SPECIAL REPORT

HEALTH EFFECTS INSTITUTE

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Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality

A Special Report of the Institute's Particle Epidemiology Reanalysis Project

Executive Summaries and Commentary

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The Health Effects Institute, established in 1980, is an independent and unbiased source of information on the health effects of motor vehicle emissions. HEI supports research on all major pollutants, including regulated pollutants (such as carbon monoxide, ozone, nitrogen dioxide, and particulate matter) and unregulated pollutants (such as diesel engine exhaust, methanol, and aldehydes). To date, HEI has supported more than 200 projects at institutions in North America and Europe and has published over 100 research reports. Consistent with its mission to serve as an independent source of information on the health effects of motor vehicle pollutants, the Institute also engages in special review and evaluation activities.

Typically, HEI receives half its funds from the US Environmental Protection Agency and half from 28 manufacturers and marketers of motor vehicles and engines in the US. Occasionally, funds from other public and private organizations either support special projects or provide resources for a portion of an HEI study. Regardless of funding sources, HEI exercises complete autonomy in setting its research priorities and in reaching its conclusions. An independent Board of Directors governs HEI. The Institute's Research and Review Committees serve complementary scientific purposes and draw distinguished scientists as members. The results of HEI-funded research and evaluations have been used in public and private decision making.

∞ *Errata* ∞

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Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality

A Special Report of the Institute's Particle Epidemiology Reanalysis Project

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Page 161. Part II. Caption for Figure 5 should read:
City-specific relative risks in the ACS Study.

Page 162. Part II. Caption for Figure 6 should read:
Shape of concentration-response function (with standardized residuals plotted) for cities in the ACS Study.

Page 174. Part II. Table 32. After "O_3 (ppb)" in the left column, append footnote [b] that reads:
"[b] Based on daily 1-hour maximum concentrations."

Page 178. Part II. Table 33. For O_3 (second row from bottom), in the column "Description of Covariate and Source of Data", the entry should read exactly like the other three:
"Daily average concentrations averaged by year for 1980; from residential, commercial, or mobile monitors"

Page 259. Health Review Committee's Commentary. ***Gaseous Copollutants*** section. The third sentence should read:
"For four gaseous copollutants (carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide), city-specific annual means of daily average concentrations from the year 1980 were obtained from AIRS and used in the reanalysis (see Appendix E, Part II)."

At the end of the same paragraph, add this sentence:
"For this analysis, the ozone values were based on daily 1-hour maximum concentrations."

Part II, Appendix E (available on request)
Page 5. ***Gaseous Copollutants*** section. The second sentence should read:
"Daily average concentrations of NO_2, sulfur dioxide, ozone, and carbon monoxide were obtained from 1980 to 1989, in addition to the daily one-hour maximum concentrations of ozone."

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STATEMENT

Synopsis of the Particle Epidemiology Reanalysis Project

BACKGROUND

Epidemiologic work conducted over several decades has suggested that long-term residence in cities with elevated ambient levels of air pollution from combustion sources is associated with increased mortality. Subsequently, two prospective cohort studies, the Six Cities Study (as reported in Dockery et al 1993) and the American Cancer Society (ACS) Study (as reported in Pope et al 1995) estimated that annual average all-cause mortality increased in association with an increase in fine particles (all particles less than 2.5 μm in median aerodynamic diameter [$PM_{2.5}$]).

As part of the Six Cities Study, Dockery and colleagues (1993) had prospectively followed a cohort of 8,111 adult subjects in northeast and midwest United States for 14 to 16 years beginning in the mid-1970s. The authors found that higher ambient levels of fine particles and sulfate (SO_4^{2-}) were associated with a 26% increase in mortality from all causes when comparing the most polluted to the least polluted city, and that an increase in fine particles was also associated with increased mortality from cardiopulmonary disease. The relative risks in all-cause mortality were associated with a difference (or range) in ambient fine particle concentrations of 18.6 $\mu g/m^3$ and a difference of ambient sulfate concentrations of 8.0 $\mu g/m^3$, comparing the least polluted city to the most polluted city.

