passed in response to Congress's findings that the "amount and complexity of air pollution. . . has resulted in mounting dangers to the public health and welfare. . ." (20). The

Environmental Protection Agency (EPA) is required by the CAA to establish National Ambient Air Quality Standards (NAAQS) for criteria pollutants, such as PM, that endanger public health and/or welfare. The primary or health-based standards are to be set at a level sufficient to protect human health with an “adequate margin of safety” for sensitive subpopulations, such as the elderly. Because the criteria pollutants are regulated individually, epidemiological studies are generally designed to estimate the health effects from exposure to each pollutant separately, often by controlling for the potential confounding effects of other pollutants through study design or data analysis.

The Clean Air Act requires the EPA to review each NAAQS at least every five years and to recommend revisions if necessary, based on the most recent health research. The design of the periodic review process is intended to keep regulatory standards consistent with new scientific evidence (55). During this review process, the EPA is advised by the Clean Air Scientific Advisory Committee (CASAC), a Congressionally mandated panel of scientific experts. The EPA prepares a criteria document that compiles and assesses research related to the health and welfare impacts of the pollutant. The EPA evaluates the policy implications of the criteria document and makes recommendations in a staff paper, which describes evidence-based policy options. Both of these documents are subject to external review and comment from the public, industry, and other interested parties. CASAC makes final recommendations; EPA then proposes changes to regulatory standards, if needed. Whereas the EPA administrator has final authority to promulgate a NAAQS, the Executive Branch also performs a review.

Epidemiological evidence on the health impacts of particulate air pollution plays a pivotal role in the setting of regulatory standards. Findings from complementary disciplines, such as animal toxicology and clinical human exposure studies, have also contributed to the body of knowledge of how air pollution affects health, especially in characterizing the biological mechanisms underlying adverse health effects. Such evidence on mechanisms reduces uncertainty, particularly in extrapolating risks to exposures at lower pollution levels for which epidemiological data are lacking. For PM and several of the other criteria pollutants, it is largely the direct evidence of epidemiologic research that drives the setting of standards. Epidemiological evidence has prominence in the regulatory process because it directly addresses human health at exposures experienced by the population.

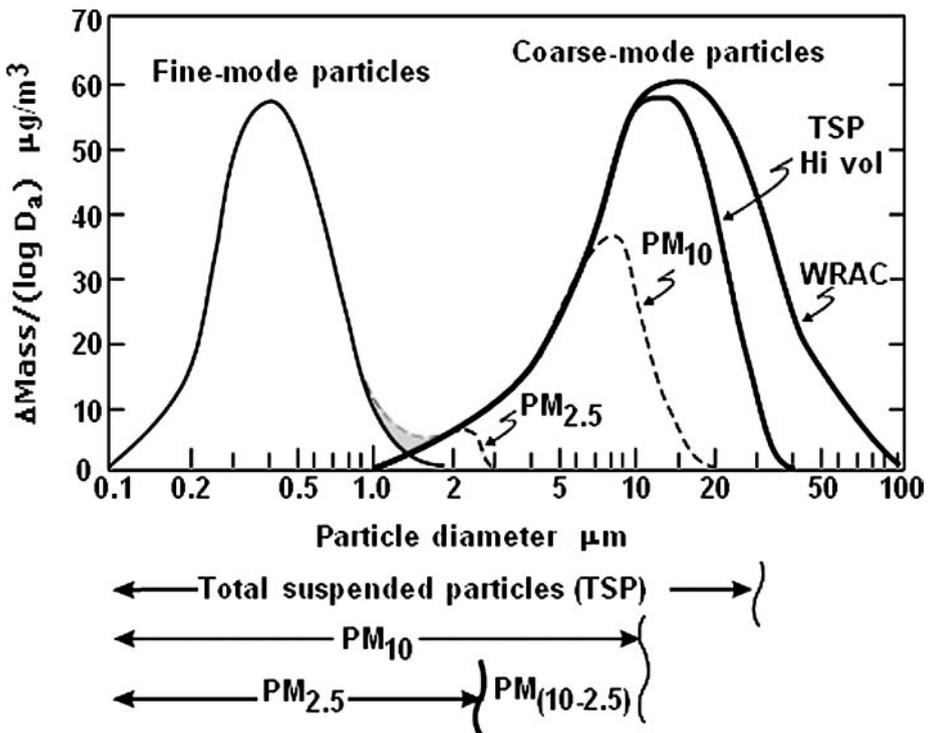
## **PARTICULATE MATTER**

The health effects of airborne particles have been vigorously investigated for five decades (45, 122). PM has been linked to numerous adverse health effects including increased hospital admissions and emergency room visits, respiratory symptoms, exacerbation of chronic respiratory and cardiovascular diseases, decreased lung function, and premature mortality (45). The broad range of epidemiological studies of the health effects of PM has been reviewed elsewhere (25, 45, 60, 122, 123, 175, 180); this review focuses on time-series approaches because of the recent

emergence of this method and the central role of time-series findings in setting health-based regulatory standards.

The term particulate matter refers to solid or liquid particles in the air. PM has many sources and can be either primary or secondary in origin. Primary PM is emitted directly and can be either coarse or fine, whereas secondary PM, which tends to be finer in size, is formed in the atmosphere through physical and chemical conversion of gaseous precursors such as nitrogen oxides ( $\text{NO}_x$ ), sulfur oxides ( $\text{SO}_x$ ), and volatile organic compounds (VOCs). Whereas most air pollutants are defined with respect to a particular chemical composition, PM is a generic term that includes a broad range of physical characteristics and chemical species. It is the only major pollutant regulated under Section 109 of the CAA to be defined without regard to chemical form (20). The pollutants regulated under this section, often referred to as criteria pollutants because of the process used to develop standards, include five others: lead, carbon monoxide (CO), sulfur dioxide ( $\text{SO}_2$ ), nitrogen dioxide ( $\text{NO}_2$ ), and ozone.

For regulatory and scientific purposes, PM is measured according to the mass concentration within a specific size range (Figure 2 and Table 1). Size



**Figure 2** Particulate matter size distribution by volume for urban areas. Adapted from Wilson & Suh (179).

**TABLE 1** Measures of particulate matter in air

Particle metric	Definition
Black smoke or British smoke (BS)	A nongravimetric measure in which air is passed through a filter paper and the darkness of the resulting stain is determined
Coefficient of haze (COH)	Measure of the intensity of light transmitted through a filter with particles relative to that of a clean filter
Total suspended particles (TSP)	Particles with an aerodynamic diameter up to approximately 45 microns
PM <sub>10</sub>	Particles with an aerodynamic diameter no larger than 10 microns
PM <sub>2.5</sub>	Particles with an aerodynamic diameter no larger than 2.5 microns
Ultrafine	Particles with an aerodynamic diameter no larger than 0.1 microns

characteristics are linked to sources and are a determinant of atmospheric transportation, environmental deposition, and the pattern of deposition in the respiratory system. Particle size is characterized by aerodynamic diameter, which is the diameter of a uniform sphere of unit density that would attain the same terminal settling velocity as the particle of interest. This measure facilitates size comparison among irregularly shaped particles and refers to the physical behavior of the particles rather than the actual size. Aerodynamic diameter is determined by a particle's shape and density. TSP can be measured by a high volume sampler (Hi Vol); however, this method does not collect all particles in the coarse mode, as does a wide area aerosol classifier (WRAC) (179) (Figure 2).

For regulatory and research purposes, several different particle metrics have been used (Table 1). Thus, the various fractions of PM in air have been defined and measured without regard to their composition, to date.

