Particulate Air Pollution and Daily Mortality

Analyses of the Effects of Weather and Multiple Air Pollutants

The Phase I.B Report of the Particle Epidemiology Evaluation Project

Health Effects Institute

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HEI Statement

Particulate Air Pollution and Daily Mortality: Analyses of the Effects of Weather and Multiple Air Pollutants

BACKGROUND

The Health Effects Institute began the Particle Epidemiology Evaluation Project in 1994 to evaluate the emerging epidemiologic evidence of a relation between particulate air pollution and daily mortality. A growing number of studies reported that daily mortality rates rose in association with levels of particulate air pollution below the current National Ambient Air Quality Standard (NAAQS) for particulate matter. Some investigators interpreted their findings as indicating that particulate air pollution has a causal effect on increases in daily mortality. Critics disputed this interpretation, and questioned whether other scientists could replicate the results. Some critics asserted that the reported associations might be artifacts of the particular statistical methods used, or might be due to incomplete statistical adjustment for the effects of weather factors or other air pollutants.

This controversy had important regulatory implications because the U.S. Environmental Protection Agency (EPA) was in the midst of reviewing the scientific evidence in support of the NAAQS for particulate matter, and the studies of particulate air pollution and daily mortality had become a central focus in that review. In this context, the EPA and interested parties from private industry and nongovernmental organizations encouraged HEI to assess the validity of key epidemiologic studies and to clarify the implications of their findings.

Recognizing the tight time constraints imposed on the EPA for its review, HEI's Oversight Committee for the project separated it into two phases; Phase I was subsequently carried out in two parts by Drs. Jonathan M. Samet and Scott L. Zeger and their colleagues at the Johns Hopkins University School of Hygiene and Public Health. Briefly, in Phase I.A, the investigators (1) reconstructed from original sources the data set for Philadelphia used in earlier studies and confirmed previous numerical results from analyzing these data; (2) developed an analytic approach (including new statistical methods) based on the Philadelphia data set; and (3) applied this approach to data sets for six locations: Philadelphia; Utah Valley; St. Louis, MO; Eastern Tennessee; Birmingham, AL; and Santa Clara County, CA.

In Phase I.B, the subject of this Special Report, the investigators (1) compared approaches for controlling the effects of weather variables when analyzing the connection between air pollution and daily mortality, primarily focusing on Synoptic Weather Categories, an approach newly proposed by Dr. Laurence S. Kalkstein of the University of Delaware; and (2) evaluated the association between particulate air pollution and daily mortality in the Philadelphia metropolitan area using statistical models that included data for five pollutants regulated under the Clean Air Act Amendments of 1990 (referred to as criteria pollutants).

In Phase II, which began in December of 1996, the investigators will extend the Phase I analyses to address scientific questions with important public health and regulatory implications, such as the impact of air pollution on years of life lost, and will develop statistical methods to address the impact of errors in measuring exposure in daily time-series studies.

This Statement, prepared by the Health Effects Institute and approved by its Board of Directors, is a summary of Phase I.B of the Particle Epidemiology Evaluation Project sponsored by HEI from 1994 through 1996. Dr. Jonathan M. Samet and colleagues of the Johns Hopkins University School of Hygiene and Public Health in Baltimore, MD and the University of Delaware in Newark, conducted the study, *Air Pollution, Weather, and Mortality in Philadelphia 1973–1988*. The following Special Report contains the Investigators' Report, a Commentary on the study prepared by the Oversight Committee of the Particle Epidemiology Evaluation Project, and Comments from the Health Review Committee. To order copies of this Special Report, refer to Related HEI Publications at the back of the book.

APPROACH

To meet the Phase I.B objectives, the investigators focused on two questions. First, could different analytic approaches used to control the effects of weather variables change the association observed between air pollution and daily mortality rates? Second, how might the association between particulate air pollution and daily mortality change if all criteria pollutants found in a given locale were analyzed simultaneously in the same statistical model?

To answer the first question, the investigators chose three different approaches to characterize weather factors in statistical models, and applied them to the Philadelphia data set from 1973 through 1980 to control the influence of weather variables in their analyses. The Philadelphia data included ambient air pollution exposure levels and daily mortality rates for relevant (cardiac and pulmonary) causes of death. The first approach reduced a relatively large number of meteorologic variables to a smaller set of summary (or synoptic) categories that describe daily weather patterns in a particular locale (referred to as the Synoptic Categories approach). The second approach used statistical regression methods to describe the temporal relation between mortality and the previous day's absolute and dew-point temperatures; a mathematical equation for that temporal relation was then incorporated into a model of daily mortality (referred to as the LOESS model; this approach also had been used in the Phase I.A analyses). The third approach incorporated into the statistical model of daily mortality the current and previous day's absolute and dew-point temperatures, plus indicator terms for hot and cold days (referred to as the S-D model because it had been used by Drs. Joel Schwartz and Douglas W. Dockery of the Harvard School of Public Health in their earlier analysis of daily mortality in Philadelphia).

To answer the second question, the investigators estimated what each individual air pollutant contributed to daily mortality in Philadelphia, a location for which data were available over a 15-year period (from 1974 through 1988) for all criteria air pollutants, and where levels of these pollutants were correlated with one another to varing degrees throughout the period of the study. The investigators developed statistical models to control weather and long-term trends in mortality, and then incorporated air pollution data into the models. These models revealed important features of the data set, such as differences in long-term mortality trends for people older than 65 years and those younger, and nonlinear patterns in the magnitude and timing of weather's effects on mortality.

Next, they estimated air pollution's effects on daily mortality, first for each of five pollutants separately (total suspended particles, sulfur dioxide, nitrogen dioxide, ozone, and carbon monoxide), then in pairs, and finally all pollutants together. Where possible, model building was guided by current knowledge of toxicology, pathophysiology, and clinical medicine, and by a statistical criterion of how well a given model described the observed daily mortality. However, the model that included all five pollutants and was "best" according to statistical criteria produced estimates for the effects of some pollutants that did not conform to prior expectations based on toxicologic knowledge. For example, nitrogen dioxide was estimated to have a statistically negative (that is, beneficial) effect on the mortality rate (meaning the rate fell, which could be misinterpreted to mean that nitrogen dioxide could somehow have a beneficial effect on human health). A result such as this most likely reflects the model's attempts to deal with inaccuracies in the measurement of an air pollutant that is closely correlated with nitrogen dioxide, and should not imply a biologic interpretation.

RESULTS AND INTERPRETATIONS

Phase I.B successfully explored the sensitivity of the air pollution--mortality relationship to different analytic approaches for statistically controlling the effects of weather on mortality, and the consequences of incorporating multiple pollutants when modeling the air pollution--mortality relationship in a single locale.

In response to the first question, the investigators found that neither the Synoptic Categories approach nor the S-D and LOESS approaches used in Phase I.A analyses substantially altered the air pollution--mortality association observed in Philadelphia. In addition, they could find no meaningful pattern of variation in the

relative risks calculated under different weather conditions, regardless of the approach used to characterize weather.

In response to the second question, the multipollutant analyses confirmed two important findings. First, certain indexes of air pollution are associated with increases in daily mortality rates: ambient concentrations of total suspended particles and sulfur dioxide (which confirmed the findings of Phase I.A), and ozone (which had not been included in the Phase I.A analyses). Second, in Philadelphia during this time period, and given the correlation among a number of pollutants, no single criteria air pollutant could account completely for the observed increases in daily mortality.

However, the results of the current analyses also differ from the earlier findings. First, although the same range of concentrations of total suspended particles was still associated with a small relative increase in the daily mortality rate, the magnitude of this increase was not as large as that seen in earlier studies. This change is most likely attributable to more flexibly modeling long-term mortality trends, and particularly to allowing the long-term trends to vary for different age groups. Second, the season-specific associations between pollutants and daily mortality, observed in the Phase I.A analyses and by other analysts, were not found in Phase I.B; this may be the result of improved models for weather and long-term mortality trends. Nonetheless, seasonal variation in the effects of air pollutants remains plausible and requires further study.

The analyses of the Philadelphia data conducted during Phases I.A and I.B have limitations that are common to most studies of air pollution and daily mortality. First, we would like to be able to interpret these results in terms of how personal exposure to air pollution might affect an individual's risk of mortality. However, these analyses rely on measurements of ambient pollutant levels from centrally located monitors, which may not be accurate assessments of an individual's actual exposure. The inaccuracies in exposure measurements may introduce errors in mortality risk estimates that are difficult to quantify. Second, the amount of life-shortening that underlies the increased mortality rates associated with air pollution has not been estimated, and the statistical approaches to do so are only now being developed. Third, in Phases I.A and I.B, the detailed analyses were restricted to data from a single locale and time period in which major changes in both air pollution and mortality occurred, and during which changes in ambient levels of various air pollutants were correlated over time. It is difficult to draw conclusions about the effects of individual or combined air pollutants from such data alone. Such conclusions might be based more reliably on the results of a nationwide study using data bases on mortality and air pollution from a large number of sites with different air pollution profiles. Phase II of this project, the National Morbidity, Mortality, and Air Pollution study, will address the limitations described above.

The current findings corroborate previous results, reported by these investigators and others, that the association between air pollution and daily mortality in Philadelphia from 1973 through 1988 is not explained by other known factors associated with mortality, nor by variations in analytic approaches to adjust for weather factors. Although individual air pollutants (total suspended particles, sulfur dioxide, and ozone) are associated with increased daily mortality in these data, the broader association of pollution with daily mortality in this city cannot be reliably attributed to any single criteria air pollutant. Given the limitations discussed above, it is not possible to establish the extent to which particulate air pollution by itself is responsible for the widely observed association between mortality and air pollution in Philadelphia, but we can conclude that it appears to play a role.

PARTICLE EPIDEMIOLOGY EVALUATION PROJECT

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Air Pollution, Weather, and Mortality in Philadelphia 1973–1988

Jonathan M. Samet, Scott L. Zeger, Julie E. Kelsall, Jing Xu, and Laurence S. Kalkstein

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This document is one section of the Health Effects Institute Phase I.B Report of the Particle Epidemiology Evaluation Project, *Particulate Air Pollution and Daily Mortality: Analyses of the Effects of Weather and Multiple Air Pollutants*, which also includes an HEI Statement about the research, a Commentary by the Oversight Committee, and Comments from the Health Review Committee. Correspondence concerning this section may be addressed to Dr. Jonathan M. Samet, Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, 615 N. Wolfe Street, Suite 6039, Baltimore, MD 21205--2179.

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ABSTRACT

This report provides the findings of Phase I.B of the research program initiated by the Health Effects Institute through its Particle Epidemiology Evaluation Project. The work of Phase I.B addressed specific methodologic issues related to the association between particulate air pollution and mortality that had not been addressed in Phase I.A (which focused on replicating and validating selected studies). In Phase I.B, we continued to explore the sensitivity of the findings to analytic approaches and assumptions; specifically addressed the choice of approach used to control for two variables: (1) the effects of weather on mortality, and (2) the consequences of multipollutant models, rather than models considering only one or a few pollutants, on estimates of effects.

The association between temperature—and, more generally, weather—and mortality has long been known. Because of the potential for either confounding or modifying the pollution-mortality relationship by weather, researchers have "controlled" the effects of weather to estimate the independent effect of air pollution on mortality. In most reported analyses of pollution and mortality, ad hoc approaches for describing the effect of weather on mortality were followed; investigators typically used descriptive analyses and model fit as guides to developing a model for the effect of weather on mortality. One alternate approach to control potential confounding by weather is to use a synoptic categorization of weather, which classifies days by the weather patterns exhibited. Using data for Philadelphia for 1973--1980, we compared estimates of the effects of total suspended particles (TSP)* and sulfur dioxide (SO_2) by applying four different approaches for including weather in the regression model: the variables selected in the analysis published by Schwartz and Dockery (S-D), an approach using locally weighted smoothing scatter plots (LOESS) (previously applied in Phase I.A), and two different sets of synoptic categories, the Total Synoptic Index (TSI) and the Spatial Synoptic Classification (SSC), developed by Dr. Laurence Kalkstein at the University of Delaware.

We found that the association between mortality and air pollution indexes, as measured by either TSP alone, SO_2 alone, or TSP and SO_2 together, cannot be explained by replacing the original Schwartz and Dockery weather model with either a nonparametric regression (LOESS), or with synoptic categories using either Kalkstein's TSI or SSC system. Some variation in the estimated effects of the air pollution variables was noted among the models, but no indication of a systematic pattern of variation could be identified on the basis of the approach used to control the effects of weather variables. In addition, little evidence in the analyses of total mortality indicated that weather conditions modify the effect of pollution regardless of the approach used to represent weather in the model.

There has been persistent concern that the effect attributed to particles could represent uncontrolled confounding because of failure to include the full set of ambient pollutants in the models. Consequently, we assembled a data base for Philadelphia for the years 1974 through 1988 that included the full suite of criteria air pollutants, with the exception of lead. Lead was not considered because current ambient exposures to inhaled lead should not result in acute cardiopulmonary toxicity (Mahaffey et al. 1992). These data were analyzed *de novo*, without drawing on previously developed models, in order to more fully characterize the consequences of alternative approaches to controlling for time trends and weather. We then addressed the effects of particles while simultaneously considering other pollutants. The data base included TSP, SO_2, nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO). Our analytic strategy systematically developed a multipollutant model. We used model fit and a priori considerations to guide the model development. Initially, we developed a model to control long-term and short-term trends in the mortality data; this model included a 160-degrees-of-freedom (df) smooth of time, separate smooths of time for each age group (8 df) to account for differing temporal trends of mortality by age, and separate harmonic seasonal effects for each age group, allowing for the larger effect of season on mortality in older persons. To control the effects of weather, we added variables to the model for the current day's temperature and dew point and for the mean temperature and dew point for the three previous days.

We then examined the effect of the air pollution variables on total and cause-specific mortality in a model that included the terms for time trends and weather described above. The concentrations of TSP, SO_2, NO_2, and CO were moderately correlated with one another, whereas the concentration of O_3 was correlated to a much lesser degree with the concentrations of the other pollutants. Based on preliminary explorations, we selected the average of the concentrations on the current and prior days as the primary analytic variable for all pollutants, as well as the average of the third and fourth previous days for CO, the lag time for which the model fit was best. We initially explored the effects of the pollutants in univariate models and then assessed the effect of adding the other pollutants one by one into bivariate models. When pollutants were considered individually, we found statistically significant effects for

* A list of abbreviations appears at the end of this report.

TSP, SO_2, CO (lagged), and O_3. Including other pollutants did not change the estimated effect of O_3. The effect of TSP dropped by about one-third with the inclusion of SO_2 in the model, increased with the addition of NO_2, and did not change with the addition of the other pollutants. The estimated effect of SO_2 was reduced similarly with the inclusion of TSP, although remaining significant, and increased with the addition of NO_2. Further assessment of effect modification showed that the effect of TSP increased with increasing age of subjects, but no evidence was found for effect modification by season.

Consequently, the final models included separate effects of TSP by the three age categories selected for the analysis. For total mortality, with all five pollutants considered in the model, we found a statistically significant effect of TSP for subjects 75 years of age and older, and significant effects of SO_2 and O_3 that were not dependent on age groupings. Positive associations also were noted between each of three pollutants—TSP, SO_2, and O_3—and cardiovascular and respiratory deaths. As a measure of the fit of the models to the data, we calculated an overdispersion parameter that estimated the excess variation relative to Poisson variation; reducing the overdispersion parameter to unity would indicate that the model explained all variation beyond that expected from a Poisson process. We were successful in reducing the estimated excess variation relative to Poisson counts from 25% to 7% by modeling mortality on time alone, and then to 5% by including the weather and pollution terms in the models. These models were thus highly successful in explaining the variation in mortality counts. However, given the strong association between TSP and SO_2, it was not possible, based solely on these Philadelphia data, to identify one or the other pollutant as the principal cause of the effect on mortality of the correlated group of combustion pollutants. These analyses addressed only short-term effects and not longer-term effects of air pollution on mortality.

INTRODUCTION

OVERVIEW AND SPECIFIC AIMS

This report provides the findings of Phase I.B of the program of research initiated at the request of the Health Effects Institute under its Particle Epidemiology Evaluation Project. The findings of Phase I.A have been published (Health Effects Institute 1995; Samet et al. 1995a). That report focused primarily on replicating and validating selected studies previously reported in the literature, and on assessing the sensitivity of analytic findings to modeling approaches. Phase I.B continued to explore the sensitivity of findings to analytic approaches and assumptions, addressing specifically the choice of approach used to control the effect of weather on mortality, and the consequences of building multipollutant models, rather than models considering only one or a few pollutants, on estimates of effect. These analyses were motivated in part by persistent concerns about the methodology used to characterize the effect of air pollution on mortality. The initial findings of both sets of Phase I.B analyses have been released and provided to the Environmental Protection Agency in the form of preliminary, peer-reviewed manuscripts (Samet et al. 1995b, 1996). This report provides a more comprehensive and updated summary of the findings of Phase I.B, and combines the findings of both sets of analyses into one unified report. The findings from the two sets of analyses, each involving different data sets, are presented separately in this report.

The association between temperature—and, more generally, weather—and mortality has long been known. Because of the potential that weather variables could confound or modify the pollution-mortality relationship, researchers have "controlled" the effects of weather variables to estimate the independent effects of air pollution on mortality. The usual analytic approach is to include variables for weather—typically measures of temperature and humidity—in regression models. A model may yield a biased estimate of the effect of pollution on mortality if an incorrect set of variables for weather is used or if the model does not properly specify the weather-mortality relationship. In most reported analyses of pollution and mortality, empiric approaches for describing the effect of weather on mortality were followed; investigators typically used descriptive analyses and model fit as guides to developing a model for the effect of weather on mortality. One alternate approach for controlling potential confounding by weather is to use the synoptic categorization of weather proposed by Kalkstein and coworkers (1987). This approach categorizes weather patterns using factor analysis and offers categories that represent groupings of meteorological variables as they actually occur at a locale. The potential advantages of the synoptic approach over the generally used alternatives had been considered in the draft document, Air Quality Criteria for Particulate Matter of the Environmental Protection Agency (1996). Consequently, we performed analyses to compare the synoptic approach with other methods, including models for weather and mortality for the city of

Philadelphia, previously developed by Schwartz and Dockery (1992) and by us for Phase I.A (Samet et al. 1995a). We worked in collaboration with Dr. Laurence Kalkstein of the University of Delaware to accomplish the following specific aims:

- To develop synoptic categories for weather for the city of Philadelphia for 1973 through 1980; and
- To compare models of the effects of particulate pollution on mortality that incorporate either the weather variables used by Schwartz and Dockery in their 1992 report, a model developed in Phase I.A based on a nonparametric approach (generalized additive models with a LOESS smoother), or synoptic weather groupings.