In the much larger ACS Study, Pope and colleagues (1995) followed 552,138 adult subjects in 154 US cities beginning in 1982 and ending in 1989 (3 cities did not overlap between the 151 and 50 cities studied, resulting in a total of 154 cities). Again, higher ambient levels of fine particles were associated with increased mortality from all causes and from cardiopulmonary disease in the 50 cities for which fine particle data were available (sampled from 1979 to 1983). Higher ambient sulfate levels were associated with increased mortality from all causes, cardiopulmonary disease, and lung cancer in the 151 cities for which sulfate data were available (sampled from 1980 to 1982). The difference between all-cause mortality in the most-polluted city and the least-polluted city was 17% and 15% for fine particles and sulfate, respectively (with a range of 24.5 $\mu g/m^3$ for fine particles and of 19.9 $\mu g/m^3$ for sulfate).

Both of these studies came under intense scrutiny in 1997 when the EPA used the results to support new National Ambient Air Quality Standards for fine particles and to maintain the standards for particles less than 10 μm in median aerodynamic diameter (PM_{10}) already in effect. Members of Congress and industry, the scientific community and others interested in regulation of air quality scrutinized the studies' methods and their results. Some insisted that any data generated using federal funding should be made public. Others argued that these data had been gathered with assurances of confidentiality for the individuals who had agreed to participate and that the concept of public access to federally funded data did not take into account the intellectual property rights of the investigators and their supporting institutions. To address the public controversy, Harvard University and the ACS requested that the Health Effects Institute organize an independent reanalysis of the data from these studies. Both institutions agreed to provide access to their data to a team of analysts to be selected by HEI through a competitive process.

APPROACH

To conduct the reanalysis, the HEI Board of Directors, with support from the EPA, industry, Congress, and other stakeholders, appointed an Expert Panel chaired by Dr Arthur Upton from the University of Medicine and Dentistry of New Jersey and former Director of the National Cancer

Continued

This Statement, prepared by the Health Effects Institute, is a summary of a research project conducted by the Reanalysis Team, led by Dr Daniel Krewski at the University of Ottawa from 1998 to 2000. The following Special Report contains the detailed Investigators' Report (Summary, Introduction, and Parts I and II), a Commentary on the project prepared by a special panel of the Institute's Health Review Committee, and Comments on the Reanalysis Project by the Original Investigators (Drs Douglas W Dockery, C Arden Pope III et al).

Institute. The Expert Panel selected competitively a Reanalysis Team—led by Dr Daniel Krewski of the University of Ottawa—and oversaw all aspects of the team's work. They were assisted in their oversight efforts by a broad-based Advisory Board of knowledgeable stakeholders and scientists who, in the project's early stages, provided extensive advice to the Expert Panel on the key questions to be analyzed. The final results of the Reanalysis Team were intensively and independently peer reviewed by a Special Panel of the HEI Health Review Committee, which was chaired by Dr Millicent Higgins of the University of Michigan.

The overall objective of what became the Particle Epidemiology Reanalysis Project was to conduct a rigorous and independent assessment of the findings of the Six Cities and ACS Studies of air pollution and mortality. This objective was met in two parts. In *Part I: Replication and Validation*, the Reanalysis Team sought to replicate the original studies via a quality assurance audit of a sample of the original data and to validate the original numeric results. In *Part II: Sensitivity Analyses*, they tested the robustness of the original analyses to alternate risk models and analytic approaches.

RESULTS AND IMPLICATIONS

PART I: REPLICATION AND VALIDATION

- An extensive audit of the study population data for both the Six Cities and ACS Studies and of the air quality data in the Six Cities Study revealed the data to be of generally high quality with a few exceptions. In both studies, a few errors were found in the coding and inclusion of certain subjects; when those subjects were included in the analyses, they did not materially change the results as originally reported. Because the air quality data used in the ACS Study could not be audited, a separate air quality database was constructed for the sensitivity analyses described in Part II.
- The Reanalysis Team was able to replicate the original results in both studies using the same data and statistical methods as used by the Original Investigators. The Reanalysis Team confirmed the original point estimates: For the Six Cities Study, they reported the relative risk of mortality from all causes associated with an increase in fine particles of 18.6 $\mu g/m^3$ as 1.28, close to the 1.26 reported by the Original Investigators. For the ACS Study, the relative risk of mortality from all causes associated with an increase in fine particles of 24.5 $\mu g/m^3$ was 1.18 in the reanalysis, close to the 1.17 reported by the Original Investigators.