Particles in the air can be characterized both physically and chemically. In typical urban environments, there are two broad sets of source categories: (a) combustion sources, including mobile sources (predominantly vehicles) and stationary sources (primarily industrial sources and power plants); and (b) mechanical forces, including wind, and vehicle traffic and other activities. The smaller particles result from combustion and stationary sources, whereas the larger particles tend to come from mechanical forces, such as wind or road traffic. Particles in urban air tend to have a multimodal distribution, reflecting these sources (Figure 2). Three basic size modes have been identified: nuclei (particles with a diameter less than about 0.1  $\mu\text{m}$ ), accumulation (particles with a diameter of about 0.1 to 1 or 2  $\mu\text{m}$ ), and coarse (particles with a diameter above 1 or 3  $\mu\text{m}$ ) (45). In a sample of urban air, coarse particles typically make up a small fraction of all particles with regard to number density but comprise a large fraction with respect to volume or mass. Smaller particles contribute less to total volume and mass but more to surface area and the total number of particles. In recent health effects research, emphasis has been placed on the smaller particles because they are in the size range that penetrates into the lung without being removed in the upper airway (45).

Although PM is classified by size for regulatory purposes and also for health research, other physical and chemical characteristics may also be relevant to health. The composition of PM differs by geographic area and can vary with season, source, and meteorology (43, 45). In the eastern United States, PM often has a substantial sulfate component, reflecting the contributions of emissions from power plants; in the West, transportation emissions contribute a larger fraction of PM, and hence PM samples in some western locations tend to have a substantial nitrate component. In the Northwest, wood burning may be a dominant source during colder seasons. These regional differences in emissions sources account for some of the variation in PM composition across the country, and these compositional differences may be relevant to risk to health, a topic currently of research interest; however, mass-based PM measures do not index composition and hence may not adequately capture the risk to health posed by exposure to PM.

PM and other major air pollutants in urban air have common sources and exist as a complex mixture. Sulfur dioxide and PM are both generated by the combustion of sulfur-containing fuels, particularly coal, although PM has numerous other sources. The heat of combustion generates sulfur oxides, which can contribute to the formation of PM via secondary aerosol formation. VOCs are a key precursor to tropospheric ozone (smog), which is also regulated as one of the criteria pollutants under the Clean Air Act. Although the gaseous pollutants  $\text{NO}_2$  and  $\text{SO}_2$  contribute to PM formation, they are also separately regulated pollutants that can independently cause adverse health effects at sufficiently high concentrations (1, 142). Thus, although PM is regulated specifically, it is one component of the complex mixture of pollutants present in outdoor air. In investigating the health effects of air pollution, researchers face the challenge of attempting to disentangle effects of the components of a complex air pollution mixture.

As researchers have gained a deeper understanding of how PM affects human health, and evidence for adverse health effects has mounted, the NAAQS have been revised. In 1971, the EPA established a 24-h average NAAQS for TSP of  $260 \mu\text{g}/\text{m}^3$  and an annual average of  $75 \mu\text{g}/\text{m}^3$  (38). In 1987, the EPA replaced the TSP standards with requirements for  $\text{PM}_{10}$ : a 24-h average of  $150 \mu\text{g}/\text{m}^3$  and an annual average of  $50 \mu\text{g}/\text{m}^3$  averaged over three years (39). This change reflected an evolving understanding of the dosimetry of particles in the respiratory tract and improving measurement capability.

In the early 1990s, new evidence on PM, coming primarily from time-series studies, led to a further revision of the PM NAAQS. Motivated by the new time-series evidence and the EPA's tardiness in developing a new PM criteria document, the American Lung Association and other organizations successfully sued the EPA to perform the required review of the PM and ozone NAAQS, eventually leading to the 1997 revisions. The revised PM standards, largely reflective of epidemiological evidence coming from the time-series and longer-term cohort studies of mortality, added a new standard for  $\text{PM}_{2.5}$  (24-h standard of  $65 \mu\text{g}/\text{m}^3$  and an annual average of  $15 \mu\text{g}/\text{m}^3$ ), while retaining the  $\text{PM}_{10}$  standard (41). These changes to the regulatory requirements were based on an enhanced understanding of the potential health

effects associated with particles of smaller size. In these revisions to the NAAQS, the EPA also made modifications to the details of how exceedances and attainment are calculated. For instance, the 24-h  $PM_{2.5}$  standard is not to be exceeded by a three-year average of each year's 98th percentile of the 24-h values.

American Trucking and other industries challenged the EPA's 1997 revisions to the NAAQS for PM and tropospheric ozone (48, 103). A Washington D.C. Circuit Court found that  $PM_{10}$  is not an appropriate indicator for coarse particles and that the regulation of both  $PM_{10}$  and  $PM_{2.5}$  constitutes double regulation because the matter in  $PM_{2.5}$  would also be a part of  $PM_{10}$ . The EPA recently called for a risk-analysis plan for  $PM_{10-2.5}$  (the "coarse fraction" between 2.5  $\mu\text{m}$  and 10  $\mu\text{m}$ ) and  $PM_{2.5}$  and may revise the NAAQS to include a standard for the coarse fraction rather than  $PM_{10}$ .

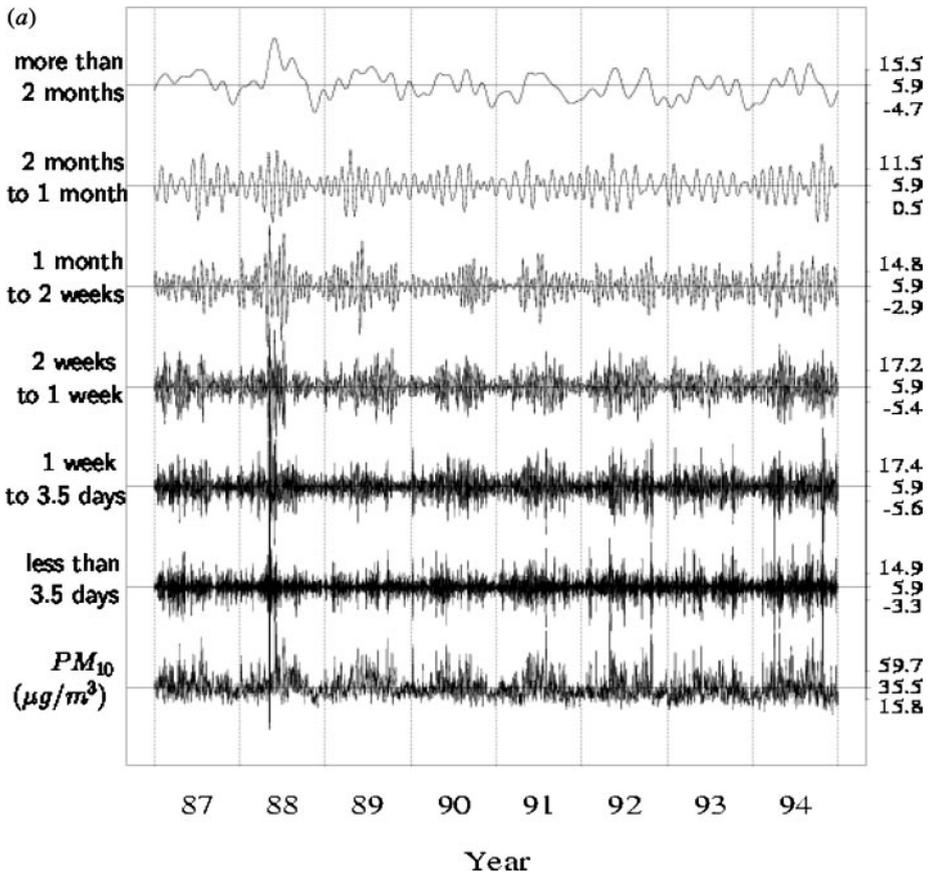
## EPIDEMIOLOGICAL STUDY DESIGNS: TIME-SERIES AND COHORT STUDIES

Several epidemiological study designs have been used to investigate air pollution and health (133). These studies use different methods for estimating health risks associated with variation in exposure across spatial and temporal gradients. Study types are often distinguished by their use of individual- or aggregate-level data on exposure, health, and modifying and confounding factors. A confounder, possibly a copollutant, is associated with both the outcome and the exposure of interest but is not in the causal pathway between the exposure and health endpoint. Most air pollution studies use exposure indicators aggregated over a specific geographic area, and some studies use a mixture of individual- and group-level exposures.