The Phase I.A report (Samet et al. 1995a) provided an analysis of data made available by Schwartz and Dockery for Philadelphia for 1973 through 1980. The data set included only TSP and SO_2, leaving concerns that the TSP-mortality association could be confounded by other pollutants. Consequently, we assembled a data base for Philadelphia for the years 1974 through 1988 that included the full suite of criteria air pollutants, excluding lead. These data were analyzed *de novo*, without drawing on previously developed models, to accomplish the following specific aims:

- To further investigate approaches for modeling long-term and short-term trends in mortality, and to further characterize the relationship between weather and mortality;
- To describe the correlations among the criteria pollutants in the data set; and
- To compare single- and multipollutant models in estimating the effect of TSP on mortality.

The present analyses differ from those in the interim reports of Phase I.B results to the Health Effects Institute, which were submitted to the Clean Air Scientific Advisory Committee (Samet et al. 1995b, 1996), although the interpretation and conclusions of both the interim and final reports are in agreement. The analysis summarized in this final report is based on a more systematic model-building strategy than we described in the interim report.

BACKGROUND

Weather, Mortality, and Air Pollution

Researchers have long known about the association between weather and mortality. The extremes of temperature, both hot and cold, cause deaths in excess of those predicted for usual temperatures; in some locations an optimum range of temperature can be identified from which mortality rates rise at higher or lower temperature levels. The form of this relationship has often been referred to as "J-shaped," because of a somewhat asymmetrical pattern of association, with a rise in mortality counts that is steeper and shorter at the hot temperatures than at the cold temperatures. There is also an association between weather and pollutant concentration, and much is understood about the many ways that weather influences the emission, mixing, and transport of air pollutants. In the more recent research to accurately assess the effects of air pollution on mortality, scientists have been concerned that the weather-pollution association could confound (or bias) how we measure the effects of pollution on mortality. It also is possible that weather could actually modify the effect of pollution on mortality: that is, as weather and pollution interact, they may produce different effects on mortality than would be produced by either factor alone.

Because of the potential for weather to either confound or modify the pollution-mortality relationship, researchers have adjusted for weather, using either stratification or more continuous modeling of the weather, to estimate the independent effect of air pollution on mortality. The usual analytic approach has been to include variables for weather, typically measures of temperature and humidity, in regression models. A variety of model forms have been used, including linear and nonlinear variables for temperature and humidity (Samet et al. 1995a). For example, the model applied to the Philadelphia data by Schwartz and Dockery (1992) included variables for the concurrent day's temperature and dew point temperature, a one-day-lagged temperature variable, and an indicator variable for hot days ($\geq 80°F$). This model was based on initial descriptive findings and on the basis of model fit. This general approach, followed in most other investigations of air pollution and mortality, could result in models that fit the data satisfactorily but not appropriately from biologic and clinical perspectives. A model may yield a biased estimate of the effect of pollution on mortality if an incorrect set of variables for weather is used or if the model does not properly specify the weather-mortality relationship. In Phase I.A of the Particle Epidemiology Evaluation Project, we conducted initial analyses on the sensitivity of findings to the choice of the model used to control for weather. Two analytic strategies were compared: the empiric approach used by Schwartz and Dockery (1992) in their initial study on pollution and mortality in Philadelphia, and a nonparametric regression method (generalized additive models with a LOESS smoother). The latter method fits a smooth function to the data to describe the effect of the weather variables on mortality. The two methods, both intended to optimally

predict mortality in the data at hand, were found to give comparable results concerning the effects of the air pollution variables (TSP and SO_2) on mortality (Samet et al. 1995a).

One alternate approach to control for potential confounding by weather is to use the synoptic categorization proposed by Kalkstein and coworkers (1987). This method for categorizing weather applies factor analysis to routinely collected meteorological data (air temperature, dew point temperature, visibility, total cloud cover, sea-level air pressure, wind speed, and wind direction measured four times daily) to identify the independent components of the data. Scores are then calculated for the components for each day, and the days are grouped into meteorologically similar clusters on the basis of the component scores. Kalkstein and colleagues (1995) have described two types of synoptic groupings: the TSI and SSC. The SSC differs from the TSI by initially selecting and including a set of representative "seed days" in the discriminant analysis that produces the categorization of the days. Both the TSI and SSC categories are chosen to cluster "similar" weather days, not to optimally predict mortality. However, the categories do represent realistic groupings of meteorological variables as they actually occur at a locale ("air masses"), and the character and frequency of these air masses vary from place to place.

The synoptic categorization has proven to be an informative approach for classifying weather patterns (Kalkstein et al. 1995). Kalkstein has identified categories that are associated with increased mortality, and has proposed that synoptic categories may be preferable to the widely used empirical approaches for controling confounding by weather. Two relevant analyses have been reported to date. Pope and Kalkstein (1996) analyzed data for the Utah Valley, 1985–1989, and compared the findings from models using TSI categories to those from models using either categorical variables for temperature and relative humidity or generalized additive models. They found that the choice of approach for controlling for weather had no substantive impact on the effect of pollution on mortality. For cardiovascular and pulmonary mortality, a significantly better fit of the model was found when the synoptic categories were added to a base model that included variables for season. Fit was not improved significantly for this same base model by adding indicator variables for quintiles of temperature and humidity, and on this basis Pope and Kalkstein concluded that synoptic categorization did a somewhat better job of controlling for weather in this data set. They cautioned that the findings could be different in other cities.

A second study, also for Philadelphia, utilized a TSI to identify an "oppressive" weather category (associated with a very high mean mortality), and determined the impact of O_3 and TSP concentration within, and outside of, this category (Kalkstein et al. 1997). When days outside the oppressive category were divided into O_3 and TSP pollution concentration quintiles, mortality response was sensitive to both pollutants, and deaths rose systematically toward the highest concentration quintile. However, when similar concentration quintiles were developed for days within the oppressive weather category, mortality response was sensitive to variations in meteorological factors only.

The two general approaches to controlling the effects of weather on mortality (empiric and synoptic) contrast sharply. Kalkstein and colleagues identify patterns of weather, assign them to categories, and then assess the relationships between the categories and mortality. The synoptic categories have been used directly in models (Pope and Kalkstein 1996) or the pollution-mortality association has been assessed within synoptic categories (Kalkstein et al. 1997). In the empiric approaches followed by others, models for weather and mortality have been constructed based on data exploration and model fit, with little a priori consideration of weather patterns. Formal comparisons between the empiric and synoptic approaches have been limited.

Multipollutant Models

The findings on particulate air pollution and mortality have been questioned because few of the analyses considered the full set of outdoor air pollutants that may potentially affect daily mortality counts (Samet et al. 1995a; Moolgavkar and Luebeck 1996). In locations where stationary combustion sources are the dominant contributors of particles, concentrations of particles are correlated with the concentrations of other combustion-related pollutants: SO_2, NO_2, and CO. We would anticipate a less consistent pattern of correlation between indexes of particles and O_3 because of the dominant role of vehicle exhaust as a precursor to O_3 formation. Failure to consider these other pollutants might result in overestimating the independent effect of particulate air pollution because the estimated particle effect would include effects of other, uncontrolled pollutants. Alternately, the estimated effect of a particulate matter index might be misinterpreted as capturing the effect of a complex mixture of pollutants, with some having correlated concentrations.

In published analyses of particulate air pollution and mortality, the extent to which other pollutants have been considered has been variable. Of the six studies considered in Phase I.A, the data bases of three (Utah Valley, Birmingham, and Santa Clara) included indicators of particle concentration only. For Philadelphia, both TSP and SO_2 were considered, whereas the data sets for St. Louis and Eastern Tennessee contained concentrations of SO_2, NO_2, O_3, and

hydrogen ion. Analytic approaches have focused on identifying effects of individual pollutants, with little consideration given to the combined effects of pollutants or to constructing summary measures that combine multiple pollutants. In the Phase I.A analyses for Philadelphia, we found evidence that the effects of TSP and SO_2 were independent of each other (Samet et al. 1995a). Analyses by Moolgavkar and colleagues for Philadelphia have included pollutants in addition to TSP and SO_2 (Moolgavkar et al. 1995; Moolgavkar and Luebeck 1996), and still found an association between TSP and mortality.

Researchers have interpreted the epidemiologic evidence as indicating an effect of particles; this has been based largely on integrating findings across locations with differing mixtures of pollutants. An effect of particles on mortality (and morbidity) is consistent with the pattern of findings across the many locations where studies have been carried out. Nonetheless, further analyses, involving particles and all other relevant pollutants, are needed to strengthen the interpretation of regression models conducted within single locations.

METHODS

ALTERNATIVE APPROACHES TO CONTROLLING THE EFFECTS OF WEATHER VARIABLES, PHILADELPHIA 1973–1980

Data Set

These analyses were based on data for the city of Philadelphia for the years 1973 through 1980. The data set corresponded to the one we developed from original data sources in Phase I.A to validate the data set provided by the original investigators (Schwartz and Dockery). The data base was supplemented by the two sets of synoptic categories: the TSI and the SSC.

Modeling Approach

We reanalyzed the total mortality data for Philadelphia for 1973 through 1980 (the same data base used in Phase I.A) using four distinct weather models. The analysis method in each case was log-linear (Poisson) regression with the assumption of constant overdispersion: that is, a fixed degree of extra-Poisson variation. The first weather model, used by Schwartz and Dockery (1992), included the previous and current days' average temperatures, current day's average dew point, indicator variables for hot days and winter days, and an interaction between the winter days' and the current day's temperatures. The second model, a nonparametric function of previous day's temperature and dew point estimated using LOESS, was described in detail in the Phase I.A report (Samet et al. 1995a). The LOESS approach produces an optimal, smooth set of mortality predictions as a function of dew point and temperature. The third model assumes that the weather effects on mortality are constant within Kalkstein's TSI categories (Kalkstein et al. 1987). Separate analyses were conducted using 22 categories from all seasons, of which 15 categories were for summer days alone, and 11 categories for winter days alone. The fourth model assumes that weather effects on mortality are constant within Kalkstein's SSC categories (Kalkstein et al. 1995), which were created separately for winter and summer days, with five and eight categories, respectively. The synoptic categories used were based on data for the previous day. The SSC categories cannot yet be readily developed for the transition seasons of spring and fall.

We considered two measures of the sensitivity of the findings to how weather was specified in the model: changes in the estimated effects of TSP and SO_2, and model fit. The sensitivity of the inferences about the effects of the pollutants, TSP and SO_2, is reflected in the variation of the estimated regression coefficients and their associated statistics across the models with different weather specifications. Joint confidence intervals for the fit of TSP and SO_2 in the same model also were calculated to indicate the sensitivity of the relative effects of these two pollutants to the choice of weather model.

To compare the relative quality of the mortality predictions across these nonnested models, we used Akaike's Information Criterion (AIC) as a measure of how well the model fit the data (Akaike 1970; McCullagh and Nelder 1989; Hastie et al. 1990). The AIC is one of several sensible criteria available that balance the model's complexity against its ability to explain the observed data. More complex models constructed purposely to predict the observed data will reproduce the observations better than simpler models. However, increasingly complex models require more degrees of freedom. The AIC incorporates the deviance, which measures the fidelity of the model predictions to the observed data, with a penalty for adding more parameters (predictors) into the model. Smaller values indicate the preferred model; AIC values can be compared across nonnested models. For example, predicting a response with a linear function of a single explanatory variable uses two degrees of freedom, whereas a quadratic function uses three. Adding the quadratic term would have to improve the likelihood function by at least one to improve the AIC. In our application to log-linear regression, the penalty function is scaled by the degree of overdisper-

sion so that the penalty is larger for adding one or more degrees of freedom when there is more overdispersion. More technically, AIC is a first-order approximation of the expected deviance between the model predictions and a new, independent set of data from the same underlying process. It can be expressed as the deviance penalized for the number of estimable parameters, p, in the model:

$$\text{AIC} = \text{deviance} + 2\,\hat{\Phi}\,p$$

where $\hat{\Phi}$ is an estimate of overdispersion.

Because it approximates an expected log-likelihood, a difference of 5 (or 10) units between the AIC values for two models means that the preferred model (lower AIC) is about 12 (or 150) times more consistent with the new data.

We have used AIC as a guide and not as a rigid optimization criterion. We have chosen specific groups of models to consider, based upon prior understanding and clinical and biologic judgment. We have used AIC to select from models when there was little *a priori* support for a particular model. In comparing alternative models for weather, we considered both AIC and the change in the estimated effect. Less emphasis should be placed on models having larger AIC values; changes in effect also should be given less emphasis for models fitting the data poorly, as judged by AIC.

We also examined the question of whether the effects of SO_2 and TSP vary across the different weather conditions as represented by the TSI categories, ordered S-D weather categories, and ordered LOESS categories. To do so, we estimated a separate SO_2 and TSP regression coefficient in the log-linear model for each TSI, S-D, and LOESS category. Stratifying the weather conditions into a large number of subcategories leads to highly imprecise estimates of the pollutant's effects. To avoid overinterpretation of variation among the regression coefficients across weather categories, we have used an empirical Bayes approach to estimation (Efron et al. 1972), which dampens the variation arising by chance in the pattern of interaction. Here we adopted the prior assumption that the set of TSP or SO_2 coefficients across the different weather categories can be viewed as an independent sample from a normal distribution with unknown mean and variance. We then determined the posterior mean and variance by combining this prior distribution with the likelihood function of the observed mortality data. The unknown mean and variance of the prior distribution can be estimated by maximizing the marginal distribution of the observed data with respect to these parameters. The empirical Bayes estimates are a compromise between the maximum likelihood estimates and the overall estimate of the regression coefficients obtained from a model assuming no interaction between air quality and weather category. If there is little evidence for this interaction, the overall estimate is favored. When there is substantial evidence for interaction, the maximum likelihood values are favored. In the Results section, Figures 2 and 3 summarize our findings and present both (1) the maximum likelihood estimates with their approximate 95% confidence intervals as dashed lines, and (2) the overall estimates (left-most data point in each panel) and the corresponding empirical Bayes estimates with their approximate 95% confidence intervals as solid lines. These confidence intervals for empirical Bayes estimates do not take into account the imprecision in estimating the prior variances, and may therefore underestimate the true uncertainty. Appendix A presents the derivation of this methodology in detail.

AIR POLLUTION AND MORTALITY IN PHILADELPHIA 1974–1988: A MULTIPOLLUTANT ANALYSIS

Data Sources

Data were taken from national data bases on mortality, air pollution, and weather, as described in our previous reports (Samet et al. 1995a,b, 1996). In brief, data on weather (four daily readings of temperature and dew point) were obtained from the National Weather Center through Dr. Kalkstein, mortality data were read from tapes from the National Center for Health Statistics, and air pollution data were extracted from the Aerometric Information Retrieval Service data base of the U.S. Environmental Protection Agency. For this analysis, we selected all available data for TSP, SO_2, NO_2, CO, and O_3. Lead was not considered because exposures to inhaled lead at current ambient levels have been shown to not have cardiopulmonary toxicity (Mahaffey et al. 1992). Because of missing data for these pollutants, the analysis was limited to the years 1974 through 1988. All available pollutant data from population-oriented monitors were used.

Only the deaths of Philadelphia residents at time of death were selected. For the analysis, the mortality data were stratified by age and cause of death. The age strata were younger than 65, 65–74, and 75 years and older. In addition to total mortality, three cause-of-death groupings were used: cardiovascular, respiratory, and the residual categories, referred to as "other" (Table 1). The respiratory category grouped deaths from chronic obstructive pulmonary disease (COPD) and related disorders, and from influenza and pneumonia. Death from COPD commonly results from respiratory infection and morbidity; mortality rates from COPD and respiratory infections typically vary together (Glezen 1982). In addition, the numbers of deaths were small within the category of COPD.

A data set for the period January 1, 1974, through December 31, 1988, was created from the data bases above and used in these analyses.

Statistical Methods

To assess the effects of air pollution on daily mortality counts, we estimated the percentage of change in daily mortality per one unit of change scaled as the interquartile range (IQR) for each of the air quality variables. We controlled for long-term and weather-related trends. We used Poisson regression to model the log expected mortality counts, $\log[E(Y)]$, as a linear combination of the covariates (McCullagh and Nelder 1989). However, it is not reasonable *a priori* to assume a log-linear relationship of mortality with some variables, such as time. We thus used generalized additive models (Hastie et al. 1990), extending Poisson regression to model the log mean mortality as a sum of terms representing each of the covariates, with some terms modeled as linear and others as nonlinear but smooth functions.

To control for unmeasured time-related variables in $\log[E(Y)]$ (that is, the trend of declining cardiovascular mortality, and seasonal and shorter-term effects related to respiratory illnesses), we used smoothing spline functions of time. We specified the amount of smoothness as the approximate number of degrees of freedom to be assigned to that particular term. A linear function has 1 df; increasing degrees of freedom adds flexibility in describing patterns in the data. Modeling mortality as a smooth function of time with q df over some number of days (n) is approximately equivalent to a moving average of mortality of approximately n/q days.

Because variation in the day-to-day mortality counts was anticipated to exceed the variation expected of Poisson data, we allowed the variance to be proportional to, rather than equal to, the expected rate of mortality on a given day by including a constant overdispersion parameter in the analysis. The overdispersion parameter is defined as

$$\Phi = \frac{\mathrm{Var}(Y)}{E(Y)}.$$

The models were fitted by maximum likelihood under the Poisson model (maximal quasilikelihood with overdispersion [McCullagh and Nelder 1989]). We adjusted standard errors to take account of the extra-Poisson variation by multiplying them by the square root of an estimate of the overdispersion parameter, Φ, which we calculated as the residual deviance divided by the number of residual degrees of freedom of the fitted model (McCullagh and Nelder 1989). The value of Φ is of interest in its own right as a measure of success in model specification. Larger values mean that less variation has been accounted for by the model, whereas values less than unity can indicate a model with too many predictors.