PART II: SENSITIVITY ANALYSES

Once the original results of the studies had been validated, the Reanalysis Team sought to test an array of different models and variables to determine whether the original results would remain robust to different analytic assumptions.

- First, the Reanalysis Team used the standard Cox model used by the Original Investigators and included variables in the model for which data were available from both original studies but had not been used in the published analyses (eg, physical activity, lung function, marital status). The Reanalysis Team also designed models to include interactions between variables. None of these alternative models produced results that materially altered the original findings.
- Next, for both the Six Cities and ACS Studies, the Reanalysis Team sought to test the possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of the population. Although different subgroups did show some variation in their estimated effects, the results were not statistically significant with one exception. The estimated effects of fine particles did appear to vary with educational level; the association between an increase in fine particles and mortality tended to be higher for individuals without a high school education than for those who had completed high school or for those with more than a high school education.
- In the ACS study, the Reanalysis Team tested whether the relationship between ambient concentrations and mortality was linear. They found some indications of both linear and nonlinear relationships, depending upon the analytic technique used, suggesting that the

issue of concentration-response relationships deserves additional analysis.

- In the Six Cities Study where data were available, the Reanalysis Team tested whether effect estimates changed when certain key risk factors (smoking, body mass index, and air pollution) were allowed to vary over time. One of the criticisms of both original studies has been that neither analyzed the effects of change in pollutant levels over time. In general, the reanalysis results did not change when smoking and body mass index were allowed to vary over time. The Reanalysis Team did find for the Six Cities Study, however, that when the general decline in fine particle levels over the monitoring period was included as a time-dependent variable, the association between fine particles and all-cause mortality dropped substantially, but the effect continued to be positive and statistically significant.
- Using its own air quality dataset constructed from historical data to test the validity of the original ACS air quality data, the Reanalysis Team found essentially the same results.
- Any future analyses using the sulfate data should take into account the impact of artifactual sulfate. Sulfate levels with and without adjustment differed by about 10% for the Six Cities Study. Both the original ACS Study air quality data and the newly constructed dataset contained sulfate levels inflated by approximately 50% due to artifactual sulfate. For the Six Cities Study, the relative risks of mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS Study, adjusting for artifactual sulfate resulted in slightly higher relative risks of mortality from all causes and cardiopulmonary disease compared with unadjusted data.
- Because of the limited statistical power to conduct most sensitivity analyses for the Six Cities Study, the Reanalysis Team conducted the majority of its sensitivity analyses using only the ACS Study dataset with 154 cities. In that dataset, when a range of city-level (ecologic) variables (eg, population change, measures of income, maximum temperature, number of hospital beds, water hardness) were included in the analyses, the results generally did not change. Two exceptions were that associations for both fine particles and sulfate were reduced when city-level measures of population change or sulfur dioxide were included in the model.
- A major contribution of the Reanalysis Project is the recognition that both pollutant variables and mortality appear to be spatially correlated in the ACS Study dataset. If not identified and modeled correctly, spatial correlation could cause substantial errors in both the regression coefficients and their standard errors. The Reanalysis Team identified several methods for dealing with this, all of which resulted in some reduction in the estimated regression coefficients. The full implications and interpretations of spatial correlations in these analyses have not been resolved and appear to be an important subject for future research.
- When the Reanalysis Team sought to take into account both the underlying variation from city to city (random effects) and the spatial correlation between cities, only sulfur dioxide as a city-level variable continued to decrease the originally reported associations between mortality and fine particles or sulfate. This effect was more pronounced for sulfate.
- When the Reanalysis Team conducted spatial analyses of sulfur dioxide, the association between sulfur dioxide and mortality persisted after adjusting for sulfate, fine particles, and other variables.
- As a result of these extensive analyses, the Reanalysis Team was able to explain much of the variation between cities, but some unexplained city-to-city variation remained.