Some contemporary studies use individual-level health outcomes and risk factors but rely upon aggregate-level exposure (e.g., concentration recorded by nearest monitor) (78). These studies cannot account for differences in exposure based on subregional scale changes in pollution levels or people's activity patterns. As an example, the Children's Health Study is a 10-year prospective cohort study in southern California that combines multiple design approaches to investigate the effects of air pollution on ~6000 children in 12 California communities (51–52, 111, 118–119). Data regarding indoor air pollution and confounders are collected at the individual level, whereas outdoor air pollution is assessed at the community level. Geographical information systems (GIS) are used to assess differences in exposure within a community, such as varying exposure to pollution from traffic. This hybrid design combines comparisons among individuals' exposure with comparison among particular groups (e.g., across communities).

Most contemporary epidemiological research of air pollution's health effects uses either cohort or time-series approaches. Some studies are cross-sectional in design, and associations between environmental pollutants and health outcomes are assessed at one point in time. Time-series studies assess the effects of short-term changes in air pollution on acute health effects by estimating associations between

day-to-day variations in both air pollution and in mortality and morbidity counts. Thus, the data for daily time-series analysis include daily measures of the number of health events (e.g., daily mortality count), concentrations of PM and other pollutants (e.g., 24-h average  $PM_{10}$ ), and weather variables (e.g., daily temperature) for a given area. Short-term effects from time-series studies are estimated by using regression models where the concentration of PM is included in the model lagged for 0 (current day) to a few days. Recent methodological developments in time-series analyses allow estimation of subchronic health effects associated with changes in exposure averaged over a few weeks. The different timescales of pollution, mortality, and weather are shown in Figures 3a and b, which provide the daily  $PM_{10}$  concentrations and cardiovascular mortality for Pittsburgh as the



**Figure 3** (a) Frequency decomposition of daily  $PM_{10}$  levels [ $\mu g/m^3$ ] for Pittsburgh. Source: Dominici et al. (33). (b) Frequency decomposition of daily cardiovascular mortality for Allegheny County (Pittsburgh).

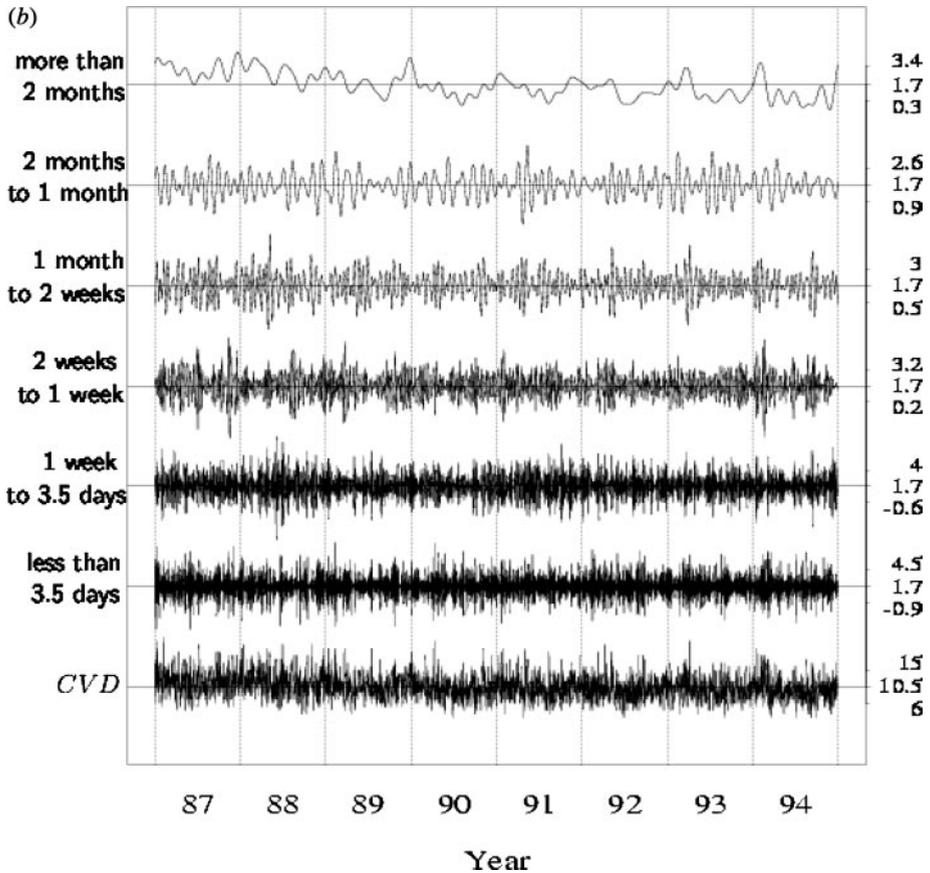


Figure 3 (Continued)

components representing various timescales. The first line represents the long-term fluctuations in the series that have a cycle larger than two months. The last line shows the daily data. The PM data shows seasonal behavior, with higher concentrations during the summer months. Cardiovascular mortality also shows cyclical behavior, with higher mortality in winter and an overall decline. A time-series analysis of these data would investigate the association between daily PM<sub>10</sub> and mortality, controlling for daily variations in temperature and seasonal trends.

Time-series studies assess the association of short-term variation in pollution and health outcomes within the same geographical area; thus, the population serves as its own control, and confounding by population characteristics is negligible as they are quite stable day to day. However, time-series studies can be affected by confounding bias arising from factors such as influenza epidemics and temperature, which vary on short timescales, and may be associated with pollution and health

outcomes. For example, PM concentrations in some regions peak during the winter months, as does the occurrence of respiratory illnesses, such as influenza. However, factors such as smoking are not likely confounders for time-series studies because they do not vary on short-term timescales and are not associated with air pollution levels.

Statistical concerns for estimating short-term effects from analyses of time-series data include: (a) controlling for observed and unobserved confounding factors, such as season and temperature, that might confound the true association between pollution and health; (b) accounting for serial correlation in the residuals that might underestimate statistical uncertainty of the estimated risk; (c) selecting the lag of the exposure variable; (d) accounting for exposure measurement error; and more in general, (e) assessing and reporting uncertainty associated with the choice of statistical model.

Regression models are used in time-series analysis to estimate the increase in risk for a health outcome, such as mortality, associated with a unit increase in ambient air pollution levels on a short-term basis. Frequently used statistical methods for time-series analysis include regression models with smooth functions of time and temperature to adjust for seasonal variations, long-term trends, and temporal changes in temperature that might bias the estimation of the health risk. The most common choices for the regression models are the generalized linear model (GLM) with parametric regression splines (e.g., natural cubic splines) and generalized additive models (GAM) with nonparametric splines (e.g., smoothing splines or loess smoothers). GLM uses iteratively reweighted least squares (IRWLS) to estimate the health risk, whereas GAM uses the backfitting algorithm. Previous analyses suggest that the difference between the health risk estimates from GAM and GLM depends on (a) the unknown underlying nonlinear functions of time, weather, and seasonality; (b) the degree of adjustment for confounding factors; and (c) the correlation between the time-varying predictors, also called concurrency (33).