We assessed the statistical significance of the coefficient estimates by their t values, the coefficient value divided by the standard error. We defined approximate 95% confidence intervals for the coefficients as the estimates, plus or minus two standard errors. We used the AIC to compare models.

Modeling Strategy

We used a systematic approach, building from simple models to more complicated models with increasing numbers of covariates (Table 2). We developed the model for total mortality, and then used the same variables to develop new models for the cause-specific mortality counts to determine if the pollutant effects differed for different causes of death. *A priori*, we expected longer-term seasonal variations, weather effects, and pollution effects to differ by cause of death.

Dealing with total mortality in each of the three age groups, we first fit the simplest model with a constant mean for each age group. We then incorporated nonlinear time effects, deciding on the degrees of freedom at each stage on the basis of the AIC values. We next incorporated weather terms into the model. We allowed nonlinear weather relationships using generalized additive models, and then in some cases we approximated the generalized additive model predictors with simpler parametric forms to describe the effects of weather. After controlling for time and weather, we introduced the pollutants into the model. We used the AIC to guide the choice of lag times for pollutant variables. We fitted models with different combinations of pollutants to assess the stability of individual effects. Finally, we investigated whether there were different pollut-

Table 1. International Classification of Disease[a] Codes Used to Group Deaths in Philadelphia

Cause of Death	ICD 8 (1974–1978)	ICD 9 (1979–1988)
Cardiovascular	390–448	390–448
Respiratory		
COPD & related disorders	490–493, 519.3	490–496
Influenza	470–474	487
Pneumonia	480–486	480–486, 507
Other	Residual	Residual

[a] Abbreviated as ICD.

ant effects for the four seasons or for the three age groups, and then fitted the final model to the mortality count series corresponding to each of the cause-of-death categories.

Because some values of some predictor variables were missing on some days, we restricted analyses to days with no missing values across the full set of lag times considered (Table 2). For the initial model, which included only time relationships, there were no missing values. In deciding on an appropriate weather model, we restricted analyses to days with complete weather for the current day and up to six days previously. This allowed us to compare models with a variety of lag structures. Similarly, in modeling the pollutant effects, we restricted analyses to days with no missing pollutants up to a six-day lag period. Once the lag structures were decided upon, the final models were restricted to days with no missing values for all of the final weather and pollutant variables.

All analyses were carried out using S-PLUS (Statistical Sciences, Seattle).

RESULTS

ALTERNATIVE APPROACHES TO CONTROLLING THE EFFECTS OF WEATHER VARIABLES, PHILADELPHIA 1973–1980

The data are described in Table 3. Table 4 presents the results of analyses of weather confounding the air pollution–mortality associations. Separate results are reported for all seasons combined ("overall") and for summer and winter separately. Total Synoptic Index categories were available for all four seasons; SSC categories were available only for the winter and summer. Within seasons, TSI categories were available for more days than SSC categories. This is because we eliminated transition days on which the weather was intermediate between one SSC category and another. Table 4 presents the estimated regression coefficients for models with TSP or SO_2 alone, and for TSP and SO_2 together.

Table 2. Sequential Development of Models to Describe the Variation in Daily Mortality, Philadelphia 1974–1988

Model	Description	Number of Days	AIC[a]	$\hat{\varphi}$[b]
Time				
T0	Intercept for each age group	5,479	20,590	1.252
T1	T0 + smooth function of time (160 df)	5,479	18,860	1.136
T2	T1 + separate smooths of time (8 df) for each age group	5,479	17,831	1.073
T3	T2 + separate harmonic season effects for each age group	5,479	17,770	1.069
Weather				
W0	T3	5,429	17,568	1.066
W1	W0 + current temp. below 70°F + current temp. above 70°F + lag 1,2,3 mean temp. below 80°F + lag 1,2,3 mean temp. above 80°F	5,429	17,271	1.048
W2	W0 + current temp. above 70°F + lag 1,2,3 mean temp. below 80°F + lag 1,2,3 mean temp. above 80°F + current dew point + lag 1,2,3 mean dew point	5,429	17,247	1.046
Pollutants				
P0	W2	5,173	16,486	1.049
P1	P0 + TSP + SO_2 + NO_2 + CO + O_3	5,173	16,475	1.048
P2	P0 + TSP + SO_2 + NO_2 + LCO[c] + O_3	5,173	16,467	1.047
P3	As P2 with separate pollutant effects by season	5,173	16,478	1.047
P4	As P2 with separate pollutant effects by age group	5,173	16,474	1.047
P5	As P2 with separate TSP effects by age group	5,173	16,461	1.047

[a] Akaike's information criterion; see the Methods section.

[b] Overdispersion parameter.

[c] Mean of CO values for the third and fourth prior days.

In the full-year analysis, when TSP or SO_2 were fit as the only pollution variables the results are qualitatively similar regardless of how the effects of weather were controlled. When TSP and SO_2 were fit simultaneously, the S-D and LOESS models produced qualitatively different results. Weather adjustment, using TSI, attributed a larger proportion of the pollution effect to SO_2 than to TSP. However, model fit, as assessed by AIC, was substantially poorer for TSI.

In the overall analysis, the S-D model is slightly better than LOESS at predicting mortality. The S-D model and LOESS are substantially better than TSI, as measured by AIC.

In the analysis of winter days, applying the TSI and S-D weather adjustments led to similar coefficients for TSP alone (Table 4). The LOESS approach produced a coefficient for TSP alone that was much higher than the TSI and S-D values, and the SSC weather adjustment produced a coefficient even higher still. The LOESS model fit the data best. The results with SO_2 as the only air pollutant were qualitatively similar across the different methods of weather adjustment. When TSP and SO_2 were fit together, the results were again qualitatively similar, regardless of the adjustment method. The models that adjusted for weather using LOESS were slightly better than those using the S-D method, but these two approaches were considerably better than using either TSI or SSC alone.

The summer analyses produced qualitatively similar results when TSP was modeled alone across the four different methods for weather adjustment. When SO_2 was fit alone, the S-D model led to smaller coefficients than either the LOESS, TSI, or SSC adjustments, which were similar to one another. When TSP and SO_2 were fit simultaneously, the results were qualitatively similar for TSP, regardless of the type of weather adjustment; the SO_2 effect varied more. For the summer days, the LOESS weather adjustment consistently resulted in the lowest AIC values.

Figure 1 shows the joint 95% confidence ellipses for the TSP and SO_2 regression coefficients, with different models used to control weather variables, as described in Table 5. In each case, the results are very similar for the S-D and LOESS weather models. In the winter and summer analyses, the TSI and SSC adjustment models produced ellipses that substantially overlapped the S-D and LOESS ellipses. In the analyses for all seasons, the TSI interval overlapped less and corresponded to a greater relative SO_2 effect than was estimated with the S-D and LOESS models. However, in each case, the S-D and LOESS weather models fit the observed mortality data better than the TSI and SSC models.

The results in Table 5 were obtained using the S-D regression model described in the Phase I.A report (Samet et al. 1995a), which included a linear adjustment for time trend, indicators for each year, and indicators for the day of the week. To ensure that the Table 5 results were not sensitive to the method used to control for longer-term trends or seasonality, we reestimated the models, including a smooth function of time with 20 df. The results obtained (not shown) were qualitatively the same as those reported above.

Figures 2 and 3 present the results of our analyses to assess whether the TSP and SO_2 effects were modified by the weather conditions. Table 5 provides information on the fit of the models with and without considering an interaction between weather and either of the pollution variables. When TSP was the only air pollution variable in the model (Figure 2), little evidence was found of effect modification regardless of whether the weather categories were created using TSI, 20 ordered quantiles of the S-D

Table 3. Summary Statistics for Pollutant Concentrations, Weather Variables, and Mortality, Philadelphia 1973--1980

Unit	TSP ($\mu g/m^3$)	SO_2 (ppb)	Temperature[a] (°F)	Dew Point (°F)	Mortality Count
Mean	76.9	21.1	54.8	42.8	48.2
Standard deviation	25.4	12.0	17.8	19.2	9.0
Minimum	24.5	0.0	4.0	1.0	26.0
Lower quartile	59.0	13.0	41.0	28.0	42.0
Median	73.5	18.5	56.0	44.0	48.0
Upper quartile	90.5	26.5	71.0	59.0	54.0
Maximum	233.0	105.0	89.0	76.0	92.0
Percent missing	8.7	7.7	0.0	0.0	0.0

[a] 24-Hour mean values.

Table 4. Comparison of Poisson Regressions of Total Mortality on TSP and SO_2, Controlling for Season, Date, Year, and Weather, for Four Different Methods of Weather Adjustment, Philadelphia 1973–1980

		$\hat{\beta}$ (× 1000)[a]	SE ($\hat{\beta}$ × 1000)	Corrected *t* Value[b]	Residual Deviance	df	φ[c]	AIC[d]
Overall								
TSP alone	S-D[e]	0.84	0.13	6.0	3,344.1	21	1.26	3,397.0
	LOESS[f]	1.1	0.12	8.0	3,348.7	22	1.27	3,404.4
	TSI[g]	1.0	0.13	6.6	3,480.0	36	1.33	3,575.8
SO_2 alone	S-D	1.7	0.27	5.7	3,358.9	21	1.26	3,411.8
	LOESS	2.1	0.25	7.5	3,367.8	22	1.26	3,423.2
	TSI	2.6	0.27	8.4	3,465.1	36	1.31	3,559.4
TSP (with SO_2)	S-D	0.46	0.17	2.3	3,234.0	22	1.25	3,289.0
	LOESS	0.58	0.17	3.0	3,237.1	23	1.26	3,294.9
	TSI	0.20	0.17	1.0	3,331.3	37	1.31	3,428.2
SO_2 (with TSP)	S-D	1.2	0.38	2.7	3,234.0	22	1.25	3,289.0
	LOESS	1.4	0.37	3.3	3,237.1	23	1.26	3,294.9
	TSI	2.5	0.36	6.1	3,331.3	37	1.31	3,428.2
Winter								
TSP alone	S-D 1	0.19	0.25	0.66	843.2	18	1.35	891.8
	LOESS 1	0.57	0.23	2.10	812.8	24	1.30	876.7
	TSI	0.18	0.25	0.62	837.5	25	1.36	905.5
	S-D 2	0.19	0.28	0.58	682.2	18	1.34	730.5
	LOESS 2	0.63	0.25	2.20	664.7	24	1.30	729.3
	SSC[h]	0.90	0.26	2.96	710.4	19	1.40	767.6
SO_2 alone	S-D 1	1.2	0.46	2.2	845.8	18	1.35	894.4
	LOESS 1	1.6	0.43	3.2	816.8	24	1.30	880.9
	TSI	1.4	0.47	2.6	838.4	25	1.35	906.1
	S-D 2	1.2	0.51	2.0	683.8	18	1.34	732.0
	LOESS 2	1.9	0.46	3.5	666.6	24	1.30	731.7
	SSC	2.4	0.47	4.4	702.1	19	1.38	754.6
TSP (with SO_2)	S-D 1	−0.30	0.34	−0.75	836.8	19	1.36	888.5
	LOESS 1	0.03	0.34	0.08	807.0	25	1.30	874.0
	TSI	−0.42	0.34	−1.05	826.0	26	1.36	896.8
	S-D 2	−0.35	0.38	−0.78	672.2	19	1.36	727.7
	LOESS 2	−0.10	0.38	−0.24	660.4	25	1.30	728.8
	SSC	−0.05	0.38	−0.12	696.3	20	1.40	752.2
SO_2 (with TSP)	S-D 1	1.4	0.65	1.9	836.8	19	1.36	888.5
	LOESS 1	1.4	0.64	2.0	807.0	25	1.30	874.0
	TSI	1.8	0.64	2.4	826.0	26	1.36	896.8
	S-D 2	1.5	0.71	1.8	672.2	19	1.36	727.7

(Continued on next page.)

Table 4. Comparison of Poisson Regressions of Total Mortality on TSP and SO_2, Controlling for Season, Date, Year, and Weather, for Four Different Methods of Weather Adjustment, Philadelphia 1973--1980 *(continued)*

		$\hat{\beta}$ ($\times$ 1000)[a]	SE ($\hat{\beta} \times 1000$)	Corrected t Value[b]	Residual Deviance	df	φ[c]	AIC[d]
	LOESS 2	2.0	0.70	2.4	660.4	25	1.30	728.8
	SSC	2.4	0.70	2.9	696.3	20	1.40	752.2
Summer								
TSP alone	S-D 1	0.97	0.33	2.8	784.6	19	1.17	829.1
	LOESS 1	1.3	0.30	3.9	737.5	24	1.1	790.9
	TSI	1.6	0.31	4.7	777.6	29	1.18	845.9
	S-D 2	1.1	0.33	3.0	711.5	19	1.20	757.2
	LOESS 2	1.3	0.32	3.7	666.8	24	1.1	721.9
	SSC	1.9	0.30	5.8	718.7	21	1.21	769.9
SO_2 alone	S-D 1	0.67	0.65	0.96	786.3	19	1.17	830.7
	LOESS 1	1.6	0.63	2.4	741.6	24	1.1	794.7
	TSI	1.1	0.65	1.6	788.9	29	1.19	857.9
	S-D 2	0.75	0.68	1.0	712.6	19	1.21	758.5
	LOESS 2	1.5	0.65	2.2	668.7	24	1.1	724.3
	SSC	1.6	0.65	2.2	744.2	21	1.26	797.3
TSP (with SO_2)	S-D 1	0.92	0.39	2.2	739.2	20	1.15	785.3
	LOESS 1	1.1	0.37	2.7	692.6	25	1.1	746.9
	TSI	1.6	0.37	3.9	731.8	30	1.16	801.4
	S-D 2	1.1	0.4	2.5	667.9	20	1.19	715.3
	LOESS 2	1.2	0.39	2.9	624.8	25	1.1	681.3
	SSC	1.9	0.37	4.7	673.6	22	1.20	726.5
SO_2 (with TSP)	S-D 1	0.25	0.90	0.26	739.2	20	1.15	785.3
	LOESS 1	1.0	0.89	1.1	692.6	25	1.1	746.9
	TSI	0.17	0.91	0.18	731.8	30	1.16	801.4
	S-D 2	0.14	0.95	0.14	667.9	20	1.19	715.3
	LOESS 2	0.63	0.94	0.63	624.8	25	1.1	681.3
	SSC	–0.11	0.95	–0.10	673.6	22	1.20	726.5

[a] $\hat{\beta} \times 1000$ is interpreted as approximately the percentage of change in mortality per 10-unit change in TSP or SO_2.

[b] Corrected for constant overdispersion.

[c] Estimated constant of overdispersion (deviance method).

[d] Akaike's Information Criterion; see the Methods section.

[e] Schwartz-Dockery weather model. Variables included as interpreted in Samet and associates (1995a). Appropriate subsets of the data were used in each case (S-D, S-D 1, S-D 2).

[f] Nonparametric function of previous day's temperature and dew point estimated using LOESS approach. Appropriate subsets of the original data were used in each case (LOESS, LOESS 1, LOESS 2).

[g] Kalkstein's Total Synoptic Index categories.

[h] Kalkstein's Spatial Synoptic Classification categories.

weather predictors, or 20 ordered quantiles of the LOESS weather predictors. In every case, the empirical Bayes estimates coincided with the maximum likelihood estimate obtained from the model without a weather-TSP interaction. Hence, the solid lines for each weather category were nearly identical to the estimate for all weather categories together with its confidence interval. A similar result was found when SO_2 was the only predictor, as shown in the bottom panels of Figure 2.

When TSP and SO_2 were fitted simultaneously (Figure 3), no evidence was found of effect modification by weather, as represented by either the S-D or the LOESS models (Table 5). Some evidence of effect modification was seen for TSP but not for SO_2 when the TSI categories were used. In this case, the S-D and LOESS weather models led to predictions that were considerably more consistent with the data than the predictions obtained using the TSI weather model.

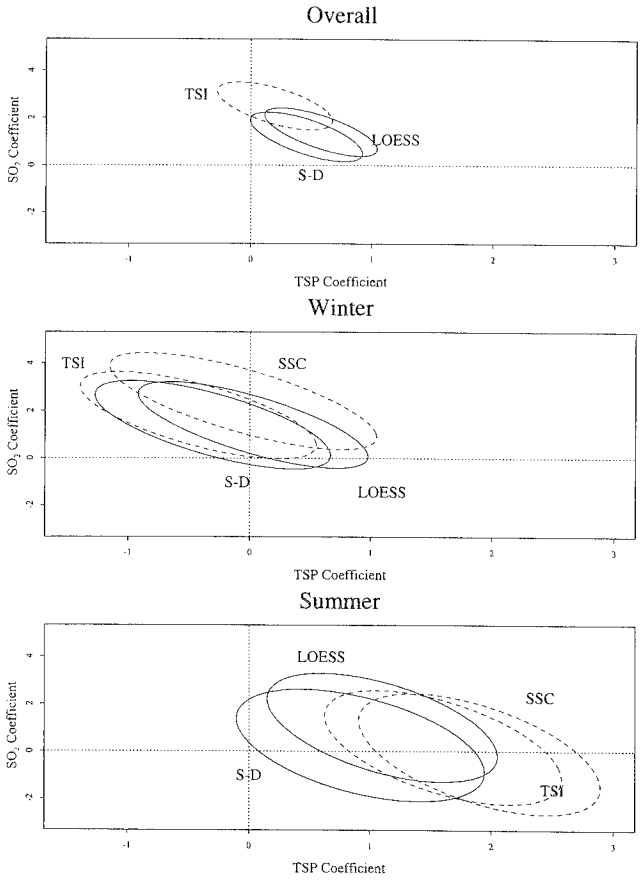

Figure 1. Approximate 95% confidence ellipses for the TSP and SO_2 coefficients in the log-linear models including both variables, with different specifications for weather, as reported in Table 1, Philadelphia 1973–1980.

AIR POLLUTION AND MORTALITY IN PHILADELPHIA 1974–1988: A MULTIPOLLUTANT ANALYSIS

Most of the pollutant concentrations (Table 6) were below the relevant National Ambient Air Quality Standards (U.S. Environmental Protection Agency 1993), although the 24-hour averages that we used do not correspond to the averaging times for the CO and O_3 standards. Figure 4 shows plots of the square-root–transformed pollutant variables, including the temporally smoothed plots and the residuals from these smooths. Long-term trends of decline in the levels of TSP, SO_2, NO_2, and CO were evident; by contrast, levels of O_3 have risen slightly across the 15-year timespan of the data. Strong seasonal variation of O_3 is evident in Figure 4. Levels of SO_2 and CO also tended to vary by season and were highest in the winter.