CONCLUSIONS

The Reanalysis Team designed and implemented an extensive and sophisticated series of analyses that included a set of new variables, all the gaseous copollutants, and the first attempts to apply spatial analytic methods to test the validity of the data and the results from the Six Cities Study and the ACS Study. Overall, the reanalyses assured the quality of the original data, replicated the original results, and tested those results against alternative risk models and analytic approaches

without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality.

At the same time, the reanalyses did extend and challenge our understanding of the original results in several important ways.

- The Reanalysis Team identified a possible modifying effect of education on the relation between air quality and mortality in that estimated mortality effects increased in the subgroup with less than high school education.
- The use of spatial analytic methods suggested that, when the analyses controlled for correlations among cities located near one another, the associations between mortality and fine particles or sulfate remained but were diminished.
- An association between sulfur dioxide and mortality was observed and persisted when other possible confounding variables were included; furthermore, when sulfur dioxide was included in models with fine particles or sulfate, the associations between these pollutants (fine particles and sulfate) and mortality diminished.

In reviewing these results, the Special Panel of the HEI Health Review Committee identified the following factors to consider when interpreting the results from the Reanalysis Team.

- The inherent limitations of using only six cities, understood by the Original Investigators, should be taken into account when interpreting results of the Six Cities Study.
- The Reanalysis Team did not use data adjusted for artifactual sulfate for most alternative analyses. When they did use adjusted sulfate data, relative risks of mortality from all causes and cardiopulmonary disease increased. This result suggests that more analyses with adjusted sulfate might result in somewhat higher relative risks associated with sulfate.
- Findings from spatial analyses applied to the ACS Study data need to be interpreted with caution; the spatial adjustment may have overadjusted the estimated effect for regional pollutants such as fine particles and sulfate compared with the effect estimates for more local pollutants such as sulfur dioxide.
- After the Reanalysis Team completed its spatial analyses, residual spatial variation was still noticeable; this finding suggests that additional studies might further refine our understanding of the spatial patterns in both air pollution and mortality.
- No single epidemiologic study can be the basis for determining a causal relation between air pollution and mortality.

In conclusion, the Reanalysis Team interpreted their findings to suggest that increased relative risk of "mortality may be attributed to more than one component of the complex mix of ambient air pollutants in urban areas in the United States". The Review Panel concurs. In the alternative analyses of the ACS Study cohort data, the Reanalysis Team identified relatively robust associations of mortality with fine particles, sulfate, and sulfur dioxide, and they tested these associations in nearly every possible manner within the limitations of the datasets. Future investigations of these issues will enhance our understanding of the effect of combustion-source air pollutants (eg, fine particles, sulfate, and sulfur dioxide) on public health.

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Particle Epidemiology Reanalysis Project

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PREFACE

Particle Epidemiology Reanalysis Project

SCIENTIFIC AND REGULATORY CONTEXTS

In the *New England Journal of Medicine* in 1993, Dockery and associates reported their findings from an epidemiologic analysis of mortality and certain measures of air pollution (the Harvard Six Cities Study), which had led them to conclude: "Although the effects of other, unmeasured risk factors cannot be excluded with certainty, . . . fine particulate air pollution, or a more complex pollution mixture associated with fine particulate matter, contributes to excess mortality in certain US cities." A similar epidemiolgic analysis (the American Cancer Society [ACS]* Study), published in 1995 by Pope and colleagues in the *American Review of Respiratory and Critical Care Medicine*, also reported: "Particulate air pollution was associated with cardiopulmonary and lung cancer mortality but not with mortality due to other causes. Increased mortality [was] associated with sulfate and fine particulate air pollution at levels commonly found in US cities. The increase in risk [was] not attributable to tobacco smoking, although other unmeasured correlates of pollution cannot be excluded with certainty."† In 1997, the US Environmental Protection Agency (EPA) relied, in part, on the results of these two prospective cohort studies in promulgating a new National Ambient Air Quality Standard (NAAQS) for fine particles (particulate matter 2.5 μm or smaller in aerodynamic diameter [$PM_{2.5}$]) (US EPA 1996a,b).