In the regression formulation it is assumed that the daily number of deaths  $Y_t$  has an overdispersed Poisson distribution with expected value  $E[Y_t] = \mu_t$  where, for example,

$$\ln(\mu_t) = \beta_{PM} PM_{10,t-1} + [DOW] + s(T_t, 8) + s(D_t, 3) + s(Time, 7), \quad 1.$$

where  $PM_{10,t-1} = PM_{10}$  concentration on the previous day,  $DOW =$  indicator variables for day of week,  $T_t =$  temperature on day  $t$ ,  $D_t =$  dew point on day  $t$ ,  $s(T_t, 8) =$  smooth function of temperature with 8° of freedom,  $s(D_t, 3) =$  smooth function of dew point with 3° of freedom,  $s(Time, 7) =$  smooth function of time with 7° of freedom, and  $\beta_{PM} =$  log relative rate.

Time-series models can also include additional terms for other confounders, including other pollutants. Distributed lag models simultaneously include terms for multiple lagged measures of the pollutant, as shown in the following example, which includes terms for the effect of  $PM_{10}$  up to a week previously:

$$\ln(\mu_t) = \sum_{l=0}^6 \beta_{PM_{10,l}} PM_{10,t-l} + [DOW] + s(T_t, 8) + s(D_t, 3) + s(Time, 7). \quad 2.$$

Complementary information on longer-term associations of air pollution exposure with health outcomes is obtained from cohort studies. Cohort studies generally compare long-term average pollution levels (e.g., years) and adjusted mortality rates across geographical locations rather than day-to-day variations in pollution and mortality counts within a geographic location. In cohort studies, exposures to air pollution generally have been estimated by using place of residence as the link to air pollution concentrations at the community level. In most major cohort studies published to date, exposure is based on a single measure of air pollution that represents the exposure at a specific time or cumulative exposure. The measurement error associated with this approach can be estimated using nested validation studies with measurements made at home locations or using personal monitors. Model-based approaches using GIS have been incorporated into several recent studies (64–65). Cohort studies have incorporated discrete outcomes, including mortality, as well as changes in physiologic indicators such as lung-function level. Key advantages of the cohort study are the ability to assess individual risk factors of susceptibility and to adjust for individual-level confounders such as smoking status, race, body mass index, and occupation. Although the use of individual level information reduces the potential for residual confounding, cohort studies are limited by the adequacy of data on these confounders, the appropriateness of models used for confounder adjustment, and often the lack of personal exposure data.

A prominent cohort study of particulate air pollution and mortality was the Harvard Six Cities Study, which identified a relationship between air pollution levels and adjusted mortality rates in a cohort of more than 8000 adults in six U.S. cities. The adjusted mortality-rate ratio was 1.26 [95% confidence interval (CI) 1.08 to 1.47] comparing the most polluted city, Steubenville, Ohio, to the least polluted city, Portage, Wisconsin, which corresponds to an  $18.6 \mu\text{g}/\text{m}^3$  difference in  $\text{PM}_{2.5}$  averaged over  $\sim 9$  years (26). Another cohort study, the American Cancer Society (ACS)'s Cancer Prevention Study (CPS) II, considered  $\sim 500,000$  adults in 151 U.S. metropolitan areas (121, 126). The adjusted relative risk ratio for total mortality comparing the most polluted to the least polluted areas was 1.17 (95% CI 1.09 to 1.26), which corresponds to a  $24.5 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  averaged over  $\sim 5$  years.

## THE EVOLUTION OF THE TIME-SERIES APPROACH TO STUDYING AIR POLLUTION AND HEALTH

Early epidemiological evidence on the health effects of air pollution came largely from studies of extreme episodes, when high air pollution levels over several days were accompanied by noticeably large increases in mortality and morbidity (2, 24). Analyses of severe air pollution episodes examined the association between

pollution levels and mortality through correlations and found strikingly similar patterns between high air pollution concentrations over several days and excess morbidity and mortality in several industrial and urban locations including London, Donora, the Meuse Valley, and New York City (e.g., 7, 8, 50, 56–58, 99, 177).

As such high levels became less frequent, more formal time-series analysis was recognized as a useful tool for the study of air pollution and health (10). Many of these studies utilized growing public databases on health outcomes, weather variables, and pollution. Even in the decade following the 1952 London event, it was possible to track mortality and air pollution using daily data. In early studies, time-series data were analyzed by the use of linear regression methods. Researchers were aware of the need to address potential time-varying confounders such as weather and season, included such terms in models or stratified by season or temperature, and also attempted to account for day-of-the-week and holiday effects (e.g., 53, 54, 141).

Several early analyses examined the relationship between air pollution and mortality in London [e.g., the winters of 1958–1959 and 1959–1960 by Martin (95) and Martin & Bradley (96)], in part because the air quality in London was tracked after the London Fog of 1952. Mortality in London during this period was also investigated by MacFarlane who used visual inspection to examine the relationships among low temperature, influenza epidemics, air pollution, and mortality in London from the 1950s to the early 1970s (94). Mills (102) used time-series analysis to assess respiratory and cardiac deaths in Los Angeles. Other studies found associations between air pollution and cough and eye irritation (100), bronchitis (17, 82, 83), respiratory illness (3), and lung function (5, 6, 171, 172).

In the 1970s and 1980s, research on air pollution and health largely involved the use of cross-sectional designs comparing the morbidity and mortality rates across cities with different ambient air pollutant concentrations (e.g., 18, 49, 80, 89). Sprague & Hagstrom (170) used multiple regression techniques to investigate yearly air pollution levels and fetal and infant mortality rates in Nashville. By the late 1980s, researchers were considering the effects of particle size and source (e.g., 117). These studies identified associations between PM and health, as adjusted mortality rates were higher in more polluted cities, but much of this research was limited by the ecologic design and lacked information on potentially confounding and modifying variables (133).

Time-series approaches were also used in the 1970s and 1980s to investigate the association between short-term changes in air pollution levels and mortality counts (e.g., 62, 113, 140, 167) (see 67 and 90 for review). Some research revisited mortality in London (e.g., 68, 97, 113, 163). Additional time-series analyses were performed for New York City (9, 53, 63, 84, 85, 116, 139, 141), Tokyo (87), Philadelphia (182), and 117 U.S. metropolitan areas (81). Investigators recognized the importance of the potential confounding effects of: (a) the levels of other pollutants; (b) weather; and (c) seasonal variations in mortality due to influenza, which might be associated erroneously with the seasonal variations in PM. However, these investigators faced the challenge of adjusting for all of these confounders

properly, given the constraints of the then-available statistical models and computation. Proper adjustment of confounding is still a concern today. Techniques used by these investigators to adjust for the confounding effects of current and past temperature levels included use of a moving average of past temperature (e.g., 182), stratification by temperature (e.g., 53), correction for periods of heat waves (e.g., 141), and comparison of regions with similar weather but different pollutant levels (e.g., 54).

Although many of these studies had limited data, generally they found associations between air pollution and mortality, with higher levels of mortality accompanying higher levels of air pollution. Typical measures of PM were British Smoke or KM (carbonaceous material). One early time-series study of air pollution and mortality examined daily mortality in New York City for 10 years and daily levels of SO<sub>2</sub> and smoke shade, a measure of particulate pollution, adjusted for daily temperature (141). This study reported an association between air pollution levels and total, respiratory, and cardiac mortality. Additional time-series studies identified associations between daily particulate levels and health effects including mortality, heart disease, emergency room visits, and respiratory symptoms (e.g., 86, 98, 116, 128).