The average number of daily deaths across the study interval was approximately 47 (Table 7). Nearly half of the deaths were cardiovascular; the number of respiratory deaths was far lower. The contributions of the three cause-of-death groupings to total mortality varied by age group. The proportions of cardiovascular and respiratory deaths in the oldest age group (55.5% and 6.8%, respectively) were approximately double those in the youngest age group (28.2% and 3.6%, respectively). Figure 5 shows the mortality time trends for each of the age and cause-of-death groups. During this time period, mortality rates dropped in the younger age group, whereas they rose in the oldest age category. A decline of cardiovascular deaths and an increase in respiratory deaths were evident. A seasonal pattern of increased mortality in the winter could be observed in all mortality groups, and this pattern became stronger with increasing age.

Controlling Long-Term Trends

During the years covered by the study, major changes occurred in the pattern of disease, with a steady decline of mortality from cardiovascular causes (Figure 5). Concurrently, levels of some pollutants decreased (Figure 4), and the seasons varied substantially. Using generalized additive models, we controlled for these age-specific longer-term temporal variations, which were unlikely to be related to trends in pollution. We fit the simplest model first, which allowed only a constant mean for each age group (Table 2). Adding a smooth function of time with 160 df—approximately equivalent to a moving average of one month—improved the fit considerably (model T1). In addition, by fitting a separate smooth function of time with 8 df for each age group, and allowing for anticipated differences among age groups, we further reduced the AIC to a value lower than that for a model with totally separate smooths for each age group (AIC = 17,968). Although the non–age varying smooth of time takes account of seasonal effects, Figure 5

indicates that older people were more affected by season than younger people. Consequently, we included age-dependent harmonic functions of time, each with a period of one year to pick up the main differences in seasonal effects among the age groups. Including further harmonic terms did not improve the fit. The final model to control time trends (T3) comprised a non–age varying smooth function of time (160 df) and separate smooths of time (8 df) and harmonic terms (2 df) for each age group.

Controlling Weather Variables

Using the above model terms for time trend, we introduced weather variables to improve the mortality predictions, dealing first with temperature, and then with dew point temperature (Table 2). We fit models with simultaneous smooth terms (10 df) for temperature on the current day and up to six days previously, finding that the effect of the current day's temperature was strikingly different from that of previous days. Consequently, we included both the current day's temperature and the mean temperature of the previous three days. The fitted smooths (10 df) of these temperature variables from a generalized additive model are shown in Figure 6. Hot temperatures were associated with increased mortality on the current day. Cold weather did not have an immediate effect; rather, mortality increased with lower temperatures on previous days, but was unaffected by cold weather on the current day. For the previous days' mean temperature relationship, a linear effect of temperature below 80°F was clear, and a separate linear effect above 80°F. A less clear-cut point was evident at around 70°F for the current day's temperature, so we approximated the smooths by these four linear terms (Table 2).

Table 5. Comparison of Log-Linear Models With and Without Interaction Between TSP, SO_2, and the Weather Stratum Created Using TSI, S-D, and LOESS Weather Models, Philadelphia 1973–1980[a]

		Model	Residual Deviance	df	φ[b]	AIC[c]	*p* Value
TSP and SO_2	TSI[d]	No interaction	2,958.2	35	1.31	3,049.9	< 0.001
		Interaction	2,842.4	77	1.29	3,041.1	
	S-D[e]	No interaction	2,813.7	20	1.24	2,863.4	0.69
		Interaction	2,772.4	58	1.24	2, 916.8	
	LOESS[f]	No interaction	2,810.8	21	1.24	2,862.8	0.71
		Interation	2,770.1	59	1.24	2,916.9	
TSP alone	TSI	No interaction	3,013.5	34	1.34	3,104.5	0.04
		Interaction	2,969.4	55	1.33	3,115.7	
	S-D	No interaction	2,819.3	19	1.24	2,866.6	0.31
		Interaction	2,792.7	38	1.24	2,887.1	
	LOESS	No interaction	2,820.1	20	1.24	2,870.1	0.58
		Interaction	2,798.7	39	1.25	2,896.1	
SO_2 alone	TSI	No interaction	2,962.7	34	1.32	3,052.1	0.13
		Interaction	2,925.6	55	1.31	3,069.9	
	S-D	No interaction	2,825.1	19	1.25	2,872.5	0.67
		Interaction	2,805.3	38	1.25	2,900.1	
	LOESS	No interaction	2,823.4	20	1.25	2,873.3	0.46
		Interaction	2,799.7	39	1.25	2,896.9	

[a] For the S-D and LOESS models, days were categorized into 20 quantiles of predicted mortality based on the corresponding weather component of the additive predictor of the fitted model without interaction.

[b] Estimated constant of overdispersion (deviance method).

[c] Akaike's Information Criterion; see the Methods section.

[d] Kalkstein's Total Synoptic Index categories.

[e] Schwartz-Dockery weather model, as interpreted in Samet and associates (1995a).

[f] Nonparametric function of previous day's temperature and dew point estimated using LOESS.

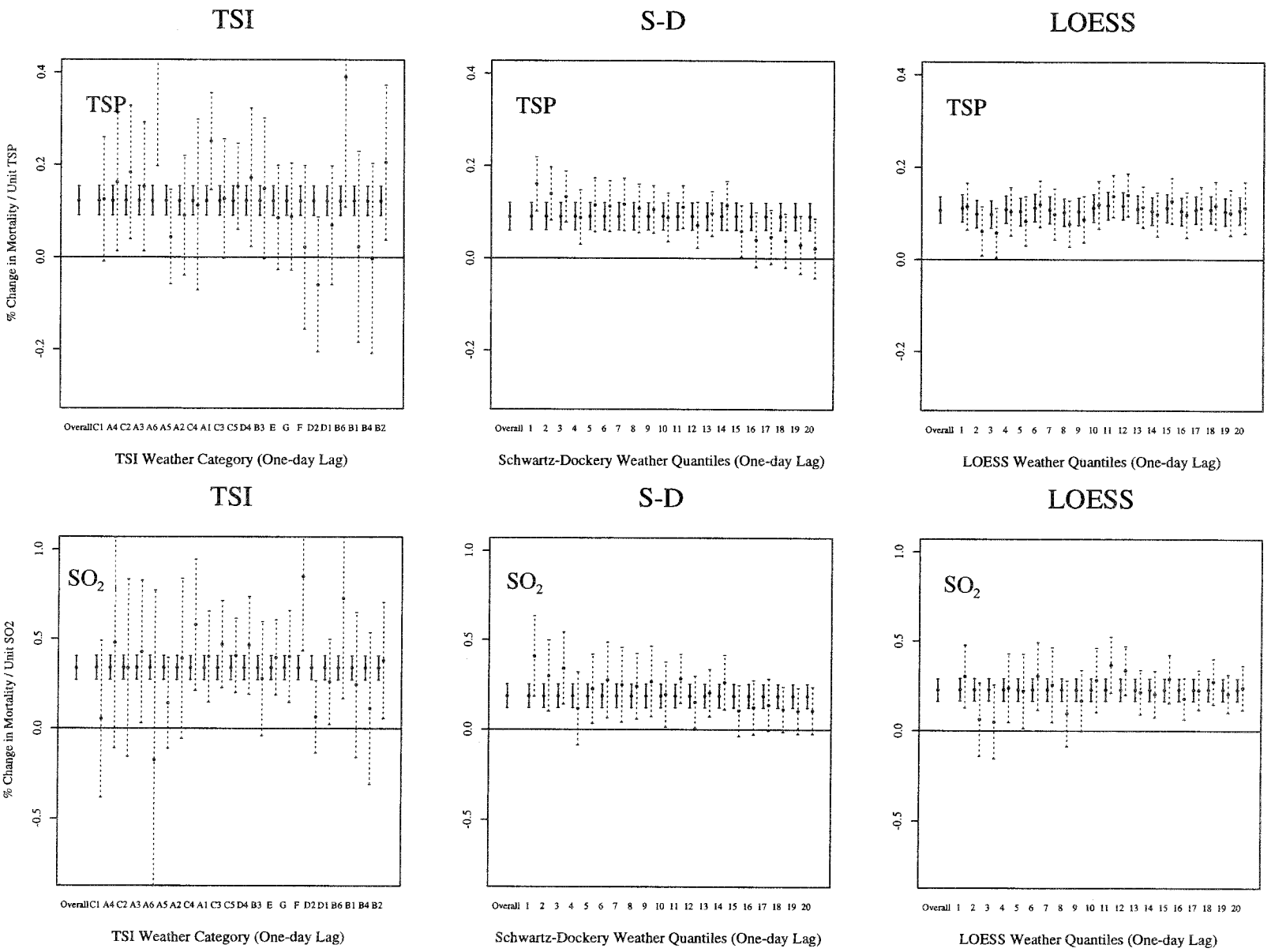

Figure 2. Maximum likelihood estimates (dashed lines) and empirical Bayes estimates (solid lines) with approximate 95% confidence intervals of the TSP and SO_2 coefficients ($\times$ 100) when included separately in Poisson regression models, Philadelphia 1973–1980. Estimates are shown both overall and within each weather category. Separate graphs are shown for the categories of the TSI, S-D, and LOESS weather models. This figure corresponds to the models summarized in Table 5 for TSP and SO_2 alone. The TSI categories are shown in order of increasing empirical mortality rate.

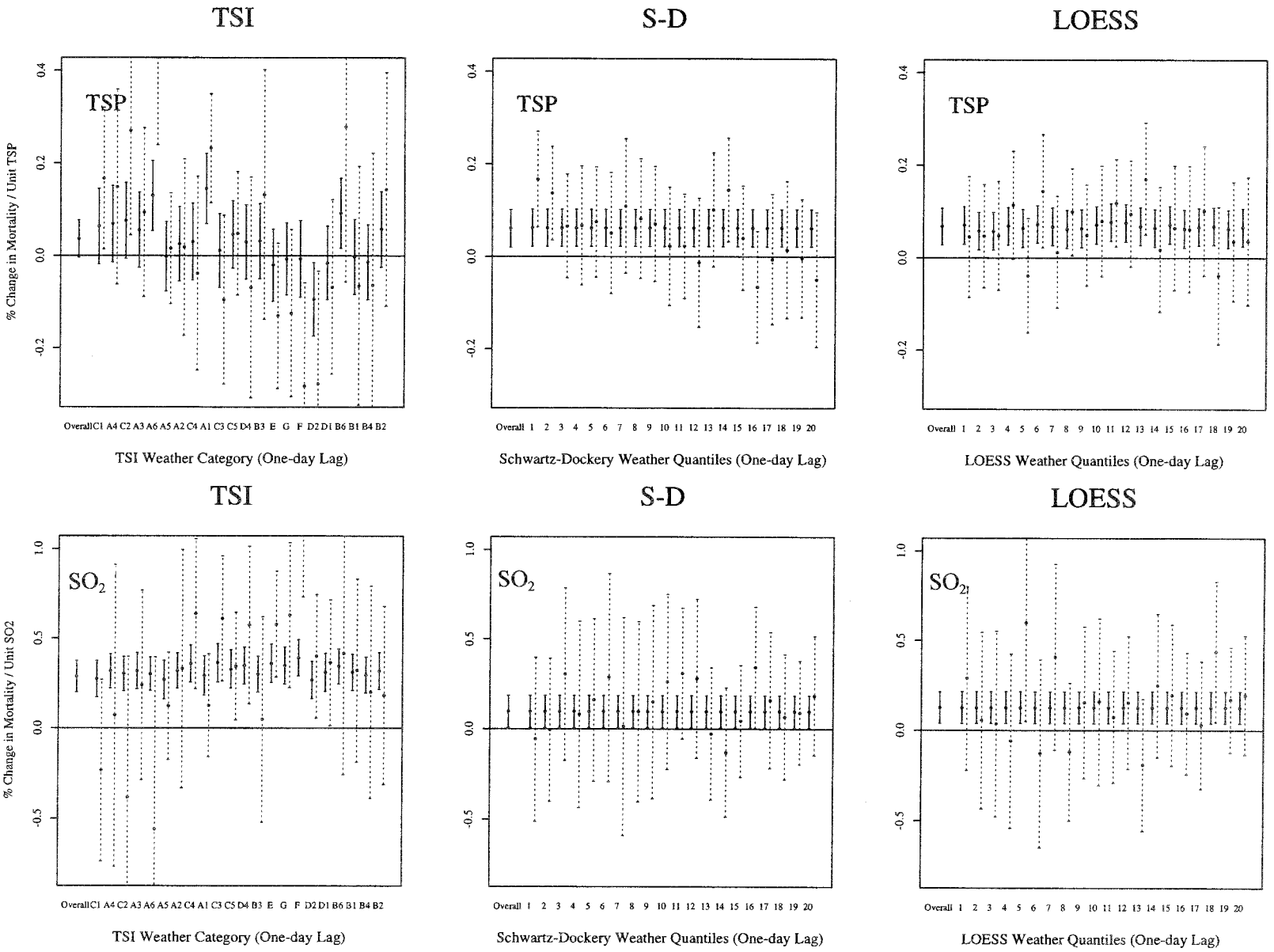

Figure 3. Maximum likelihood estimates (dashed lines) and empirical Bayes estimates (solid lines) with approximate 95% confidence intervals of the TSP and SO_2 coefficients ($\times$ 100) when jointly included in Poisson regression models. Estimates are shown both overall and within each weather category. Separate graphs are shown for the categories of the TSI, S-D, and LOESS weather models. This figure corresponds to the model fits in Table 5 where TSP and SO_2 are included jointly.

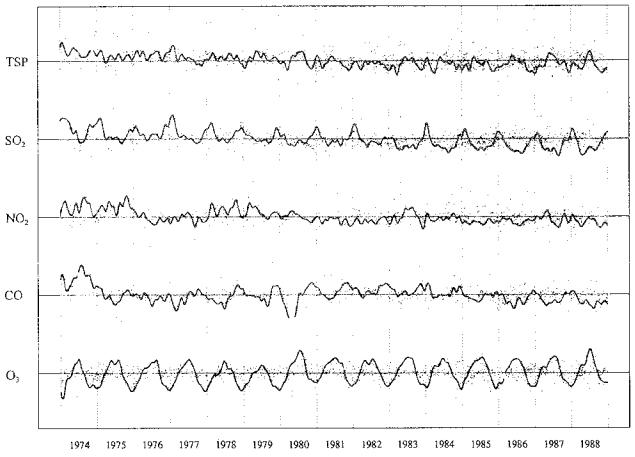

Figure 4. Time trends of square roots of daily pollutant levels, Philadelphia 1974–1988. The smooth (thick) lines were obtained by fitting smoothing splines (160 df). The dots represent the residuals from the smooths.

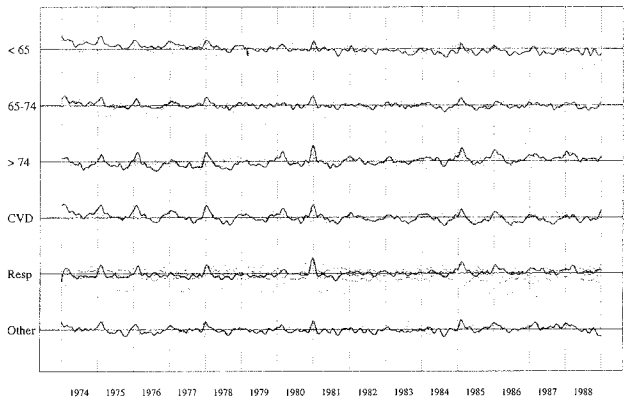

Figure 5. Time trends of square roots of daily mortality counts for each age and cause-of-death group, Philadelphia 1974–1988. The smooth (thick) lines were obtained by fitting smoothing splines (160 df). The dots represent the residuals from the smooths.

Table 6. Summary Statistics for Daily Pollutant Concentrations and Weather Variables, Philadelphia 1974–1988

Unit	TSP ($\mu g/m^3$)	SO_2 (ppb)	NO_2 (ppb)	CO (ppb × 100)	O_3 (ppb)	Temperature[a] (°F)	Dew Point[a] (°F)
Mean	67.3	17.3	39.6	17.4	19.8	54.3	42.3
Standard deviation	26.9	11.6	12.9	7.3	14.6	17.8	19.1
Minimum	14.5	0.3	0.0	1.3	0.0	−0.3	18.8
Lower quartile	47.5	9.3	30.5	12.6	8.3	40.0	27.8
Median	63.0	14.4	37.6	16.0	17.1	55.3	43.5
Upper quartile	72.0	22.2	46.1	20.5	28.5	70.3	58.8
Maximum	222.0	104.3	117.8	101.8	90.0	88.5	76.8
Percent missing	1.5	0.1	0.1	1.5	0.7	0.1	0.1

[a] 24-Hour mean values.

Table 7. Summary Statistics of Daily Mortality for Each Age and Cause-of-Death Group, Philadelphia 1974–1988

	Age			Cause of Death			
Unit	< 65	65–74	≥ 75	Cardiovascular Disease	Respiratory Illness	Other	Total
Mean	15.1	12.2	19.3	20.2	2.5	24.0	46.7
Standard deviation	4.4	3.7	5.1	5.2	1.7	5.3	8.4
Minimum	3	2	5	5	0	8	25
Lower quartile	12	10	16	17	1	20	41
Median	15	12	19	20	2	24	46
Upper quartile	18	15	23	23	3	27	52
Maximum	36	30	47	42	12	51	86

Next we added dew point temperature to the model while retaining the other variables. A model including smooth terms of the current day's dew point and the mean of the dew points for the previous three days indicated linear relationships. We thus included linear terms for these variables. Because the current day's low temperature then had a negligible effect, we removed it from the model.

Because we anticipated that hot and cold weather might affect older people more than younger people, we fitted a model that allowed separate weather effects for each age group. The AIC for this model was 17,257 (compared to 17,247), indicating no significant evidence of differing weather effects by age. Including season-specific weather effects resulted in an AIC value of 17,249, providing no evidence of effect modification by season.