These studies (Dockery et al 1993; Pope et al 1995) and another study (Abbey et al 1999) corroborated a body of epidemiologic work that has been conducted over several decades (and reviewed by the EPA), the results of which have suggested that, over the long term, living in cities with sources of combustion air pollution may cause increased morbidity and mortality from respiratory and cardiovascular disease. These studies focused attention on the fine particle component of air pollution (Lipfert 1993; US EPA 1996b).

Almost as soon as they were published, however, the findings of these studies stimulated controversy and debate. Some reviewers raised the possibility that the observed associations were invalid, or that their magnitude was exaggerated, because of confounding factors that had not been included in the analyses or errors in the measurements of pollutants. They suggested, for example, that the effects of factors such as sedentary lifestyle and cigarette smoke inhalation, both active (Lipfert 1993; Moolgavkar 1994; Moolgavkar and Luebeck 1996; Gamble 1998) and passive (US EPA 1996b), might have been inadequately controlled in the statistical analyses of the Six Cities Study and the ACS Study data; if so, this could have resulted in overestimating the magnitude of the mortality risk due to particulate air pollution. Others observed that these two studies had used air pollution measurements from a short range of years (1 to 9) that had not adequately characterized how air pollutants change over time, which would preclude firm conclusions about the effects of long-term air pollution on mortality (Vedal 1997).

Such potential sources of error notwithstanding, the Six Cities Study and ACS Study provided some of the only data available for estimating the risk of increased mortality associated with long-term exposure to particulate air pollution. Results from the studies have been used to estimate the number of deaths attributable to particulate air pollution in the United States and

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

† The original articles (Dockery et al 1993 and Pope et al 1995) appear in their entirety at the end of this Special Report.

Although this document was produced with partial funding by the United States Environmental Proection Agency under Assistance Award R824835 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

in Europe (Natural Resources Defense Council 1996; US EPA 1996a; Brunekreef 1997; Künzli et al 1999). In 1996, when the EPA reviewed the early results of a third prospective cohort study, the Seventh-Day Adventist Health Study on Smog (Abbey et al 1999), the investigators had found evidence of increased respiratory disease morbidity, but not mortality, associated with an increase in total suspended particles and particulate matter ≤ 10 μm in aerodynamic diameter (PM_{10}). However, by the time their results were published in 1999, extended follow-up of the cohort had revealed elevated mortality rates associated with long-term exposure to PM_{10} and to ozone.

Because the results of the Six Cities Study and the ACS Study figured prominently in the discussion surrounding the EPA's NAAQS for $PM_{2.5}$, and because of the ongoing debates about the validity of the findings, representatives of industry, members of the US Congress, and other scientists urged the EPA who, in turn, urged Harvard University and the American Cancer Society to make the original data from these studies available to other analysts so that the findings could be independently assessed. In response, Harvard University and the ACS requested that HEI organize an independent reanalysis of the data used in these studies and agreed to provide complete access to their data for that purpose.

PRELIMINARY NEGOTIATIONS

In April 1997, Dr James Ware, then Dean for Academic Affairs of the Harvard School of Public Health, wrote to Daniel Greenbaum, President of HEI, requesting that HEI conduct a reanalysis of the Six Cities Study and offering HEI and its designees access to the original data. HEI's Board of Directors approved the request. Later, Dr Clark Heath, then Vice-President for Epidemiology and Biostatistics at the ACS, requested that HEI include the ACS Study data in the Reanalysis Project. In response to these requests, HEI specified several guiding principles:

- **The reanalysis would be of the highest scientific quality.** It would be a thorough and rigorous reanalysis designed to contribute to advancing the broader scientific understanding of the issues under debate.
- **Both conducting the work and reporting the results would be as open and public as possible.** The guarantees of confidentiality that had been provided to study participants by the Six Cities Study and the ACS Study Original Investigators would be fully respected by the Reanalysis Team. Beyond this, any methods used, analyses undertaken, and results produced would be completely and publicly described.
- **The analyses would be conducted by independent and impartial investigators selected via a competitive process.** HEI would draw on scientific and technical experts to help specify and design the reanalyses and to review and comment on interim results; some of these experts may have publicly discussed their positions on the federal regulation of particulate matter emissions.
- **All analyses would be subject to independent and rigorous peer review** organized by the HEI Health Review Committee.
- **HEI would produce and widely distribute a comprehensive report of all analyses and findings.**