By the early 1990s, advances in computing hardware, statistical models, and software facilitated a new wave of time-series studies that were distinguished by more sophisticated approaches to account for temporal confounding. Many of these advances adopted statistical methods from other disciplines. Whereas earlier work addressed confounding through techniques such as stratification and model variables, newer approaches used harmonics and later, smoothing to remove temporal trends. Key studies in this period include analysis of mortality in Steubenville, Ohio, which used a random-effects model for yearly fluctuations of mortality and nonlinear models of weather's impact on mortality (160) and in Birmingham, Alabama using harmonics (trigonometric filtering) to remove long-term patterns of season and month (145). The regression model used by Fairley (47) to examine mortality in Santa Clara County, California included separate third-order polynomials for each year and a second-order model for temperature. Research on mortality and PM in Cincinnati used several methods of smoothing including natural splines, cubic polynomials fitted to intervals of time or temperature, and nonparametric smoothing (149).

Currently used statistical approaches for time-series analysis are generalized linear models (GLM) with parametric splines (101) and generalized additive models (GAM) with nonparametric splines (59). These regression techniques estimate the association between short-term changes in air pollution and short-term changes in mortality, while smoothing for fluctuations in time-varying confounders such as season, weather variables, and other trends. These methods are more flexible than earlier approaches in their assumptions regarding temporal confounders and effects on mortality.

The new time-series studies provided compelling evidence that short-term changes in even low levels of air pollution could be associated with short-term

changes in mortality at a single location. Several studies in the early 1990s identified associations between cause-specific mortality and air pollution using Poisson regression techniques, which are appropriate for analyzing count data such as mortality. The measure of PM was generally TSP (e.g., 73, 144, 159, 160), COH (e.g., 47), or PM<sub>10</sub> (e.g., 27, 125, 145).

Initially, the findings of these studies were quite controversial, in part because of the novelty of their methods and also because of the implications of their findings. Critics argued that the observed associations could have resulted from the specification of statistical models, with a bias toward those giving larger effect estimates and hence more likely to be statistically significant, and also from uncontrolled confounding by other time-varying factors, particularly weather (70).

Additionally, publication bias could have contributed to the reporting of results that show positive associations, whereas null findings would go unreported. However, over time, the associations were observed in data from numerous locations analyzed with differing approaches. Furthermore, the Health Effects Institute arranged for replication of several key data sets and analyses, which were published in 1995 as the Criteria Document was in development (134). This model of commissioned reanalysis was later applied to the cohort study data as well (76). Several studies have found that alternative approaches to control for confounding and effect modification by weather did not greatly alter effect estimates for pollution and mortality (124, 137). However, an investigation of bias from model selection and residual confounding in King County, Washington found the absolute amount of bias to be small in absolute terms, but on the same order of magnitude as the estimated health risk (93). Time-series studies have now identified associations between PM and mortality in many cities in the U.S. and other countries including Poland (69), Spain (4), France (187), the Netherlands (66), Mexico (91), Thailand (114), Chile (115), and the Czech Republic (120).

As experience with these methods has grown, so has an appreciation of the sensitivity of model results to the details of model specification and of subtle, technical issues that were poorly recognized previously (130). Uncertainty still exists with regard to the degree of control for temporal confounding. The choice of statistical model (e.g., GAM or GLM) was also found to affect the magnitude of the estimated effect. A recent paper reported that concurvity (the nonparametric equivalent to collinearity) in time-series studies of mortality and PM can result in underestimation of the variance of effect estimates (127).

The sensitivity of findings to details of model specification was further highlighted by the identification of a problem with the default implementation of a commonly used statistical software package, S-plus (33, 130). When the estimated regression coefficients are small and confounding factors are modeled using two or more nonparametric smoothing functions, the default settings for generalized additive models in the S-plus *gam* function were not sufficiently strict for assuring convergence of the algorithm used for estimating pollution health effects. Inappropriate implementation of *gam* for time-series analyses using default settings might bias the relative rate estimates. In addition, *gam* estimates the standard errors of

the relative rates through an approximation that assumes the smooth part of the model is linear and thus understates statistical uncertainty. An S-plus package, *gam.exact*, has been developed to allow a more robust assessment of the uncertainty of air pollution effects (32). The improved analyses show lower air pollution effects but still demonstrate a consistent harmful impact of PM on daily mortality. Thus, the key health implications of results remain unchanged (22). Reanalysis of the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) work indicates that daily mortality from all causes is increased 0.21% per 10- $\mu\text{g}/\text{m}^3$  increase in PM<sub>10</sub>, rather than the original estimate of 0.4% generated using S-plus default parameters (61). Other research was reanalyzed as well, and results are summarized in a Health Effects Institute report (61).

The use of multicity studies is a major advance in time-series research on air pollution. Results from single-city studies are potentially limited in their generalizability to other areas because the statistical approaches used to analyze data vary with each study and the city and population characteristics may differ. With multicity studies it is also possible to map variation in the magnitude of the effect of air pollution across geographic regions and to explore the sources of this variation. The following is an example of a hierarchical model in which the estimates generated by city-specific models, such as shown in Equations 1 or 2, are combined in a second stage to produce a regional or national effect estimate:

$$\beta_R^C = \beta_R + \sum_{j=1}^P \alpha_j x_j^C + \varepsilon_R^C, \quad 3.$$

where  $\beta_R^C$  = log relative rate for the city  $C$  in region  $R$ ,  $\beta_R$  = log relative rate for the region  $R$ ,  $x_j^C$  = city-specific characteristic  $j$  for city  $C$  (e.g., population density, pollutant concentrations, temperature), and  $\varepsilon_R^C$  = error.

The use of standardized approaches to examine time-series data from numerous cities allows a more comprehensive assessment of the air pollution health effects than meta-analyses of separate studies of individual cities that may have used inconsistent methods. More conventional meta-analysis also has been used to produce a weighted average of single-city results (e.g., 88, 145a). Unlike traditional meta-analysis that combines published findings of individual cities, multicity studies are not subject to publication bias resulting from failure to publish insignificant or negative results. Some cities included in multicity research have not been studied previously with time-series analysis. Multicity studies also benefit from consistent data analysis and model specifications and can examine systematically regional differences, which is especially valuable given the heterogeneous nature of PM (45). Another advantage is that city-specific confounding biases are likely to average out when national averages are estimated.

Several studies have examined the effects of PM across multiple cities (e.g., 11, 15, 21, 23, 29, 30, 36, 37, 74, 75, 79, 104, 105, 153, 155, 157, 158, 162, 165, 176a), including two large-scale projects: the Air Pollution and Health: A European Approach (APHEA) (71, 72) and NMMAPS (131, 135).

## RESULTS OF TIME-SERIES STUDIES OF MORTALITY AND PARTICULATE MATTER

Numerous time-series studies, in different locations and using various model specifications, have provided evidence that PM and mortality are associated. Results of time-series studies of PM are summarized in the EPA's Air Quality Criteria Documents (44, 45). The 1996 Air Quality Criteria Document incorporated results from 35 PM and mortality time-series studies published between 1988 and 1996 (44). These studies used a range of statistical approaches; however, only five used *gam* with the default convergence criteria. Thus, the EPA concluded that the studies could be summarized without undue bias relating to the problems of the default *gam* convergence criteria. Based on these studies, a  $50\text{-}\mu\text{g}/\text{m}^3$  increase in 24-h  $\text{PM}_{10}$  is associated with a 2.5% to 5% increase in premature non-accident mortality for the general population, with higher risks for the elderly and those with preexisting cardiopulmonary conditions (44). Time-series analysis of the cities used in the Harvard Six Cities study indicated that fine PM appears to be associated with a 3% increase in total mortality for a  $25\text{-}\mu\text{g}/\text{m}^3$  increase in daily  $\text{PM}_{2.5}$  (74, 157, 161).