The Pollutants

Correlation analysis of weather- and time-adjusted pollution variables showed moderately high correlations between some pollutant pairs (Table 8). Correlations among TSP, SO_2, NO_2, and CO tended to be moderately strong and positive. The correlations of O_3 with each of the other pollutants varied by season, being positive in the summer and negative in the winter.

To determine the appropriate lag times of pollutants, we fitted models including all pollutants with the same lag time, and then considered each pollutant individually to identify any differing relationships between lag time and mortality. We selected lag times based on *a priori* considerations of the time course of toxicity and on model fit as characterized by the AIC (Figure 7). For TSP and SO_2 considered alone, the current day's values were most pre-

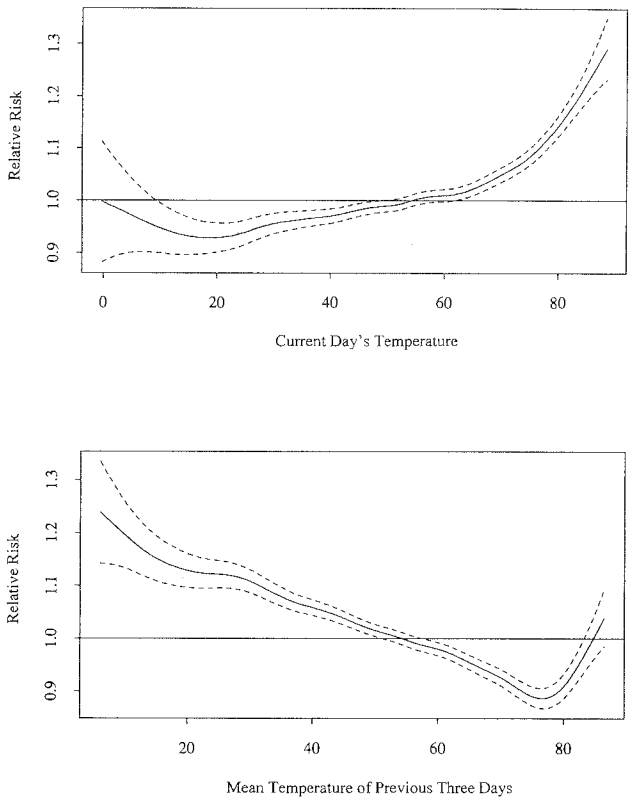

Figure 6. Variation in mortality with current day's temperature, and the mean temperature of the three previous days, resulting from the fit of a generalized additive model, as described in the text, Philadelphia 1974–1988.

Table 8. Pearson Correlations[a] (× 100) Between Pairs of Pollutants by Season and for the Full Year, Philadelphia 1974–1988

Pollutants	Winter	Spring	Summer	Fall	All Year
TSP and O_3	−36.7	19.8	36.8	13.4	11.6
SO_2 and O_3	−47.0	3.1	29.3	3.5	−2.0
NO_2 and O_3	−51.6	−6.5	27.9	4.1	0.1
CO and O_3	−46.2	−29.4	2.6	−24.1	−19.8
TSP and CO	57.4	38.8	30.8	56.4	48.0
SO_2 and CO	53.5	34.4	21.4	44.2	41.7
NO_2 and CO	72.7	66.4	48.2	65.7	63.0
TSP and NO_2	70.0	62.4	57.2	75.7	66.6
SO_2 and NO_2	68.3	57.8	55.1	66.0	60.9
TSP and SO_2	71.6	58.4	55.2	69.7	64.8

[a] Residuals after regressing each of the pollutants on time and weather variables.

dictive; for O_3 it was the previous day, and for CO it was three days previously, whereas NO_2 alone did not have predictive power at any lag time. Including all pollutants together, current days' values fit best, reducing the AIC by 7 units compared to the model with no pollutants included. An exploratory analysis of the mean of more than one day's values indicated that the mean of the current and two previous days' pollutant values was most predictive, reducing the AIC by 14 units. Because CO seemed to have predictive ability at longer lag times, we also included the mean of the three- and four-day–lagged values of this pollutant, which we denoted as LCO. This pattern of effect of lagged CO concentrations was not anticipated on the basis of our understanding of the mechanisms of CO toxicity and the half-life of carboxyhemoglobin. The LCO values were not correlated with other pollutant variables.

Final Air Pollution Models

Table 9 provides the results of fitting models with different combinations of the pollutants. Applying two-pollutant models allowed us to gain some understanding of the pair-

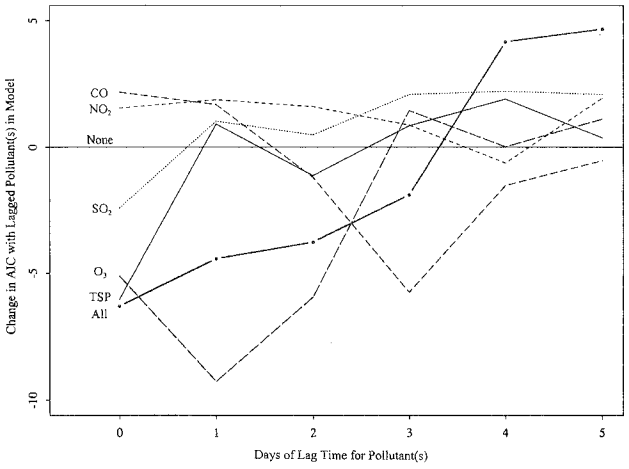

Figure 7. AIC values for models with different lag times of pollutants (CO, NO_2, SO_2, O_3, TSP), when included in the model both simultaneously and separately, Philadelphia 1974–1988.

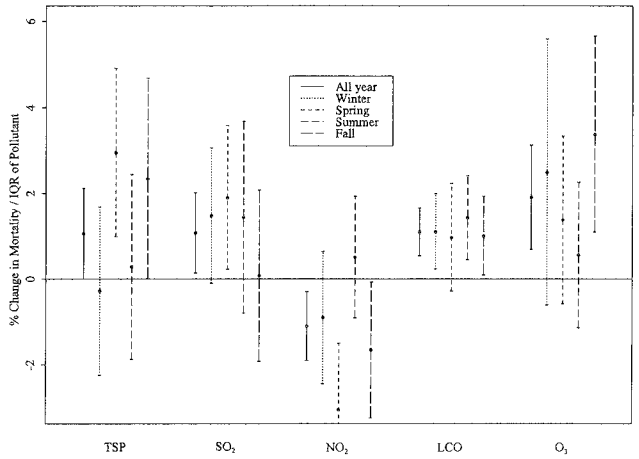

Figure 8. Approximate 95% confidence intervals for pollutant effects within seasons, Philadelphia 1974–1988.

Table 9. Pollutant Coefficients[a] for Models[b] with Pollutants Alone, and with One Pollutant Paired with Each of the Other Pollutants, Philadelphia 1974–1988

Pollutants	TSP	SO_2	NO_2	CO	LCO[c]	O_3
Alone	$1.15^{(3)}$	$1.08^{(3)}$	0.20	0.06	$1.13^{(4)}$	$2.28^{(3)}$
TSP	—	$0.30^{(1)}$	$-0.93^{(2)}$	$-0.54^{(1)}$	$1.17^{(4)}$	$2.04^{(2)}$
SO_2	$0.74^{(1)}$	—	$-0.63^{(1)}$	$-0.38^{(1)}$	$1.16^{(4)}$	$2.25^{(3)}$
NO_2	$1.79^{(4)}$	$1.45^{(3)}$	—	−0.05	$1.14^{(4)}$	$2.27^{(3)}$
CO_2	$1.43^{(3)}$	$1.23^{(3)}$	0.21	—	$1.14^{(3)}$	$2.37^{(3)}$
LCO[c]	$1.21^{(3)}$	$1.12^{(3)}$	0.23	0.12	—	$2.11^{(3)}$
O_3	$0.96^{(2)}$	$1.05^{(2)}$	0.14	0.27	$1.04^{(3)}$	—
All others	$1.04^{(1)}$	$1.08^{(2)}$	$-1.14^{(2)}$	0.08	$1.07^{(3)}$	$1.95^{(3)}$
All except CO	$1.06^{(2)}$	$1.08^{(2)}$	$-1.10^{(2)}$	—	$1.10^{(3)}$	$1.91^{(3)}$

[a] Coefficients are expressed as approximately the percentage of change in mean mortality for an increase of one interquartile range of the corresponding pollutant. (IQR values are: TSP, 34.5 $\mu g/m^3$; SO_2, 12.927 ppb; NO_2, 15.6 ppb; CO, 790 ppb; and O_3, 20.219 ppb.) The numbers in parentheses are rounded down absolute *t* values. A value of 2 or greater is usually taken to indicate significance.

[b] Including long-term time trends, and seasonal and weather effects in the model.

[c] Mean of CO values for the third and fourth prior days.

wise pollutant relationships. The coefficients shown represent the estimated percentage of change in total mortality for a concentration change of one IQR of the corresponding pollutant. When pollutants were considered individually, statistically significant effects were found for TSP, SO_2, LCO, and O_3. In these analyses, LCO presented a consistent effect, but the current CO levels did not. Including other pollutants did not change the estimated effect of O_3. The effect of TSP dropped by about one-third with the inclusion of SO_2 in the model, increased with the addition of NO_2, and did not change with the addition of other pollutants. The estimated effect of SO_2 was similarly reduced with the inclusion of TSP, but increased with the addition of NO_2. Nitrogen dioxide had no effect, except for the models with SO_2 or TSP considered simultaneously, in which instances the estimated effect was negative. When all pollutants except CO were included in the model, the estimated individual pollutant effects were all statistically significant.

Table 10 shows the results of further model fits. Of the two-pollutant models, the one with the lowest AIC was that including O_3 and LCO. Because of their stable effects (Table 9), we concentrated on the results of models including LCO and O_3, along with some combination of TSP, SO_2, and NO_2. We further investigated the model with all five pollutants, because of *a priori* interest.

Seasonal Interactions Because pollutant levels vary substantially by season, as do other factors, we investigated the possibility of different pollutant effects for each of the seasons using the model with all pollutants except CO (Table 2). In Figure 8, we show point estimates with approximate 95% confidence intervals of the air pollution relative risk for the entire year and for each season. These estimates were obtained by fitting two models: the first had a single all-year coefficient for each pollutant (model P2), and the second model had four seasonal coefficients for each pollutant (model P3). Both the AIC values and the coefficients showed little evidence of different pollutant

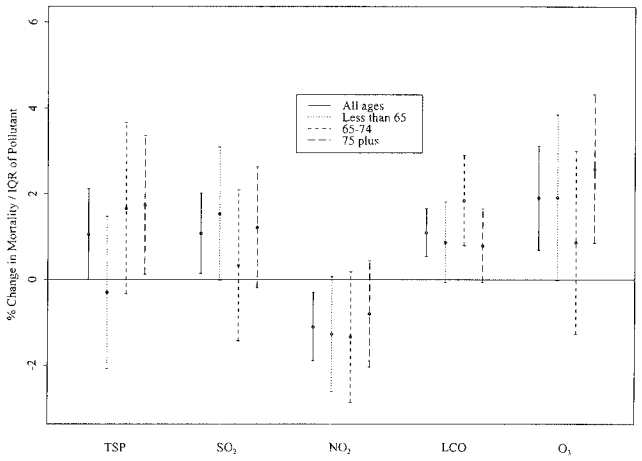

Figure 9. Approximate 95% confidence intervals for pollutant effects for the three age groups, Philadelphia 1974–1988. "All ages" reflects the results of model P2 in Table 2. The three independent age groups show results from model P4.

Table 10. Coefficients[a], Change in AIC Values, and Overdispersion Parameter Estimates for a Series of Models[b] with Different Combinations of Pollutant Variables, Philadelphia 1974--1988

TSP	SO_2	NO_2	LCO[c]	O^3	Δ AIC[d]	$\hat{\varphi}$ [e]
—	—	—	—	—	0	1.049
—	—	—	$1.04^{(3)}$	$2.11^{(3)}$	−15	1.048
$1.03^{(2)}$	—	—	$1.09^{(3)}$	$1.85^{(3)}$	−18	1.048
—	$1.10^{(3)}$	—	$1.08^{(3)}$	$2.08^{(3)}$	−19	1.047
—	—	0.18	$1.04^{(3)}$	$2.10^{(3)}$	−13	1.048
$0.49^{(1)}$	$0.79^{(1)}$	—	$1.09^{(3)}$	$1.96^{(3)}$	−18	1.047
$1.62^{(3)}$	—	$-0.84^{(2)}$	$1.10^{(3)}$	$1.78^{(2)}$	−18	1.047
—	$1.51^{(3)}$	$-0.69^{(1)}$	$1.07^{(3)}$	$2.13^{(3)}$	−19	1.047
$1.06^{(2)}$	$1.08^{(2)}$	$-1.10^{(2)}$	$1.10^{(3)}$	$1.91^{(3)}$	−19	1.047

[a] Each row provides results of a regression model. Coefficients are expressed as approximately the percentage of change in mean mortality for an increase of one interquartile range of the corresponding pollutant. (IQR values are: TSP, 34.5 μg/m^3; SO_2, 12.927 ppb; NO_2, 15.6 ppb; CO, 790 ppb; and O_3, 20.219 ppb.) The numbers in parentheses are rounded down absolute *t* values. A value of 2 or greater is usually taken to indicate significance.

[b] Including long-term time trends, and seasonal and weather effects.

[c] Mean of CO values for the third and fourth prior days.

[d] Changes in Akaike's information criterion from base model (16,486).

effects within each of the seasons. We also investigated each pollutant individually for seasonal interactions, but none was apparent.

Age Interactions Because older people tend to be more frail and to have a higher prevalence of cardiorespiratory conditions, it is plausible that they may have increased sensitivity to pollutant effects. Figure 9 shows approximate 95% confidence intervals for the pollutant effects resulting from two models (Table 2): one with a single coefficient for each pollutant (model P2), and the other allowing separate effects for each age group (model P4). On the basis of the figure and the AIC values, we found no evidence of an interaction of pollutant effects by age. Considering pollutants individually, however, revealed an increasing effect of TSP with age.

Effects by Cause of Death Based on the preceding analyses, we selected the final model for total mortality to include separate effects of TSP for the three age groups, and effects of SO_2, NO_2, LCO, and O_3 that were not age-dependent (Table 2, model P5). We fitted the same model to the mortality counts for the three cause-of-death groups, which resulted in three separate model fits. The resulting estimated percentages, in mean mortality for a change of one pollutant IQR, are shown in Table 11. Approximate 95% confidence intervals for the pollutant effects are illustrated in Figure 10. The estimated effects within cause-of-death groups appeared to be consistent with those seen for total mortality. The increasing effects of TSP by age for each cause-of-death group were particularly evident. TSP had a larger estimated effect for respiratory deaths, but these estimates were imprecise because of the small number of deaths.

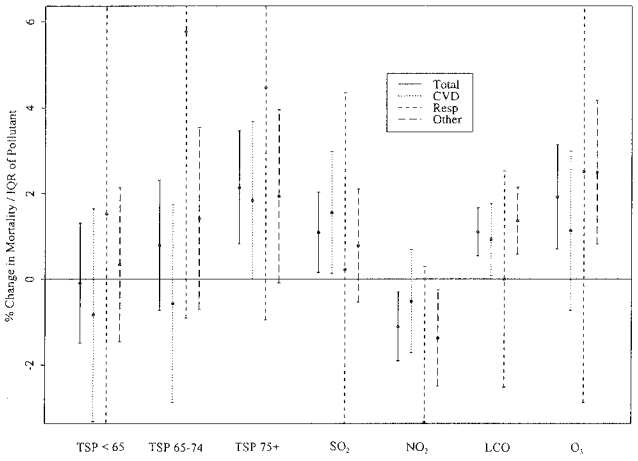

Figure 10. Approximate 95% confidence intervals for pollutant effects using the final model for total mortality and for the three cause-of-death groups, Philadelphia 1974–1988.

Table 11. Pollutant Coefficients[a] of Final Model[b] for Each Cause-of-Death Category, Philadelphia 1974–1988

		Cardiovascular Disease		Respiratory		Other		Total	
Pollutant	Age Group	$\hat{\beta}$	exp ($\hat{\beta}$)	$\hat{\beta}$	exp ($\hat{\beta}$)	$\hat{\beta}$	exp ($\hat{\beta}$)	$\hat{\beta}$	exp ($\hat{\beta}$)
TSP	< 65	−0.83	1.24	1.53	3.53	0.34	0.90	−0.09	0.70
	65–74	−0.57	1.15	$5.77^{(1)}$	3.34	$1.42^{(1)}$	1.06	$0.79^{(1)}$	0.76
	≥ 75	$1.84^{(2)}$	0.92	$4.47^{(1)}$	2.71	$1.93^{(1)}$	1.01	$2.14^{(3)}$	0.66
SO_2		1.55	0.71	0.22	2.06	$0.78^{(1)}$	0.66	1.09	0.47
NO_2		−0.52	0.60	$-3.33^{(1)}$	1.81	$-1.38^{(2)}$	0.56	$-1.11^{(2)}$	0.40
LCO[c]		$0.92^{(2)}$	0.42	0.00	1.26	$1.36^{(3)}$	0.39	$1.10^{(3)}$	0.28
O_3		$1.13^{(1)}$	0.93	2.51	2.69	$2.49^{(2)}$	0.84	$1.92^{(3)}$	0.61

[a] Coefficients are expressed as approximately the percentage of change in mean mortality for an increase of one interquartile range of the corresponding pollutant. (IQR values are: TSP, 34.5 $\mu g/m^3$; SO_2, 12.927 ppb; NO_2, 15.6 ppb; CO, 790 ppb; and O_3, 20.219 ppb.) The numbers in parentheses are rounded down absolute t values. A value of 2 or greater is usually taken to indicate significance.

[b] Including long-term time trends, and seasonal and weather effects in the model.

[c] Mean of CO values for the third and fourth prior days.

DISCUSSION

ALTERNATIVE APPROACHES TO CONTROLLING THE EFFECTS OF WEATHER VARIABLES, PHILADELPHIA 1973–1980

We have extended the analyses conducted in Phase I.A on Philadelphia data for 1973--1980 to assess how sensitive the findings might be to the way in which weather is specified in the models of daily mortality. These analyses were motivated by the possibility of controlling for weather better by using synoptic categories, rather than empiric model-based approaches, and by concerns expressed by the Clean Air Science Advisory Committee that residual confounding from uncontrolled effects of weather may have had an impact on the estimated air pollution--mortality relationships.