HEI described in broad terms the key elements of the reanalysis, a scientific oversight group, a stakeholder advisory group, a process for selecting investigators, and a scientific peer review of the results. These principles and the approach to organizational structure and scientific conduct consistent with them had been developed and applied in an earlier HEI-funded reanalysis of key epidemiologic studies of air pollution and daily mortality (Health Effects Institute 1995, 1997).

THE PLANNING PHASE

SELECTION OF THE EXPERT PANEL

The Health Effects Institute assembled an Expert Panel (see Contributors to the Project) that would provide scientific oversight of the Reanalysis Project on HEI's behalf and ensure that the reanalysis would be conducted by independent and impartial investigators. Candidates sought for the Expert Panel had to have several specific qualifications:

- nationally recognized expertise in epidemiology, biostatistics, or air pollution measurement;
- extensive experience in designing, conducting, and analyzing long-term prospective cohort studies, preferably in the areas of pulmonary and cardiovascular diseases;
- demonstrated through writing or public speaking their critical thought processes about the contributions and limitations of observational research designs in epidemiology; and
- contributed to the development or advancement of epidemiologic methods for observational studies.

The HEI Board of Directors considered whether candidates would have potential conflicts of interest. Individuals who had been affiliated with the Six Cities Study or the

ACS Study or other related studies were not considered. More generally, scientists with current or past connections with the Original Investigators were evaluated with respect to the extent and recency of their connection. Individuals who had publicly expressed opinions concerning the proposed NAAQS for PM were not rejected a priori; rather, the Board considered the content and tone of the opinions expressed to determine any potential source of conflict. In June 1997, the Board appointed a nine-member Expert Panel, chaired by Dr Arthur C Upton of the Environmental and Occupational Health Sciences Institute.

STAKEHOLDER PARTICIPATION: THE REANALYSIS ADVISORY BOARD

Because of the broad interest in the reanalysis, HEI organized an Advisory Board of technical experts from industry, government, academia, and nongovernmental organizations to provide a broad range of perspectives at key points during the Reanalysis Project. HEI sought the Advisory Board's comments on the scope and content of the Analytic Plan as it was being developed and on the progress of the analyses at an early stage.

PUBLIC WORKSHOP

The Expert Panel sought first to identify key issues that should be addressed in a reanalysis of the two studies. To this end, HEI convened a workshop in June of 1997 with three specific objectives:

1. to review the available epidemiologic studies that address the question of long-term measurements of air pollution and their association with mortality, including the Six Cities Study and the ACS Study;
2. to identify hypotheses that could be addressed in a reanalysis of these studies; and
3. to discuss issues related to sharing research data as they apply to the successful conduct of a reanalysis.

In addition to members of the Expert Panel, the 75 workshop participants included the Original Investigators, others who had critically evaluated these studies, representatives of the agencies who funded these studies, and other interested parties. (A transcript of the workshop is available on request from HEI.)

OBJECTIVES FOR THE PROJECT

The Expert Panel identified the overall objective of the Reanalysis Project to be a rigorous and independent assessment of the findings of the Six Cities Study and the ACS Study of air pollution and mortality. The project had two specific objectives:

- Replicate and validate the published results by conducting a Quality Assurance (QA) audit on a sample of the original data and attempting to reproduce the original numerical results.
- Conduct sensitivity analyses to test the robustness of the original findings and interpretations to alternative analytic approaches.

The Reanalysis Project would be designed and timed to inform the EPA's review of the NAAQS for PM, which will influence regulations and standards to be set in 2002.