Of the 80+ time-series studies on PM and mortality published since 1996, approximately 70% used GAM methods, quite likely with the default convergence criteria. Almost all of these showed statistically significant associations between short-term PM concentrations and mortality. Of the studies that did not use GAM methods or were reanalyzed using appropriate statistical methods, the estimated effects are largely consistent with earlier studies with a 1% to 8% increase in mortality for every  $50\text{-}\mu\text{g}/\text{m}^3$  increase in daily  $\text{PM}_{10}$  and a 2% to 6% increase in daily mortality per  $25\text{-}\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  (45).

From the time-series mortality literature, the EPA concluded that the effect estimates for PM and mortality (*a*) are unlikely to be biased to a large degree by inadequate control for temporal trends such as seasonal effects, although some research (e.g., 106, 136) found different PM effects by season; (*b*) are unlikely to be confounded by weather as evidenced by synoptic weather models; (*c*) may possibly be confounded or modified by copollutants because although the effect of PM on mortality generally remains when other pollutants are considered, it is often somewhat reduced; and (*d*) show no evidence for a threshold effect (45). However, possible publication bias in studies of PM and mortality was indicated by a comparison of NMMAPS (before reanalysis) and 21 individual studies, which found that 93% of the individual studies' results showed positive associations, 79% of which were statistically significant, whereas only 72% of the NMMAPS cities had positive associations, of which 13% were statistically significant (168).

Few studies have investigated risks of PM in relation to chemical composition; however, time-series analysis of the cities included in the Harvard Six Cities Study exploring size fraction of PM ( $\text{PM}_{2.5}$ ,  $\text{PM}_{10/15}$ , and  $\text{PM}_{10/2.5}$ ), sulfates, and  $\text{H}^+$  found  $\text{PM}_{2.5}$  to be the index most significantly associated with mortality (74, 157, 161). Analysis of daily mortality and the elemental composition of various size fractions

of PM indicated that  $PM_{2.5}$  combustion particles from mobile and coal combustion sources were associated with mortality (79). Other evidence suggesting an effect of small particles includes studies of hospital admissions and fine particles (45).

The APHEA project, supported by the European Commission, studied the short-term effects of air pollution on human health in 15 European cities. A primary goal of the study was to analyze the time-series data under a common framework so that results would be comparable. APHEA researchers used time-series analysis to estimate the relative risk of total, respiratory, and cardiovascular disease mortality and hospital admissions associated with daily changes in the concentrations of several pollutants. City-specific estimates were combined to estimate regional effects. For western European cities, an increase of  $50 \mu\text{g}/\text{m}^3$  in daily  $PM_{10}$  was associated with an estimated 2% increase in total daily mortality (95% CI 1% to 3%). In central eastern European cities, a  $50\text{-}\mu\text{g}/\text{m}^3$  increase in daily  $PM_{10}$  was associated with a 4% (95% CI 0.3% to 9%) increase in total daily mortality. Results for Black Smoke were higher for western European cities than for central eastern European cities (72). Subsequent analysis to investigate regional differences, confounding, and sensitivity of the results to model specifications provided larger pollution effect estimates and indicated that part of the heterogeneity in regional results was due to the statistical approach (138).

The second phase of this work, APHEA 2, examined mortality and pollution for 29 European cities. A  $10\text{-}\mu\text{g}/\text{m}^3$  increase in daily  $PM_{10}$  or Black Smoke levels was associated with a 0.6% increase (95% CI 0.4 to 0.8%) in total daily mortality (71). The concentration of  $NO_2$  was found to modify the relationship between PM and mortality, with a stronger association at high  $NO_2$  levels.

NMMAAPS, sponsored by the Health Effects Institute, examined the effect of PM on mortality and hospital admissions (131, 135). Initial analyses were based on methods development and estimation of relative rates of mortality associated with short-term exposure to  $PM_{10}$  in 20 large U.S. cities (37, 129, 131, 135). Further analyses were carried out to estimate relative rates for 90 large U.S. cities from 1987 to 1994 (30, 34) and on average for the entire nation. Additional methodological work included the development of statistical methods to (a) adjust for exposure measurement (36, 186); (b) investigate the question of mortality displacement (35, 185); (c) test the hypothesis of a nonlinear relationship between air pollution levels and mortality, including the possibility of the existence of a threshold effects (23, 30, 154); and (d) estimate city-specific, regional, and national relative rates, taking into account heterogeneity (28, 129, 135).

One of the most important contributions of NMMAAPS was the development and application of new methodology to address confounding and measurement error and to combine evidence. The NMMAAPS researchers developed a unified statistical framework to combine city-specific estimates to provide a national estimate of the impact of changes in daily  $PM_{10}$  on daily mortality (33, 34, 37, 129, 131). First, the relative change in mortality associated with changes in air pollution levels was estimated separately for each city using generalized additive models. Next, a Bayesian hierarchical model was used to produce regional and national average

estimates taking into account the heterogeneity of the health effects within and across regions. The results showed that a  $10\text{-}\mu\text{g}/\text{m}^3$  increase in daily average  $\text{PM}_{10}$  was associated with a 0.21% increase in total mortality (95% CI 0.04 to 0.33), with slightly larger effects for mortality related to heart and lung disease. Figure 4 provides the city-specific, regional, and national effects for the percent change in mortality associated with a  $10\text{-}\mu\text{g}/\text{m}^3$  increase in daily  $\text{PM}_{10}$ . The largest regional effect was for northeastern United States (61, 135).