The results in Table 4 show that the association between mortality and air pollution indexes, as measured by either TSP alone, SO_2 alone, or TSP and SO_2 together, cannot be explained by replacing the S-D weather model with (1) a nonparametric regression (LOESS) or (2) a set of synoptic categories such as Kalkstein's TSI or SSC systems. Some variation was noted in the estimated effects of the air pollution variables among the models, but no systematic pattern of variation by choice of approach used to control the effects of weather variables was indicated. In addition, little evidence was found in the analyses of total mortality that weather conditions modified the effects of pollution, regardless of the approach used to represent weather in the model.

Pope and Kalkstein (1996) have reported a similar analysis for air pollution and daily mortality in Utah Valley. They compared the model for weather used in the analysis first reported by Pope and colleagues (1992), LOESS smooths of temperature and relative humidity, and synoptic categories. The model used in Pope's 1992 analysis included indicator variables for five temperature categories and relative humidity with a one-day lag. Nineteen synoptic categories were created to describe weather patterns in Utah Valley. Pope and Kalkstein (1996) considered 10 different models to describe the effects of particulate matter (defined as ≤ 10 μm) across the full year. Little variation was noted in the estimated effects of air pollution on total mortality, pulmonary mortality, or cardiovascular mortality regardless of the approach to weather variables. The models with synoptic categories fit the data better than the alternatives and produced slightly higher effect estimates in some of the models. Consequently, Pope and Kalkstein concluded that synoptic categories may be useful in controlling weather variables in mortality-pollution analyses.

We found that the S-D and the LOESS weather models were better predictors of total mortality, as judged by a model fit criterion, than the TSI and SSC synoptic categorizations. This pattern of fit is to be expected because both the S-D and LOESS weather models were chosen on the basis of their ability to predict mortality. The TSI and SSC approaches were chosen to create categories with days similar to one another in weather variables and different from days in other categories. Hence, it is not surprising that those weather categorizations do not predict mortality as well as models that are chosen for that purpose. These analyses only address overall fit to weather and provide no insights concerning the prediction of episodes of weather-related mortality. Pope and Kalkstein also did not make a similar comparison for predicting mortality in their analysis of the Utah Valley data.

Additional research on the use of synoptic categories is warranted, but the present analyses and the recent report of Pope and Kalkstein (1996) indicate that the estimated pollution effects are not highly sensitive to the variables selected for weather conditions. Because synoptic categories represent a capable procedure for distinguishing weather patterns at a locale, they may have a role in controlling the effects of meteorological factors in pollution-mortality analyses. For example, although the TSI and SSC categories were utilized to control weather variables in this study, we did not attempt to dissect the categories to determine which specific parameters within them would have a major impact on mortality. A two-tiered evaluation of synoptic categories has proven useful in previous studies: first, by identifying the category associated with the highest mean mortality, and second, by determining which elements within that air mass explain much of the variance in mortality (Kalkstein 1993). Previous work has shown that meteorological elements within a particularly oppressive (e.g., hot and humid) air mass category can explain much of the variance in mortality within the days of that category. The importance of these within-category factors for mortality varies systematically from place to place, and this has not been fully explored in previous pollution-mortality research. Thus, we plan to explore more fully the temporal and spatial relationships between the synoptic weather categories and mortality. The present analysis would be extended to test the veracity of the two-tiered evaluation described above, to determine differences in interregional responses, and to consider the impact of weather across a broader period of time.

When studying the potential for effect modification, we estimated separate coefficients for TSP, SO_2, and TSP with SO_2 for each weather category. The full set of days thus was distributed into many categories, losing some precision in estimates in these categories. Consequently, there is potential to overinterpret variation in these coefficients, which

is probably due to statistical fluctuations and not to effect modification. The empirical Bayes method described in Appendix A and used in this analysis are effective methods for avoiding this problem. The empirical Bayes results showed little evidence for effect modification (Figures 2 and 3). In contrast, we previously reported statistically significant effect modification by season in the Phase I.A analysis (Samet et al. 1995a). In the current analyses, better control of longer-term fluctuation in mortality, including seasonality, has eliminated these apparent interactions. Furthermore, the test for effect modification in the Phase I.A analysis compared the fit of the fully saturated model—including main effects of season—and the interaction terms with the pollutants, to that of a model lacking variables for season. Subsequent analyses suggested, however, that the improved fit came largely from the interaction terms and not the main effects terms.

In summary, this sensitivity analysis shows that the relationship among TSP, SO_2, and all-cause mortality is not meaningfully changed by using synoptic weather categories in regression models in place of the empiric approach followed by Schwartz and Dockery, or in place of using LOESS. We did not find variation of the effect of pollution across categories of weather in analyses using the empirical Bayes methodology.

AIR POLLUTION AND MORTALITY IN PHILADELPHIA 1974–1988: A MULTIPOLLUTANT ANALYSIS

The relationship between air pollution and mortality in Philadelphia has been addressed by a number of investigators using different data sets and analytic methods. In the first of the recent analyses, Schwartz and Dockery (1992) analyzed data for 1973 through 1980, considering TSP and SO_2 only. They applied Poisson regression, accounting for long-term trends by including a quadratic time trend, year indicators, and seasonal indicators common to all age groups. Weather was controlled by including linear variables for temperature and dew point, as well as indicators for extreme weather days. They found statistically significant effects of TSP and SO_2 when included separately in the model; however, when considered simultaneously, the effect of SO_2 was reduced and was not significant, whereas the estimated TSP effect remained strong. They found a greater effect of TSP for ages older than 65 years and for deaths related to respiratory causes.

Moolgavkar and coworkers (1995) analyzed Philadelphia data for a longer time period—1973 through 1988—considering O_3 in addition to TSP and SO_2. Separate analyses were conducted by season. They noted that the pollutant concentrations had relatively high correlations, and concluded that the association seen between pollution and mortality might not be attributable to particles specifically, but possibly to O_3 in the summer and to SO_2 in the other seasons. Moolgavkar and Luebeck (1996) then extended these analyses by considering NO_2. In contrast to our multipollutant analysis of Philadelphia data for the same years, those investigators found significant effects of NO_2 in the spring, summer, and fall, and of O_3 only in the summer. Moolgavkar and Luebeck did not include CO in the model; CO and NO_2 were moderately correlated in our data (Table 8) and the differing findings could reflect inclusion or exclusion of CO, approaches used to control for time trends and weather, or other differences between the models.

Two other groups also have analyzed Philadelphia data for the same period. Li and Roth (1995) used data for 1973 through 1990 and also considered the pollutants TSP, SO_2, and O_3. They investigated how different methods of analysis can affect estimated pollutant effects, and concluded that findings were highly dependent on the choice of statistical model and the subset of mortality data considered. They concluded that they could not identify an independent effect of TSP. These same data were analyzed by Wyzga and Lipfert (1994, 1995). Their two reports also addressed how estimates of pollutant effects varied as model assumptions were changed. They considered a variety of approaches for smoothing the data, alternate selection of lag structure, and weather-pollutant interactions. Wyzga and Lipfert pointed to a need for additional analyses and the difficulty of reaching conclusions about the effects of air pollution variables based on regression models because of the sensitivity of findings to modeling assumptions.

Cifuentes and Lave (1996) have analyzed Philadelphia data for 1983 through 1988, also considering the pollutants TSP, SO_2, and O_3. In their models, they found that the effect of TSP was generally statistically significant, whereas the effects of SO_2 and O_3 were not. Results were similar to those of Schwartz and Dockery, even though a different time period was considered.

In Phase I.A of this project, Samet and coworkers (1995a) independently reanalyzed the same Philadelphia data previously analyzed by Schwartz and Dockery, and produced results that closely mirrored those of the original investigators (Schwartz and Dockery 1992). We concluded that, within the framework of Poisson regression, the results were generally insensitive to the specification of a model. Our most recent analyses of the Philadelphia data set ex-

tend the previous work by expanding the duration of the time series, including additional pollutants, and applying potentially more informative statistical methods.

In Phase I.B, we used different and improved statistical methods to assess whether the apparent relationship of mortality with pollutants could be the result of inadequate adjustment for longer-term trends. We were successful in reducing the estimated unexplained variation (overdispersion) from 25% to 7% by modeling mortality on time alone, and then to 5% by including weather terms in the model (Table 2). In previous analyses of the Philadelphia data for 1973 through 1980, the final estimates for the overdispersion parameter were 1.25 or greater (Samet et al. 1995b). This additional reduction of the overdispersion was achieved by using age-specific adjustments for long-term trends. The remaining excess variation may be due to the use of only three age classes, whereas mortality rate varies as a smooth function of age. Including all age groups in a single model in this way also leads to more precise estimates because strength is gained across the age groups in estimating common parameters.

The new models (Table 2) showed a lesser effect of TSP than the S-D model (Schwartz and Dockery 1992); in that model, an increase of approximately 2% for a change of one IQR (34.5 $\mu g/m^3$ TSP) was estimated, whereas the new model (P5 in Table 2) estimated a 1% change for the same range. This may reflect the differences in handling age in the two models, but other differences also are apparent between the models. By varying the degrees of freedom allocated to the smooth function from 1 df (linear) to 160 df, we found that the TSP effect varied smoothly from 2% to 1%. There are several potential explanations for the finding that estimates of the TSP effect made with more flexible models were lower than estimates from previous analyses. The models could actually overadjust; some of the apparent effect in previous analyses may have been due to time or weather effects that were taken into account in the models with more degrees of freedom.

The new analyses more carefully control weather effects than did our earlier approach (Phase I.A); in the Philadelphia data, weather effects were substantially greater in magnitude than pollution effects. We have found that days with temperatures in excess of 70°F were associated with increased mortality on the same day, and that the degree of excess increased roughly linearly with temperature above this cut point (Figure 6). We have further found that colder temperatures also were associated with increased mortality, but with a delay of one to three days. The final model for weather included variables for both the current day's temperature and the average temperature of the three prior days, whereas the Phase I.A model considered only the current day's temperature and humidity.

We have examined more systematically the possible modification of the effect of air pollution on mortality by season and by age group (Figures 8 and 9). Having more carefully adjusted for long-term temporal variations and weather, we found little or no evidence of different pollution effects by season, as suggested by Moolgavkar and coworkers (1996) and as we found previously for 1973 through 1980 (Samet et al. 1995a). We found evidence of increasing TSP effects on mortality with increasing age, but no significant interactions of the other pollutants with age.

We also investigated more completely the interrelations among the pollutant measurements: TSP, SO_2, NO_2, CO, and O_3. We found strong positive correlations between TSP, SO_2, NO_2, and CO that are consistent across seasons (Table 8). Ozone concentration, on the other hand, had more modest positive correlations with the concentrations of the other pollutants in summer and small negative correlations in the winter. Our analyses demonstrated a strong independent effect of O_3, which was consistent across seasons and across different models for the other pollutants (Tables 9 through 11). We also found a relatively strong independent effect of CO levels on the previous three to four days, with an increase of one IQR (790 parts per billion associated with a 1% increase in mortality. This effect of lagged CO levels cannot be explained in terms of a known biological mechanism (Bascom et al. 1996a,b) because the physiologic effects of CO on the cardiovascular system are immediate. Among the remaining intercorrelated pollutants—TSP, SO_2, and NO_2—the first two were each strongly associated with mortality, even after they were adjusted for lagged CO and O_3; the third was not. When all three were fit together, each of these pollutants showed a statistically significant association with mortality, although the NO_2 coefficient became negative (Table 11). This reversal of sign reflects the correlations among the pollutant variables and should not be misinterpreted as representing an apparent protective effect of NO_2. Including multiple correlated variables with the same model may result in such implausible effects.

Given the strong association between TSP and SO_2, it is not possible, based solely on these Philadelphia data, to identify one or the other pollutant as the principal cause of increased mortality. Final interpretation of the model results needs to be based on a full integration of the findings with those of other, similar analyses and with toxicologic evidence.

These new models confirm that air pollution is associated with increased mortality in Philadelphia. This general

conclusion is remarkably robust, repeated by different groups of investigators using diverse analytic approaches, and applied to data from Philadelphia and from other locations. Our own work, carried out on data for 1973 through 1980 and 1974 through 1988, has explored the full range of options that might reasonably be pursued in analyzing time-series data for air pollution and mortality. Some methodologic issues still need exploration: the extent of mortality displacement or "harvesting," and the consequences of measurement error for estimates of a pollutant effect based on ecologic studies. However, the analyses of Phase I.A and Phase I.B, along with the work of others who have analyzed data for Philadelphia and other cities, show that the associations of mortality with indexes of air pollution do not reflect model assumptions alone.

In this present analysis, we obtained data on all criteria pollutants relevant to mortality. Concentrations of the combustion-related pollutants were moderately correlated, and we noted that the effect of TSP showed some sensitivity to the inclusion of other pollutants in the model. The univariate and the multipollutant models might be considered as offering bounding estimates of the potential effects of individual pollutants. However, this interpretation ignores the possibility that the models improperly specify the pollutant-mortality relationship and does not consider that measurement error could be differential across pollutants. There is also the possibility of incomplete adjustment of confounding. Simple generalizations cannot be offered concerning the consequences of measurement error and residual confounding in complex data sets with multiple, correlated variables.

The public health implications of the findings in Philadelphia need further exploration. We and others have shown effects of air pollution on daily mortality counts at concentrations of pollutants that are found throughout the world and considered "acceptable" according to a number of air quality guidelines and standards. Further investigation is needed into whether the short-term associations represent the times of death of highly susceptible persons advancing by a few days, or an effect on a longer time frame. The present analysis addressed only short-term effects and not longer-term effects that may be considered more relevant to developing risk management strategies to protect the public's health. The evidence from several cohort studies suggests that long-term effects of pollution could lead to shortening of life (Dockery et al. 1993; Pope et al. 1995). We caution against using the model coefficients from this analysis directly to estimate the potential consequences of lowering concentrations of the individual pollutants through regulatory measures; the pollutant concentrations are correlated and the estimates of their effects depend on modeling assumptions. The models do indicate, however, that air pollution remains a persistent public health concern.

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APPENDIX A. Empirical Bayes Estimation

INTRODUCTION

Figures 2 and 3 (in the main text) show maximum likelihood estimates (dashed lines) and the empirical Bayes estimates (solid lines) of the TSP and SO_2 coefficients within each of the weather categories when included separately (Figure 2) or jointly (Figure 3) in the model. These are given with approximate 95% confidence intervals in the form of ± 2 standard errors. Also shown are the confidence intervals for the TSP and SO_2 coefficients when we do not

allow interaction with weather. The parameter estimates are variable and subject to overinterpretation. Empirical Bayes is a method of adjusting the estimates such that they are shrunk back toward the overall coefficient value. The amount of shrinkage depends on the strength of evidence in the data that the underlying parameters do in fact differ across weather categories.

In the next sections, we present the method of empirical Bayes estimation we used and how we implemented it to assess if weather variables modified a pollutant's effect on daily mortality.

METHOD

Suppose that as the result of fitting a regression model by maximum likelihood, we have estimates $\hat{\beta}$ of k parameters β, as well as an estimated variance matrix $V_{\hat{\beta}}$. It will often be reasonable to assume that the estimates $\hat{\beta}$ are approximately normally distributed with mean β and variance $V_{\hat{\beta}}$. An approximate 95% confidence interval for β_j is then obtained as

$$\hat{\beta}_j \pm 2[V_{\hat{\beta}}]_{jj}^{1/2}.$$

Now suppose that before fitting the model, we had a prior belief or hypothesis that the βs were related to each other in terms of a small number of underlying parameters θ. This prior belief could be that the βs are all equal, but more generally we will have $\beta = Z\theta$ for some design matrix Z.

Empirical Bayes estimation provides a means of adjusting the parameter estimates $\hat{\beta}$ to incorporate such prior beliefs. However, unlike a full Bayesian analysis, we use the data themselves to estimate the parameters of the prior distribution.

In a true Bayesian framework, we could specify a full normal prior distribution for β,

$$\beta \sim MVN(Z\theta, V_0)$$

where both θ and V_0 are known. As stated above, we also have (approximately)

$$\hat{\beta} \mid \beta \sim MVN(\beta, V_{\hat{\beta}}).$$

This results in a posterior distribution for β:

$$\beta \mid \hat{\beta} \sim MVN(\beta^*, (V_{\hat{\beta}}^{-1} + V_0^{-1})^{-1})$$

where

$$\beta^* = (V_{\hat{\beta}}^{-1} + V_0^{-1})^{-1} (V_{\hat{\beta}}^{-1} \hat{\beta} + V_0^{-1} Z\theta)$$

(Morris 1983), which is a weighted average of the prior mean $Z\theta$ and the maximum likelihood estimates $\hat{\beta}$.

Because we do not wish to specify values of θ and V_0 explicitly, they must be estimated. Rather than estimating the whole variance matrix V_0, we assume that it can be summarized in terms of a small number of parameters α.

The marginal distribution of $\hat{\beta}$ is

$$\hat{\beta} \mid \theta, \alpha \sim MVN(Z\theta, V_0(\alpha) + V_{\hat{\beta}}),$$

so we can estimate θ and α by maximum likelihood. This will lead to an estimate $\hat{V}_0 = V_0(\hat{\alpha})$, which is now assumed to be a fixed specified matrix V_0, and

$$\hat{\theta} = [Z^T (V_0 + V_{\hat{\beta}})^{-1} Z]^{-1} Z^T (V_0 + V_{\hat{\beta}})^{-1} \hat{\beta}.$$

Substituting $\hat{\theta}$ for θ in the Bayesian posterior mode estimate β^* produces an empirical Bayes estimate $\tilde{\beta} = M\hat{\beta}$ where

$$M = (V_0^{-1} + V_{\hat{\beta}}^{-1})^{-1} \cdot \left\{ V_0^{-1} Z[Z^T (V_0 + V_{\hat{\beta}})^{-1} Z]^{-1} Z^T (V_0 + V_{\hat{\beta}})^{-1} + V_{\hat{\beta}}^{-1} \right\}.$$

Now $\mathrm{Var}(\tilde{\beta}) = M\mathrm{Var}(\hat{\beta})M^T$ and we will assume that $\tilde{\beta}$ is approximately unbiased and normally distributed. This leads to approximate 95% confidence intervals for each β_j as

$$\tilde{\beta}_j \pm 2[MV_{\hat{\beta}}M^T]_{jj}^{1/2},$$

which are compromises between the overall confidence intervals (for $Z\theta$) and the individual confidence intervals for β.