SELECTION OF THE REANALYSIS TEAM

To select a team of analysts to design and conduct the reanalysis, in July 1997 the HEI Expert Panel issued "A Request for Qualifications: Epidemiologists and Biostatisticians to Design and Conduct a Reanalysis" (RFQ 97-1), which sought a multidisciplinary team of investigators. Thirteen teams from the United States, Canada, and Europe responded. First, the Expert Panel evaluated each application according to four criteria:

1. experience with the epidemiologic and statistical questions and methods relevant to the reanalysis;
2. experience in data reanalysis, pooling, and metaanalytic projects, including working with data developed by other research groups;
3. the ability of the team to bring an independent and critical perspective to the project; and
4. the ability of the team to interact effectively with the Original Investigators and the Expert Panel and to work efficiently to complete the work within the allotted time.

Having identified a few teams of qualified applicants, the Expert Panel then considered potential conflicts of interest: first, involvement in research activities designed to further specific positions of advocacy with regard to the NAAQS for PM; second, a common institutional affiliation (eg, Harvard University) or close collaboration with the Original Investigators, especially on recent studies of particulate air pollution; and third, authorship of one or more sections of the EPA's PM Criteria Document (US EPA 1996b). Ultimately, the Expert Panel recommended a team of scientists from leading Canadian universities, headed by Dr Daniel Krewski of the University of Ottawa, to carry out the reanalysis. Their recommendation was approved by the HEI Board of Directors in November 1997.

AGREEMENTS ON DATA ACCESS: THE MEMORANDUM OF UNDERSTANDING

A key aspect of designing and planning the reanalysis concerned the terms under which the Reanalysis Team would have access to the original data. Ultimately, these conditions were specified in a Memorandum of Understanding that was signed by HEI, the Expert Panel, the Original Investigators, and the Reanalysis Team in March 1998. It was included in the contracts that HEI subsequently executed with the Reanalysis Team and the Original Investigators.

The Memorandum defined two general types of data: Original Data, which comprised data collected or generated (in electronic or paper form) by the Original Investigators before the Reanalysis Project began; and Reanalysis Project Data, which comprised data generated by the Reanalysis Team that might take the form of replications of the Original Data, datasets that include the Original Data plus additional variables, computer programs, analytic files, or aggregations of data that do not allow the identification of individual study subjects and might include other information.

The Memorandum specified that each group of participants had, or would have by the end of the Reanalysis Project, certain rights of data ownership and rights of access to data that all participants would mutually agree to honor. Key specifications included:

- The Original Investigators (and their sponsoring or host institutions) would retain full rights to and ownership of the Original Data and of Reanalysis Project Data to the extent that they included copies or replications of the Original Data.
- The Reanalysis Team (and their host institutions) would maintain ownership of the Reanalysis Project Data with the exception of copies or replications of the Original Data.
- HEI would maintain the right of access to the Original Data for the purposes of the Reanalysis Project and the right to provide access to the Reanalysis Project Data to its independent reviewers (under confidentiality agreements).
- HEI would maintain the right to have full copies of all Reanalysis Project Data, with the exception of copies or replicated versions of the Original Data, in keeping with its intention for all research projects it funds to make all data produced available to the scientific community.
- HEI and the Reanalysis Team agreed not to knowingly provide access to Original Data or Reanalysis Project Data that include copies and replications of the Original Data to anyone without the written consent of the Original Investigators.

The Memorandum of Understanding also specified safeguards and requirements to protect the confidentiality of research subjects and the integrity of the Original Data. The Reanalysis Team and HEI agreed to make every effort to ensure that confidential data neither consciously nor inadvertently be revealed to anyone not covered by the Memorandum of Understanding. Specifically HEI agreed to:

- respect the assurances provided to study subjects by the Original Investigators as conditions for providing personal data; and
- respect the assurances provided to and the agreements made with the US National Death Index by the Original Investigators, the Reanalysis Team, and their respective institutions in order to obtain data on the mortality of cohort members.

The Reanalysis Team agreed to:

- ensure the confidentiality and integrity of the Original Data and Reanalysis Project Data by establishing a dedicated and secure computing facility; and
- return all copies of the Original Data to the Original Investigators, or dispose of them in a manner agreed upon with the Original Investigators and HEI, upon completion of the Reanalysis Project and the publication of the HEI Special Report.