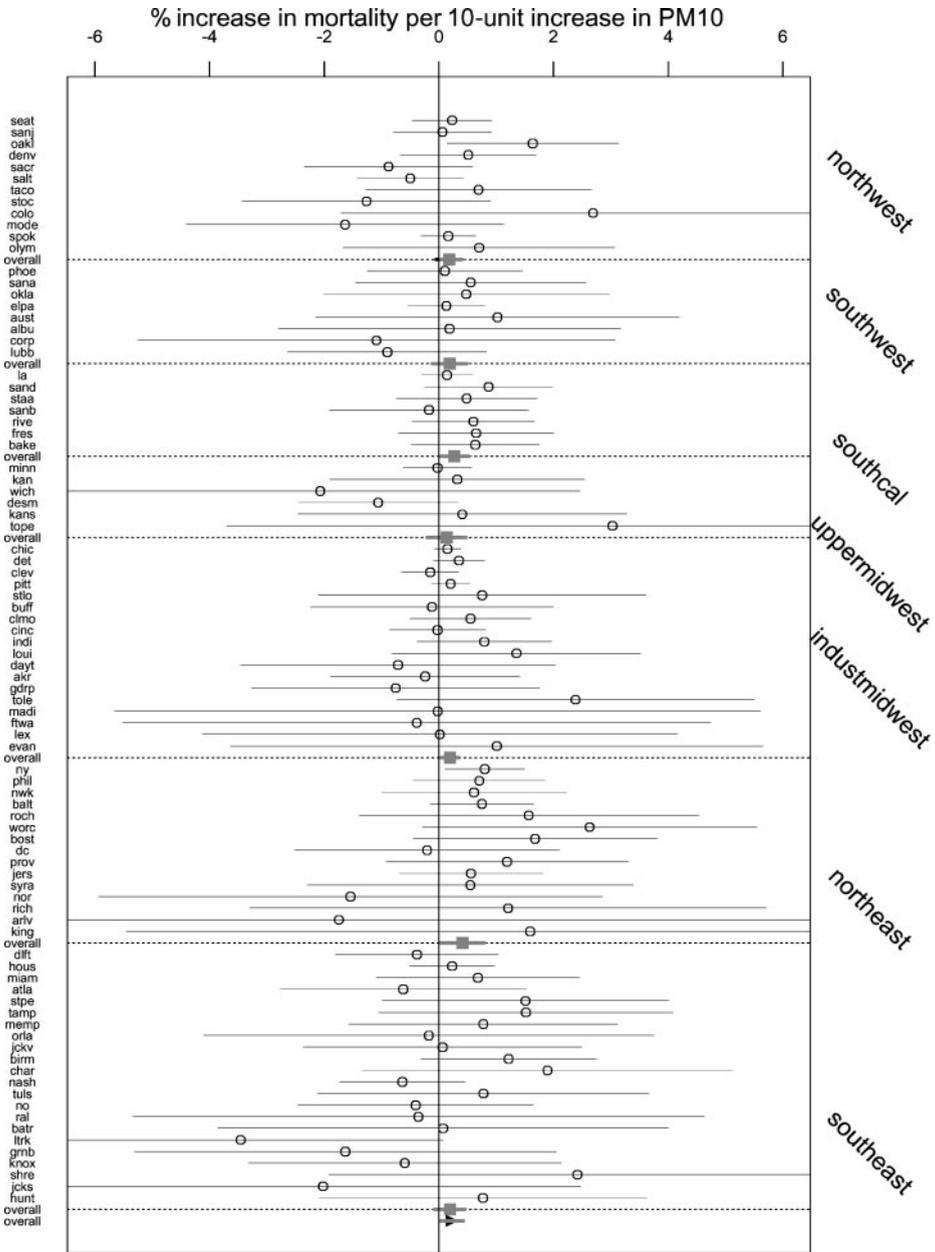
One approach for the future is Air Pollution and Health: A Combined European and North American Approach (APHENA), which builds upon the multicity studies conducted in the United States and Europe (NMMAPS and APHEA). A primary goal of APHENA is to characterize the effects of air pollution on mortality and morbidity in Europe and North America using a common analytic framework and building upon previous work in Europe, the United States, and Canada. This approach will explore the spatial variation in the health effects of air pollution.

## CURRENT AND FUTURE DIRECTIONS IN TIME-SERIES PARTICULATE MATTER RESEARCH

Time-series methods have advanced greatly since the earliest studies. For example, multisite time-series analyses have estimated regional and national averages of pollution effects, which are important pieces of evidence for setting air pollution quality regulations. Availability of national databases in pollution, weather, and health, and the progress in computational tools and statistical methods, have made possible the estimation of national average pollution effects and the exploration of potential sources of heterogeneity in the effects of air pollution across countries or regions. Time-series studies have also benefited from the work of complementary disciplines, especially with respect to PM speciation and biological mechanism. However, interpretation of the findings of time-series analysis of PM needs to take several challenging issues into consideration, including possible uncontrolled confounding and the resolution of seemingly conflicting results from time-series and cohort studies. Additionally, interpretation of time-series studies is made more difficult by the need to consider the degree of mortality displacement caused by air pollution exposure.

### Mortality Displacement/Years Life Lost

A key uncertainty in interpreting the findings of time-series studies is the extent of life shortening attributable to short- and long-term pollution exposure, i.e., how many lives are shortened and by how much is the time of death advanced by pollution? If the deaths attributable to air pollution exposure occur only among those frail persons who would otherwise have died a few days later, their lifespans are not greatly shortened and the public health significance of pollution health effects is reduced. Such a short-term effect would lead to an association between



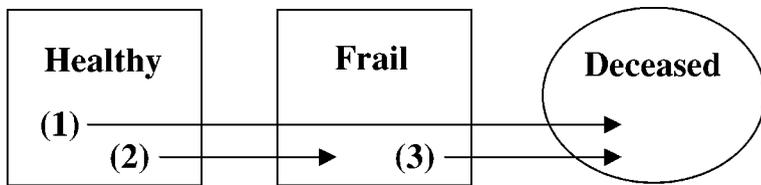
**Figure 4** NMMAPS city, regional, and national estimates for the percent change in mortality per 10- $\mu\text{g}/\text{m}^3$  increase in daily PM<sub>10</sub>. Source: Health Effects Institute (61). Note: The solid squares with bold segments represent the posterior means and 95% posterior intervals of the pooled regional effects. The triangle at the bottom of the figure represents the overall PM<sub>10</sub> effect for 88 U.S. cities.

air pollution and mortality. This phenomenon of only brief life shortening has been called mortality displacement or “harvesting,” an unfortunate term.

Mortality from air pollution can be quantified using several approaches. Excess deaths, also called extra deaths or premature deaths, are the number of deaths that occurred with exposure minus the number of deaths that would be expected without exposure (or with a lesser exposure) for a given timeframe. This measure does not consider the degree of prematurity of the death. Potential life years lost or the loss-of-life expectancy is the life expectancy without exposure minus the age of death under exposure, usually reported as the average over a population. This approach accounts for the ages of those who die and depends on the age distribution of the population. Some studies aim to quantify the impact of pollution on mortality by estimating the monetary value of excess deaths or of potential life years lost (40, 42).

The years of life lost will depend on how PM affects mortality. Air pollution exposure could raise mortality rates in several ways: (a) increased risk of underlying diseases leading to frailty and higher short-term risk of death among frail individuals; (b) increased risk of chronic diseases leading to frailty, but not related to the timing of death; or (c) increased short-term risk of deaths among frail individuals, but not related to the risk of chronic disease (77) (Figure 5). Time-series analysis can capture the first and third of these effects but cannot estimate the influence of air pollution on increased risk of chronic conditions. Cohort studies can capture the first two of these effects but cannot examine increased short-term risk of death among the frail population. Cohort studies, unlike time-series, can be used to estimate the years of life lost.

Time-series data can be used to evaluate the magnitude of mortality displacement: If pollution exposure only advances death by a few days, then an association



Possible relationships between air pollution and mortality [as described in Kunzli et al. (77)]:

- (1) Increased risk of underlying diseases leading to frailty and higher short-term risk of death among frail individuals
- (2) Increased risk of chronic diseases leading to frailty, but not related to the timing of death
- (3) Increased short-term risk of deaths among frail individuals, but not related to the risk of chronic disease

**Figure 5** Model of mortality for the healthy and frail populations.

would only be detected at very brief timescales, but not on longer timescales, and would not have broad public health implications (45). Under the assumption that only frail persons are affected by air pollution, the air pollution episode depletes the pool of the frail people, and thus the increase in mortality immediately after the air pollution episode would be followed by a decrease in mortality that persists until the pool of the frail people is replenished. However, evidence from time-series analyses is inconsistent with this hypothesis and shows an association between air pollution and mortality at longer timescales as well (35, 154, 185). Sustained exposure to air pollution may lead to an increase in frailty and to the occurrence of a health outcome (e.g., death or hospitalization) that is unrelated with short-term air pollution exposure. Because time-series studies estimate short-term effects associated with temporal variations in air pollution and health, they are unable to detect such chronic health events and the corresponding life-span indicators.