Morris (1983) provides an overview of the theory and applications of the empirical Bayes approach of parameter shrinkage, and more sophisticated methods based on bootstrap sampling are discussed by Laird and Louis (1987).

APPLICATION

In assessing the interaction between pollution effects (TSP and SO_2) and weather (Figure 3 in the main text), there are $k = 2m$ parameters β of interest, where m is the number of weather categories. We parameterize the prior distribution for β as

$$\beta \sim N(Z\theta, V_0),$$

with $\theta = (\theta_1, \theta_2)^T$, where θ_1 and θ_2 are the TSP and SO_2 coefficients, respectively. We arrange β such that the first m elements refer to TSP and the last m elements to SO_2.

The design matrix Z is thus specified as:

$$Z = \begin{bmatrix} 1 & 0 \\ & \\ 0 & 1 \end{bmatrix},$$

where 1 and 0 are $m \times 1$ vectors.

The variance matrix V_0 is specified to be of the form:

$$V_0 = \begin{bmatrix} \sigma_1^2 I_m & 0 \\ 0 & \sigma_2^2 I_m \end{bmatrix},$$

where I_m is the $m \times m$ identity matrix. Also, although not done here, it would be sensible to introduce a correlation parameter ρ between the TSP and SO_2 pairs producing

$$V_0 = \begin{bmatrix} \sigma_1^2 I_m & \rho\sigma_1\sigma_2 I_m \\ \rho\sigma_1\sigma_2 I_m & \sigma_2^2 I_m \end{bmatrix},$$

In Figure 2, where the effects of TSP and SO_2 are assessed separately in the regression model, β is a vector of length m (the number of weather categories),

$$Z = 1(m \times 1 \text{ vector}), \text{ and } V_0 = \sigma_2^2 I_m.$$

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PUBLICATIONS RESULTING FROM THIS RESEARCH

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ABBREVIATIONS

AIC	Akaike's Information Criterion
CO	carbon monoxide
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
df	degrees of freedom
IQR	interquartile range
LCO	mean of CO values on third and fourth prior (lagged) days
LOESS	locally weighted smoothing scatterplots
NO_2	nitrogen dioxide
O_3	ozone
PM_{10}	particulate matter ≤ 10 μm in aerodynamic diameter
ppb	parts per billion
S-D	Schwartz and Dockery
SO_2	sulfur dioxide
SSC	Spatial Synoptic Classification
TSI	Total Synoptic Index
TSP	total suspended particles

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Particulate Air Pollution and Daily Mortality: Analyses of the Effects of Weather and Multiple Air Pollutants

This document is one section of the Health Effects Institute Phase I.B Report of the Particle Epidemiology Evaluation Project, *Particulate Air Pollution and Daily Mortality: Analyses of the Effects of Weather and Multiple Air Pollutants*, which also includes an HEI Statement about the research, the Investigators' Report, and Comments from the Health Review Committee.

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INTRODUCTION

In July 1994, the Health Effects Institute initiated the Particle Epidemiology Evaluation Project in response to a widely perceived need to evaluate independently the epidemiologic studies in several U.S. cities that have observed associations between changes in daily mortality rates and particulate air pollution levels below the current National Ambient Air Quality Standard (NAAQS)* for particulate matter (U.S. Environmental Protection Agency [EPA] 1996a). This need was particularly acute because the EPA was evaluating the evidence on the health effects of particulate air pollution as part of its review of the particulate matter standard, and the results of these epidemiologic studies had been questioned with respect to both the reproducibility of the findings and the sensitivity of the results to different analytic approaches. The Particle Epidemiology Evaluation Project was designed to achieve three main objectives by reanalyzing the data sets from several U.S. cities:

1. to evaluate the evidence of associations between particulate air pollution and (a) mortality from all causes and (b) mortality from cardiac and respiratory causes;
2. to examine how sensitive the observed associations are to key analytic assumptions and data features; and
3. to the extent that a consistent association was found, to extend the analyses to address scientific questions with important public health and regulatory implications, such as the impact of air pollution on years of life lost and the role of single or multiple pollutants.

The HEI Board of Directors appointed an Oversight Committee, which, in a competitive process among fifteen teams, selected Drs. Jonathan Samet and Scott Zeger of The Johns Hopkins University School of Hygiene and Public Health to reanalyze the data from six studies linking particulate air pollution with daily mortality. The investigators who had conducted the original studies contributed their data and other information to Drs. Samet and Zeger, and discussed the reanalyses with them and with the Oversight Committee during the course of the project.

The project was divided into two phases to respond more efficiently to an accelerated timetable for the EPA's review of the NAAQS for particulate matter. Phase I, conducted from July 1994 through December 1996, addressed objectives 1 and 2 described above. Phase II, called the National Morbidity, Mortality, and Air Pollution Study, began in December 1996 and is addressing objective 3 using nationwide U.S. data.

* A list of abbreviations appears at the end of the Investigators' Report for your reference.

Phase I was further divided into two parts. Phase I.A, conducted between July 1994 and August 1995, focussed on replicating and validating six time-series studies of particulate air pollution and daily mortality in six U.S. cities (Samet et al. 1995). In particular, from the same publicly available data bases used in earlier studies, Dr. Samet and colleagues were able to reconstruct a data set for Philadelphia, PA, for the years 1973 through 1980 that closely matched the data set used in the original study (Schwartz and Dockery 1992). They applied statistical methods developed specifically for this project to the data used by the original investigators and produced numerical results that closely agreed with and, in general, confirmed results from the earlier studies.

In analyzing the Philadelphia data from 1973 through 1980, Samet and colleagues found that the results were consistent even when a variety of statistical techniques and assumptions about the effects of weather and other pollutants were applied (Samet et al. 1995). Although the reanalysis generally agreed with the original findings, namely that daily deaths increased with increases in measured levels of particulate air pollution (measured as total suspended particles [TSP]), it also revealed that the relation between the effects of particulate air pollution and the effects of sulfur dioxide (SO_2) was more complex than the earlier studies had suggested, and that the increased mortality associated with air pollution could not be attributed to increased levels of either TSP or SO_2 alone. The results were peer-reviewed and published in August 1995 as an HEI Special Report entitled *Particulate Air Pollution and Daily Mortality: Replication and Validation of Selected Studies (The Phase I.A Report of the Particle Epidemiology Evaluation Project).*

Phase I.B, conducted between August 1995 and December 1996, extended the analyses from Phase I.A to address two issues of interest to the scientific community and to the EPA's Clean Air Scientific Advisory Committee as they continued to evaluate the epidemiologic data on daily mortality and particulate air pollution:

1. Would changing the methods used to control the effects of weather in analyses of air pollution and daily mortality change the association observed in earlier analyses; and
2. Would statistical models that include data for all relevant criteria pollutants (rather than just one or two) change the observed association in a specific locale.

The current Investigators' Report, *Air Pollution, Weather, and Mortality in Philadelphia 1974–1988,* presents the results of these Phase I.B analyses.

In addition, Phase I.B had a third objective: to develop epidemiologic and statistical methods to use in Phase II, the

planned nationwide study of air pollution, morbidity, and mortality. To fulfill this objective, the investigators developed methods for (1) modeling the effects of weather and multiple pollutants, (2) addressing the effects of exposure measurement errors on daily time-series studies, and (3) estimating from daily time-series data the extent of life shortening due to short-term air pollution exposure. Their methods for modeling weather and multiple pollutants are discussed in this Special Report.

EVALUATION OF PHASE I.B

ALTERNATIVE APPROACHES TO CONTROLLING THE EFFECTS OF WEATHER, PHILADELPHIA 1973–1980

In time-series studies of daily mortality, the behavioral or demographic characteristics of a population, which do not vary from day to day, are not likely to confound (that is, to bias) estimates of the effects of air pollution on daily mortality; any characteristics that might be confounders must vary in sequence with both exposure and mortality. However, certain meteorologic variables, which exhibit both daily variability and an independent association with mortality, are clearly potential confounders, and investigators have attempted to control their effects in virtually every contemporary analysis of the effects of air pollution on daily mortality. Of the many individual meteorologic variables, temperature has been shown to affect health outcomes to a significant degree (World Health Organization 1996). Relative humidity (or dew-point temperature) also was considered in some analyses because it was assumed to have an effect based on observed associations with mortality in some, but not all, studies (World Health Organization 1996).

The prevailing empirical practice of using only temperature and humidity to control the effects of weather in models of air pollution and health effects has been criticized as providing inadequate control (Kalkstein 1994). In response to these concerns, Kalkstein and coworkers (1997) proposed using synoptic weather categories to adjust for the effects of weather in daily time-series mortality studies. This approach uses the statistical technique of factor analysis to reduce a relatively large number of meteorological variables to a smaller set of categories that describe weather patterns in a particular locale.

In the current analysis, the investigators evaluated three different approaches to control the effects of weather variables on the association between air pollution and daily mortality in Philadelphia from 1973 through 1980:

1. two sets of synoptic categories developed by Kalkstein for Philadelphia;
2. nonparametric regression methods that fit a smooth function of the previous day's temperature and dew point to daily mortality data (referred to as the LOESS model); and
3. an empirical approach that incorporates the current and previous days' absolute and dew-point temperatures and indicator terms for hot and cold days. This is the approach that Schwartz and Dockery (1992) used in their original analysis of daily mortality in Philadelphia (referred to in the Investigators' Report as the S-D model).

The major objective of the Phase I.B analysis was to determine if the association between daily mortality and two indexes of air pollution (concentrations of TSP and SO_2) observed in the Philadelphia data by several investigators (Cifuentes and Lave 1997; Schwartz and Dockery 1992; Moolgavkar et al. 1995; Wyzga and Lipfert 1995) could be explained by the effects of weather variables as described by synoptic weather categories. (In Phase I.A, Drs. Samet and Zeger had already demonstrated that the LOESS approach and the S-D model, both used to control the effects of weather, produced similar results using the Philadelphia data from 1973 through 1980, and analyses using both approaches found an association between daily mortality and particulate air pollution, as characterized by the concentration of either TSP or SO_2 [Samet et al. 1995]). The second objective was to determine whether the strength of the association between air pollution and daily mortality would vary under different weather conditions.

Using synoptic categories, the investigators found (1) a pattern of associations between air pollution and daily mortality, and (2) an association between either TSP or SO_2 and daily mortality that was consistent with those observed with the LOESS and S-D approaches. The authors argue convincingly that, with the synoptic category approach, the most apparent changes in the associations between TSP or SO_2 and daily mortality were found in results from models that fit the data relatively poorly, and therefore should not be given great interpretative weight.

In general, the authors observed that models based on the synoptic categories fit the data less well than either the LOESS approach or the S-D model. This result is not surprising; the synoptic categories are designed to describe weather patterns rather than to predict mortality. However, as the authors note, Pope and Kalkstein (1996), in reanalyzing an earlier study of particulate air pollution and daily mortality in Utah County (Pope et al. 1992), found just the opposite: Models using synoptic categories to control the effects of weather fit the data better than models using

approaches similar to the LOESS and S-D models. This discrepancy leaves open the question of what is the optimal method to control confounding by weather variables, and suggests that it may depend to some extent on the locale being studied. Continued research into the use of synoptic categories, including which meteorologic elements within them account for associations between weather and mortality, seems well justified.

The investigators carefully examined how the strength of the association between air pollution and daily mortality varied with weather, and found no meaningful pattern of variation in the relative risks, regardless of the approach used to characterize weather variables. Such analyses unavoidably require subdividing the data into smaller strata, which may itself result in increased variability of the relative risk estimates. To guard against overinterpreting this variability, the authors used an estimation procedure known as the empirical Bayes method to account for the increased variability introduced by subdividing the data. The estimates derived with this method can be viewed as a statistical compromise between a single overall estimate of the relative risk of mortality from air pollution (which assumes no systematic variation of the relative risk between different weather scenarios) and the individual estimates of relative risk of mortality from air pollution for each weather scenario. The empirical Bayes analyses (see Figures 2 and 3 in the Investigators' Report) show little evidence that weather modifies the association between air pollution and daily mortality. The sole exception to this assessment is that the association between TSP and mortality appears to vary among synoptic categories of weather in models that evaluate TSP and SO_2 together (see Figure 3, panel A). However, as the investigators have stated, the fit of the synoptic category approach to the data is markedly poorer than the fit of the S-D and LOESS models (see Table 5), which argues against affording as much weight to this approach as one would to the results from better-fitting models.

In addition to the three methods compared in Phase I.B, other approaches to characterizing weather have been proposed and recently applied in analyses of air pollution and daily mortality. For example, Li and Roth (1995) fitted models wherein temperature was characterized as a simple linear function, or as the absolute value of the difference between observed temperature and 70°F (a presumed ideal temperature). However, these approaches are at odds with current knowledge about the effect of temperature on mortality, which is both nonlinear and more marked for higher than for lower temperatures (World Health Organization 1996).

The Phase I.B analyses provide perhaps the most thorough test to date of the hypothesis that controlling the effects of weather inadequately is responsible for the widely observed effects of air pollution on daily mortality. Along with other recent work (Pope and Kalkstein 1996; U.S. Environmental Protection Agency 1996a), they offer a persuasive argument against that hypothesis.

MULTIPOLLUTANT ANALYSES OF AIR POLLUTION AND MORTALITY, PHILADELPHIA 1974–1988

Much of the critical discussion of epidemiologic studies of particulate air pollution and daily mortality has focused on whether the widely observed increases in daily mortality rates are due to particulate air pollution or to some of the gaseous pollutants (e.g., SO_2 and O_3) that are invariably also present, and whose levels are often correlated over time with particulate air pollution. Some analysts have argued that to ensure valid estimates of the effects of particulate matter alone, statistical models for daily mortality should incorporate all criteria pollutants present in a given locale (Moolgavkar and Luebeck 1996). Others contend that multipollutant models fitted to data from single locations where the various pollutants are highly correlated will not produce reliable estimates of the relative risk of mortality from particulate matter alone, and that reliable estimates can best be achieved by fitting models that include limited numbers of copollutants, or perhaps only particulate matter, to data from a variety of locales with different levels of copollutants (Pope et al. 1995a).

In the current analysis, the investigators estimated what each individual air pollutant contributed to daily mortality in Philadelphia, an eastern U.S. city where data were available over a 15-year period (1974–1988) for all criteria air pollutant, and where levels of these pollutants are correlated with one another over the period of the study. Their previous work in Phase I.A, using Philadelphia data for 1973–1980 and only two pollutants (TSP and SO_2), had led them and the Health Effects Institute to conclude that the increased daily mortality associated with air pollution in that city could not be attributed to particulate air pollution alone (Health Effects Institute 1995).

The investigators proceeded sequentially to build statistical models for air pollution and daily mortality, first modeling the long-term trends in the 15-year mortality time series, and then expanding the model to address weather variables. Only after having studied these other factors did they consider the effects of air pollution on daily mortality. Model building was guided by current knowledge of toxicology, pathophysiology, and clinical medicine where possible, and by one statistical criterion, Akaike's Information Criterion (AIC) (Hastie and Tibshirani 1990), a measure of the fit of a proposed model to the data. The criterion of model fit guided the choice of models when existing knowl-

edge provided little guidance. The authors provide a description of the model building steps and intermediate results that helps the reader follow and critically evaluate their modeling decisions (see Table 2 in the Investigators' Report).

The sequential approach to model building yielded several important insights about what approaches should be pursued to control long-term mortality trends and weather. Detailed modeling of long-term mortality trends revealed their dependence on the age of the population at risk: between 1974 and 1988, the mortality rate in Philadelphia had declined for those individuals less than 65 years of age, but had risen in older persons, whose mortality rate was also more dependent on season than that of persons under the age of 65. Detailed modeling of weather effects revealed (1) a nonlinear relation between temperature and daily mortality across the entire temperature range, and (2) different time courses for the effects of cold and hot temperatures on daily mortality. Taking these patterns into account in the statistical models for mortality and air pollution substantially improved the model's fit to the observed data (see Table 2), as indicated by marked reductions in the AIC value. The statistical models for daily mortality assume that the distribution of deaths over time follows a Poisson distribution, and that, theoretically at least, the interpretation of the estimates of mortality risk from those models depends on the tenability of that assumption. It is therefore reassuring that the more flexible modeling of the interactions of age with time and season improves the conformity of the model estimates to a Poisson distribution (as measured by the reduction in the overdispersion parameter from 1.252 in model T0 to 1.069 in model T3, where a value of 1.00 indicates perfect conformity of the data to a Poisson distribution).

When the investigators added air pollution to the models, they initially examined the effects of each of the pollutants alone, then in pairs, and finally the five relevant criteria pollutants together (TSP, SO_2, nitrogen dioxide, ozone, and carbon monoxide). As one might have anticipated, the individual pollutants TSP, SO_2, nitrogen dioxide, and carbon monoxide were moderately correlated due to their common sources and well-known seasonal patterns, whereas the correlation of ozone with the other pollutants varied with season. The investigators chose the exposure interval for each pollutant (i.e., a span of hours or days referred to as lag period) on the basis of toxicologic information, prior epidemiologic findings, and model fit. For most of the pollutants, the lag period that provided the best fit to the data was the average of the ambient pollutant concentration measurements on the day of death (current day) and on the previous day, a choice that one might have made on a priori information and that is consistent with prior epidemiologic results (Health Effects Institute 1995). However, for carbon monoxide the best-fitting model for daily mortality included the average of the ambient levels on the third and fourth prior days (referred to as lagged carbon monoxide). Therefore, the investigators retained this model despite their view that such a lagged effect is at odds with the current knowledge of the toxicology of carbon monoxide, whose effect on carboxyhemoglobin levels is relatively rapid (minutes or hours rather than days). It is not clear, however, that current scientific knowledge is sufficient to support definite statements about the timing of the effects of short-term exposure to carbon monoxide on mortality, so lag times of three or four days should not be dismissed.