Strategies to assess the degree of mortality displacement involve examining pollution effects at multiple timescales. A study of mortality in Boston classified data into three time-series representing seasonal and long-term trends, short-term trends, and immediate changes. The effect of mortality displacement on different timescales was explored by varying the cutoff between the three different timescales (154). Another study used a multi-day (15, 30, 45, and 60 days) smoothing of mortality and hospital admissions data with seasonal trends removed (156). An analysis of mortality displacement for Philadelphia from 1983 to 1988 identified a decrease in deaths after pollution episodes, indicating some harvesting, but not enough of a decline to alter the risk estimate of daily mortality from TSP (L.A. Cifuentes, L.B. Lave, manuscript in preparation). Mortality displacement for daily mortality in Erfurt, Germany was investigated using an interaction term of pollution and the mean number of deaths for the previous 2 to 21 days (173). An analysis of the mortality displacement of air pollution decomposed the information into distinct timescales and examined the effect using information that excluded short-term effects subject to harvesting (185). A multicity analysis with a hierarchical modeling approach used a distributed lag model with up to a 40-day lag for air pollution effects as part of the APHEA 2 study (183). Each of these studies indicated that air pollution advances adverse health outcomes by more than a few days, and therefore has a much larger public health impact than would be the case under the harvesting theory.

## Resolution of Results from Cohort and Time-Series Studies

Estimates of the impact of PM on mortality from time-series studies provide smaller estimates than those from cohort studies. For example, the reanalysis of NMMAPS data found a 0.31% (95% CI 0.15 to 0.47%) increase in cardiovascular and respiratory mortality for a  $10\text{-}\mu\text{g}/\text{m}^3$  increase in the previous day's  $\text{PM}_{10}$  level, adjusted for time-varying confounders such as weather and influenza epidemics (61). The ACS II study found approximately a 4%, 6%, and 8% increase in total, lung cancer, and cardiopulmonary mortality, respectively, for a

10- $\mu\text{g}/\text{m}^3$  increase in long-term average  $\text{PM}_{2.5}$ , adjusted by individual risk factors such as age, gender, education, and smoking (121). Although the cohort and time-series studies estimate different relationships between health and pollution, resolution of their results is important to policy makers who must establish regulatory limits. Cohort studies generally have larger estimates than time-series studies, which may indicate that long-term exposure to PM has a larger effect on human health than short-term exposure. One strategy to better understand how short-term and long-term exposure affects human health is to extend the time-series modeling approaches to examine comprehensively the impacts of exposure over different timescales in a single study (184).

## Confounding in Time-Series Studies

Failure to adequately address confounding could result in observation of a spurious association that represents true events but does not reflect a causal relationship between the exposure and the outcome. Likely confounders for the relationship between PM and mortality are meteorological variables and copollutants. Temperature affects emissions patterns and thereby PM concentrations and mortality. For example, cold winter temperatures generally result in higher PM concentrations owing to elevated energy use. Stable atmospheric conditions resulting from temperature inversions are common in colder temperatures, causing higher pollutant concentrations.

Additionally, unmeasured confounders such as seasonal trends can affect mortality and pollution concentrations. Copollutants such as  $\text{CO}$ ,  $\text{NO}_2$ ,  $\text{SO}_2$ , and  $\text{O}_3$  are potential confounders because they have been associated with adverse health effects; their concentrations may also be correlated with PM owing to common sources and meteorological factors such as wind patterns. The pollutants  $\text{SO}_2$  and  $\text{NO}_2$  contribute to the formation of PM, leading to correlation among the concentrations of these pollutants (45). Other possible confounders include long-term trends of disease survival because both air pollution levels and the severity of major diseases, such as cardiovascular disease, have declined. Individual variables such as smoking history are not likely to confound time-series studies because they are generally not related to pollution levels and they are likely to vary slowly with time. Further complicating the assessment of the effect of pollution on mortality is the need to consider possible nonlinear effects of temperature on mortality and the possibility that other pollutants not only confound but modify the effect.

As methodology and computational ability have advanced, time-series analysis has accounted for potential confounding in more sophisticated ways, including the application of smoothing techniques starting in the mid 1990s (e.g., 149). Smoothing allows control for observed and unobserved time-varying confounding factors. Researchers must choose an appropriate model including smoothing parameters. Recent efforts have explored the sensitivity of results to changes in model specification, such as the degree of smoothing (32).

## Other Research Needs

Time-series methods continue to evolve with methodological advances and our greater understanding of air pollution's effects on human health. The National Research Council Committee on Research Priorities for Airborne Particulate Matter discusses key research priorities in several reports (108–110). Two of the crucial research concerns are the need to determine what properties of PM are associated with greater risk for adverse health effects and to better understand the implications of using ambient indicators as a surrogate for exposure. Other critical research needs are further characterization of the effects on the general population and susceptible subpopulations, emissions sources, deposition and fate of PM in the respiratory tract, combined effects of PM and other pollutants, and biological mechanisms.

An important assumption in many epidemiological studies of air pollution is a consistent, harmful effect from PM, as defined by size, without attention to the heterogeneous nature of PM. This heterogeneity hampers comparison across studies for different locations, because differences in risk estimates may be due to a difference in PM characteristics. The actual toxicity-determining characteristics, both physical and chemical, of PM are uncertain, with possibilities including size, metals, acidity, organics, sulfates, or some particular combination of these characteristics (60). The harmful components of PM may differ by health endpoint or subgroup of the population. Multicity studies and research incorporating speciation or source apportionment somewhat address these concerns (e.g., 162).

Increased surveillance of air quality through monitoring networks and speciation data will help to distinguish among the health consequences from various aspects of PM. The EPA Particulate Matter Supersites Program is an ambient monitoring program intended to better characterize PM and to support health effects and exposure research. This physical and chemical characterization is achieved through detailed atmospheric measurements of PM constituents, precursors, copollutants, atmospheric transport, and source categorization. The program also supports the evaluation of multiple methods of characterizing PM. Supersites have been located in Atlanta, New York City, Baltimore, Pittsburgh, St. Louis, Houston, Fresno, and Los Angeles (e.g., 169, 178).

Epidemiological studies generally use ambient air pollution concentrations as surrogates for actual exposure. This method assumes that all individuals in a geographic area experience identical exposure and ignores differences in activity patterns, indoor/outdoor concentrations, and subsatial variability. The potential for exposure misclassification is especially critical among subgroups such as the elderly whose activity patterns may differ from the general population (e.g., more time spent indoors). Additionally, the use of monitoring networks within epidemiological studies varies based on the availability of data. Exposure is typically estimated using data from a single monitor, a simple average of multiple monitors, or a weighted average of multiple monitors. The use of ambient monitoring data as a substitute for individual exposure likely misses important distinctions in different people's exposure. Therefore, this approach could introduce bias in the

estimates of health effects. Measurement error correction models have been developed to explore these effects (36, 186). Personal exposure studies, which estimate individual-level exposure to pollution, can also address this issue.

## CONCLUSIONS

Research on the association between ambient exposure to air pollution and human health has progressed from the descriptive investigation of changes in morbidity and mortality following extreme acute episodes, such as in London in 1952, to the sophisticated analysis of national databases of time-series data of pollution concentrations, cause-specific health data, and covariates such as weather. This progress has been facilitated by advances in statistical techniques including the use of smoothing approaches to adjust for temporal-varying covariates and sensitivity analysis of model specification such as the inclusion of multiple pollutants and the degree of smoothing. The metric used to define PM has been refined, moving from TSP and PM<sub>10</sub> to PM<sub>2.5</sub>, the coarse fraction, and ultrafine particles. Major findings of time-series analysis, in conjunction with those from other designs such as cohort studies and human exposure studies, have provided strong evidence supporting an association between PM levels and adverse public health impacts. Epidemiological evidence from time-series studies has played a crucial role in the setting of regulatory health-based standards.

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