The results of the Phase I.B multipollutant analyses corroborate the results of Phase I.A in three important respects. When all relevant criteria pollutants are considered, (1) a clear association is seen between air pollution indexes and daily mortality; (2) an association is observed between changes in daily mortality rates and both TSP (an index of particulate air pollution) and SO_2; and (3) no single pollutant by itself accounts for the observed increases in daily mortality.

Unscrambling the effects of multiple pollutants poses familiar but formidable problems. Single-pollutant analyses are a natural, even necessary, starting point for any investigation. If an effect is not revealed when a pollutant is considered alone in a model, that pollutant is unlikely to have a causal role unless a rather complicated pattern of correlations and interactions is masking the causal effect. However, because the various pollutants are indeed correlated with each other, and because there may be more than one causal agent among them, univariate analyses of pollution effects are very likely to produce biased estimates.

If we knew which pollutants are the causal agents, disentangling the effects of individual pollutants would be relatively straightforward: we would simply fit a correctly specified model containing only the relevant pollutants and would be assured of obtaining unbiased estimates of the magnitude of each pollutant's effects. In reality, however, we do not know which variables have a causal function; indeed, one of the purposes of the analysis is to explore competing hypotheses in an attempt to infer which combination of variables is more likely to cause health effects.

Unfortunately, no approach based on statistical criteria of model fit is guaranteed to provide unbiased results. The best-fitting model, by one criterion, will tend to provide overestimates of the effects of the variables included in the model and may even include effects that do not exist at all in the larger population to which we wish to generalize our

conclusions. Furthermore, a not uncommon observation in analyses of highly correlated data sets is that the best-fitting model may include effects that go in the opposite direction from prior beliefs. An example of this phenomenon in the present analyses is the apparently protective effect of NO_2 in the multivariate models, when no such effect is seen in univariate analyses (see Table 9). Such a result may well be a purely statistical phenomenon, reflecting perhaps an attempt by the model to adjust for some inaccuracy in characterizing another component with which NO_2 happens to be correlated. Further analyses might be warranted to see if refining the model of the effects of other pollutants could eliminate this paradoxical effect of NO_2.

It would have been reasonable to exclude from consideration models that include results that are deemed a priori to be biologically implausible, such as the apparently protective effect of NO_2 in the multipollutant models. (This form of "one-sided" hypothesis testing is appropriate if adopted a priori, but not when invoked post hoc to explain away embarrassing results.) Although the authors clearly favor giving such results little weight in the interpretation of their overall findings, they nevertheless have reported these results, along with the entire predetermined set of analyses they had undertaken, to avoid selective reporting, which can introduce bias in future attempts to quantitatively review the findings of published research (Begg and Berlin 1988).

Interpreting the coefficients for individual pollutants in multipollutant models is complicated further because the relative weight accorded to different pollutants can be distorted by differences in their respective errors of measurement, particularly if the errors are also correlated. Thus, the pollutant that remains significant, and to which the model attributes the effect, may not be the causal agent but rather the pollutant that best correlates in time with the true causal pollutant (or mixture). Even the best correlate is influenced by specific local sources, dispersion modes, and the placement of monitors.

One could legitimately ask what analyses would have allowed the investigators to distinguish one of the pollutants as the principal cause of changes in mortality. As noted above, the objective of Phase I.B was to measure the association between one index of particulate air pollution, TSP, and daily mortality in models that included all relevant criteria pollutants as separate covariates. The investigators intended specifically to address the hypothesis, raised by Moolgavkar and Luebeck (1996) among others, that each pollutant might have an independent effect on daily mortality when analyzed using models in which the concentrations of all other pollutants were held constant. Multiple regression models, such as those employed by the investigators in this study, are appropriate to estimate the effects of the separate contributions of individual pollutants under such an hypothesis. On the other hand, if the mixture of gaseous and particulate air pollutants has a complex influence on daily mortality rates, or if the various pollutant measurements are merely surrogates for some underlying "pollution effect," then treating each one as a confounder of the others would not be appropriate. Unfortunately, because Phase I.B was designed to analyze data from only one city, and because exposure data on the various pollutants, especially particles, were limited, it was not feasible to evaluate these other conceptual models of the relation between air pollution and daily mortality. Ultimately, it will require joint analyses of data sets from multiple cities with different copollutant correlations (such as those planned in Phase II) to address further the role of multiple pollutants. Major advances in designing multipollutant epidemiologic models of daily mortality, and in interpretating their results, may also require concomitant advances in understanding the biological mechanisms by which particulate and gaseous air pollutants impact mortality.

The current analyses also differ from earlier analyses of Philadelphia data in several respects. First, the relative magnitude of the estimated increase in the daily mortality rate was reduced from 2%, observed by Schwartz and Dockery (1992), to 1% in the current study over the same range of TSP concentrations. This change is most likely attributable to more flexibly modeling long-term mortality trends, and particularly to allowing the long-term trends to vary with age. Second, season-specific associations between pollutants and changes in daily mortality (observed in the Phase I.A analyses, and by Moolgavkar and colleagues [1995]) were not observed in this study. The explanation given by the investigators that the different findings could reflect improved modeling of weather and long-term mortality trends, although tenable, needs to be addressed in future studies. It is also plausible that the composition and size distribution of particulates may vary by season, due for example to different pollutant sources and meteorologic factors, which could modify effects on mortality in different seasons. It will be important to evaluate further the seasonal component in the national data set to be analyzed in Phase II.

CONCLUSIONS

Phase I.B achieved its stated objectives to explore (1) how sensitive the air pollution–mortality relation would be to different analytical methods for controlling the effects of weather on mortality, and (2) the consequences of incorporating multiple pollutants when modeling the air pol-

lution--mortality relation. The investigators' carefully qualified conclusions are appropriate, given the limited data they analyzed.

In general, the Phase I.B analyses corroborate previous results indicating an association between air pollution and daily mortality in Philadelphia between 1973 and 1988 that cannot be explained by other known causes of mortality. In our judgment, the investigators are right to dismiss the apparently protective effect of NO_2 and to focus instead on the results they consider to be biologically plausible such as the effects of TSP, SO_2, and ozone. We also endorse their words of caution to avoid overinterpreting these findings as demonstrating a causal relation. Although individual air pollutants (TSP, SO_2, and ozone) are associated with increased daily mortality in these data, the limitations of the Philadelphia data make it impossible to establish that particulate air pollution alone is responsible for the widely observed associations between increased mortality and air pollution in that city. All we can conclude is that it appears to play a role.

The investigators have not placed great weight on the magnitude or statistical precision or significance of individual results, but rather they have attempted to discern meaningful patterns in this complex data set (Greenland 1991). To accomplish this they have used an approach to statistically model epidemiologic data that incorporates both the available toxicologic and clinical knowledge and the state-of-the-art statistical methods, rather than simply fitting all possible models and applying statistical tests to the results. As discussed above, the statistical analyses of these complex, multivariable data cannot be expected to provide certainty concerning the causal role of particulate air pollution in daily mortality. They may provide considerable insight, however, and contribute to causal explanations when combined with information from toxicologic research on the biological mechanisms of action of air pollution.

One limitation of the detailed analyses in both Phase I.A and I.B is that they were restricted to data from one city, Philadelphia, during a time period, 1973--1988, when nationwide emissions of particulates and SO_2 were being reduced, and when death rates from cardiovascular disease, the leading cause of death, were declining significantly. The consequence of this single-city analysis is that the generalizability of the statistical models for controlling weather variables and for drawing conclusions about the individual or combined effects of air pollutants cannot be evaluated with this data set alone. Consistent and repeated observations in locales with different air pollution profiles can provide the most convincing epidemiologic evidence to support generalizing the findings from these models. This has been the approach reported by the EPA in its recent criteria document and staff paper (U.S. Environmental Protection Agency 1996a,b), and by Air Pollution & Health: A European Approach (Katsouyanni et al. 1996), the multicity study of air pollution and daily mortality sponsored by the European Community. In Phase II of HEI's epidemiologic research program on the short-term effects of particulate air pollution, Drs. Samet and Zeger will assemble a national data base to explore the air pollution--mortality relation in a large number of U.S. sites that differ in their air pollution profiles. This will provide an opportunity to test both the generalizability and robustness of the Phase I.B models and, hopefully, more valid estimates of the effects of specific pollutants.

An important conclusion from the Phase I.B analyses is that the association between air pollution and mortality observed repeatedly over the last two decades in Philadelphia is not explained by variations in statistical methods used to adjust for weather factors. The results of this project provide additional evidence that the observed associations between air pollution and daily mortality are not explained by uncontrolled confounding by weather.

Time-series studies of daily mortality, such as the current analysis, compare the mortality rates among days characterized similarly by the ambient pollutant level on the same or previous day or days. However, one goal of such analyses is to infer a conclusion about the mortality of individuals in relation to their personal exposure to air pollution. As many analysts have observed, what complicates our ability to draw that inference is that exposure estimates are often based only on data from monitors centrally located in a city to collect information about ambient pollution levels. Errors in exposure measurements as a result of using data provided by centrally located monitors rather than exposures or doses measured in individuals, could, in the context of complex multivariable models for daily mortality, affect the relative risk estimates in ways that are difficult to predict. The possibility of such errors are an important source of uncertainty about the true magnitude of the estimated effects of individual air pollutants on daily mortality. For this reason, developing models to assess exposure measurement errors in daily time-series studies, and applying those models to a national data set using more detailed exposure data, if available, are major objectives of Phase II of this project.

The amount of life-shortening that underlies the elevated relative risks reported in Phase I.B and other time-series studies of daily mortality has yet to be quantified. Such evidence as exists suggests that these relative risks reflect to an unknown extent the advancement of death by a matter of days for frail individuals (referred to variously as "harvesting" or "short-term mortality displacement") (Spix

1996; Cifuentes and Lave 1997). Estimating the extent of life-shortening caused by short-term elevations in air pollution remains one of the most important tasks for future studies of air pollution and daily mortality, and will be addressed by the investigators in Phase II. The investigators were careful to distinguish between the impact of short-term air pollution exposure on daily mortality rates, which was estimated in the current study, and the impact of long-term air pollution exposure on annual average mortality, which was not. Measuring the latter will require observing populations over decades, as in the recent Six Cities (Dockery et al. 1993), American Cancer Society (Pope et al. 1995b), and Seventh Day Adventist Health (Abbey et al. 1995) studies.

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Comments from the Health Review Committee

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This document is one section of the Health Effects Institute Phase I.B Report of the Particle Epidemiology Evaluation Project, *Particulate Air Pollution and Daily Mortality: Analyses of the Effects of Weather and Multiple Air Pollutants*, which also includes an HEI Statement about the research, the Investigators' Report, and a Commentary by the Oversight Committee.

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The HEI Health Review Committee is pleased to offer the following comments on the enclosed Investigators' Report, *Air Pollution, Weather, and Mortality in Philadelphia 1973–1988*, by Jonathan M. Samet, Scott L. Zeger, Julia E. Kelsall, Jing Xu, and Laurence S. Kalkstein. This report completes the studies conducted under Phase I of HEI's Particle Epidemiology Evaluation Project. It explores the impact of incorporating synoptic weather categories and multiple air pollutants into statistical models of the relationship between air pollution and daily mortality rates in Philadelphia for the period 1973 through 1988.

The Investigators' Report combines analyses that the authors first presented in two draft reports evaluated by the Health Review Committee in March 1996; we also reviewed the draft and final versions of the combined report. Overall, the Committee thought that the investigators had conducted a detailed and extensive reanalysis, and highly endorses the publication of the Investigators' Report. The Committee had no substantive disagreement with the investigators' conclusions and considered these conclusions to be appropriately qualified. During the iterative review process, the Review Committee had some concerns and suggestions for improving the clarity of the report. In general, the investigators were highly responsive to these critiques and most of the issues that the Committee raised have been addressed in either the revised Investigators' Report or the Oversight Committee's Commentary. There are, however, three areas that the Review Committee thought might benefit from more discussion: Akaike's information criterion (AIC), modeling, and variance.

AKAIKE'S INFORMATION CRITERION

To compare the quality of the mortality predictions, the investigators used the AIC as a measure of model fit (Venables and Ripley 1994). This criterion allows for comparison of models, including the nonnested models used by the investigators, and focuses on selecting models with good prediction capabilities. It is a useful criterion for selecting a model that incorporates how closely the data fit the proposed model, while adjusting for both the number of parameters in the model and the potential for the data to have more than the expected variation.

As expressed by the authors

$$\text{AIC} = \text{deviance} + 2\hat{\varphi}p$$

The term deviance, as used in the Investigators' Report is a measure of how well the data fit the model. For example, if the model were a multiple linear regression model, the deviance would be a function of the residual sum of squares, a measure quantifying how the individual data points differ from the model predictions. Basically, the deviance is an unadjusted measure of the lack of fit of the model to the data.

Because the addition of more parameters will automatically reduce the deviance, an added adjustment is needed for the number of model parameters. This is the role of p in the above formula, the number of parameters estimated in the model. The more parameters, the bigger the penalty in the AIC value. This protects against overfitting; that is, the likelihood that the model fits the data being analyzed better than might actually occur with a different data set.

Finally, the investigators also included a further penalty associated with overdispersion. Each model, such as the Poisson model, has a corresponding expected variance or dispersion. When the data display more dispersion than is anticipated by the model, overdispersion occurs. This is seen as a weakness in the model, and the AIC penalizes the model for it. This is the $\hat{\varphi}$ term.

In summary, the AIC is a composite measure that incorporates (1) how well the data fit the model, and (2) at the same time, adjusts for using "too many" parameters and for the model's inability to explain the data variation. The smaller the AIC value, the more consistent the data are with the model. Finally, the AIC is measured in log units. So, as the investigators say, "a difference of 5 (or 10) units between the AIC values for two models means that the preferred model (lower AIC) is about 12 (or 150) times more consistent with the new data."

MODELING

The investigators performed extensive modeling of the data. This is best seen in Table 2 of the Investigators' Report where there are, for example, 160 degrees of freedom used to smooth time, variables for current and lagged temperatures, multiple variables for lagged dew points and pollutant effects by season and by age groups. Even though they employed the AIC throughout to guard against overfitting, it is still legitimate to ask if the investigators could have overfit the data and whether it is possible that some of the observed statistical significance reflects this. That is, because of extensive modeling, random features of the data may have appeared as statistically significant effects.

With extensive modeling, there is always the concern of overfitting. However, for the inferences about the collection of pollutants examined by Dr. Samet and colleagues, this does not appear to be a problem. A close look at the procedures employed shows that the extensive modeling is mainly confined to the time and weather variables. For

these variables, the investigators fit elaborate functions and used a substantial number of degrees of freedom. If any problem of overfitting exists, it should have resulted in diminishing the effects of the pollutants. However, even under these conditions, there emerges an association between pollutants and mortality that cannot be dismissed. A discussion on separating the effects of the different pollutants can be found in the Oversight Committee's Commentary.

VARIANCE

In their new analysis, the investigators had substantial success in reducing the excess variance (over the minimum variance required by the Poisson model) from about 25% to 5%. This was accomplished by the successive addition of variables of time, weather, and other matters, and by using an appropriately flexible model. Questions remain, however, about whether further reduction of the excess variance (perhaps even to zero) might in theory be attainable, if we only knew the true underlying relationships and if we had direct and accurate measurements of all relevant covariates.

We are concerned that the results of this study be neither underinterpreted (because of continuing concern about whether a cause-effect relation exists between particulate pollution and the timing of death) nor overinterpreted (because the residual variance is still larger than zero). What has been conclusively demonstrated is that, if any effect is present, it must be small. We believe that the investigators have gone as far as is both feasible and reasonable, and we do not suggest further analysis; and yet some questions remain about the potential effects of (1) measurement of covariates closer to the causal chain (such as specific items in the medical history), (2) more accurate measurements on an individual basis (such as temperature in the vicinity of the individual, or sulfates in the individual breathing zone rather than measurements from central monitoring systems), (3) the use of more flexible models (such as a continuous curvilinear model for age rather than the three-step function used), and (4) further modeling of interactions (for example, treatment of nonlinear interactions, or addition of variables not yet included in the model). The above steps may well have no material effect, they may reduce the residual variance (perhaps to 0), or, less likely, they might increase it.

SUMMARY

In summary, the investigators have conducted an excellent reanalysis of a very important data set. They have confirmed that in Philadelphia during the period 1973 through 1988, air pollution was, in fact, related to daily mortality rates. We agree with the investigators that the effects of individual pollutants, including total suspended particles, cannot be disentangled on the basis of these results. Their analysis has demonstrated an association between a pool of air pollutants and mortality. It has not established a causal relation between any particular pollutant and mortality. The next stage of the Particle Epidemiology Evaluation Project should address the two important issues of validating the model used in the present analysis and separating the effects of individual air pollutants.

REFERENCES

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Related HEI Publications

Report No.	Title	Author or Principal Investigator	Publication Date
	Special Reports		
	Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects (A Special Report of the Institute's Diesel Working Group)		1995
	Particulate Air Pollution and Daily Mortality: Replication and Validation of Selected Studies (The Phase I.A Report of the Particle Epidemiology Evaluation Project)		1995
	Research Reports: Diesel Exhaust		
10	Predictive Models for Disposition of Inhaled Diesel Exhaust Particles in Humans and Laboratory Species	C.P. Yu	1987
40	Retention Modeling of Diesel Exhaust Particles in Rats and Humans	C.P. Yu	1991
	Research Reports: Oxidants (Ozone and Nitrogen Dioxide)		
38	Synergistic Effects of Air Pollutants: Ozone Plus a Respirable Aerosol	J.A. Last	1991
70	Oxidant and Acid Aerosol Exposure in Healthy Subjects and Subjects with Asthma *Part I*: Effects of Oxidants, Combined with Sulfuric or Nitric Acid, on the Pulmonary Function of Adolescents with Asthma	J.Q Koenig	1994
	Part II: Effects of Sequential Sulfuric Acid and Ozone Exposures on the Pulmonary Function of Healthy Subjects and Subjects with Asthma	M.J. Utell	1994
76	Ozone Exposure and Daily Mortality in Mexico City: A Time-Series Analysis	D.P. Loomis	1996
	HEI Communications		
3	Environmental Epidemiology Planning Project		1993

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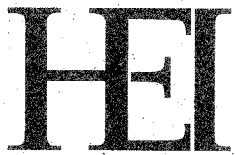

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