The Expert Panel agreed to monitor the conduct of the Project to ensure that these safeguards and assurances were respected and adhered to.

CONDUCT AND REPORTS OF THE REANALYSIS PROJECT

THE ROLE OF THE ORIGINAL INVESTIGATORS

Throughout the Reanalysis Project, the Original Investigators actively cooperated with the Reanalysis Team and the Expert Panel by providing their original data, documentation of their analyses, and clarification of the technical details of their earlier work. They were consulted during the development of the Analytic Plan and during the course of the project as needed, but were not part of the team conducting any of the reanalyses. The Memorandum of Understanding provided them with the opportunity to prepare comments on the results of the Reanalysis Project and on HEI's Health Review Committee's Commentary.

(Those comments are found in the Original Investigators' section at the end of this HEI Special Report.)

DEVELOPMENT OF THE ANALYTIC PLAN

The Reanalysis Project was conducted according to an Analytic Plan developed via discussions between the Reanlysis Team and the Expert Panel. Comments from the Original Investigators and the Advisory Board also were considered and the Analytic Plan was presented for public comment at the HEI Annual Conference in April 1998. To address the two specific objectives of the reanalysis, the Analytic Plan divided the project into two phases:

- Phase I comprised a QA audit of a sample of the data used to generate the original results and replication of the original numerical results of both studies.
- Phase II comprised an extensive series of sensitivity analyses designed to assess whether new analytic methods or adding variables to analyses would produce results that differed from those originally reported.

Content of the Audit Plan

The HEI staff, Expert Panel, and Dr Krewski developed a Statement of Specifications for the QA audit and HEI issued a Request for Qualifications to several groups experienced in auditing epidemiologic studies. From four teams that submitted qualifications, the Audit Team led by Ms Kristin Hoover was selected. On the basis of the specifications outlined, she submitted a plan for the QA audit of data from the two studies, which the Audit Team implemented in cooperation with the Reanalysis Team.

Content of the Analytic Plan

The Analytic Plan described the work to be conducted in each phase of the Reanalysis Project, but focused largely on the Phase II sensitivity analyses in three general areas: covariate adjustment, exposure characterization, and exposure-response modeling. Within each area, the Reanalysis Team specified the questions they would address. As the work evolved, certain analyses were limited or expanded on the basis of feasibility (eg, data availability and quality) and further discussion with the Expert Panel. (Copies of the Analytic Plan are available on request from HEI.)

Adjustment of Covariates (Confounders) These analyses tested the sensitivity of the original results to:

- alternative specifications of covariates (eg, cigarette smoking, age, occupation) for which original data about individuals were available; and
- the inclusion of covariates measured at the aggregate level, also referred to as group or "ecologic" level, that characterize the city itself (eg, level of unemployment, number of physicians, income disparity within the population) or for which no individual-level data had been collected about study subjects (eg, history of unemployment).

Exposure Characterization These analyses tested the sensitivity of the original results to using alternative measures of air pollutants, additional air quality data, and residential histories of subjects in the Six Cities Study to attempt to characterize air pollution exposure at the individual level.

Exposure-Response Modeling The Reanalysis Team proposed alternative statistical models with which to analyze the ACS Study data that would account for the possibility that observations for individual subjects may not be independent due to spatial correlation.

REVIEW OF THE REANALYSIS RESULTS

As with all HEI-funded research, the results of the Reanalysis Project have been independently peer reviewed under the auspices of the HEI Health Review Committee. This review has been conducted by a Special Panel chaired by Dr Millicent Higgins of the University of Michigan, and composed of members of HEI's Review Committee and additional technical experts. Their Commentary, which includes both a technical review of the methods and a critical discussion of the findings of the reanalysis, appears in a separate section of this HEI Special Report.

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CONTRIBUTORS

Particle Epidemiology Reanalysis Project

HEI Expert Panel

Arthur C Upton, Chair, *Robert Wood Johnson Medical School and Environmental and Occupational Health Sciences Institute*

Steven D Colome, *Integrated Environmental Services*

Bernard D Goldstein (ex officio), *University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, HEI Health Research Committee*

Leon Gordis, *Johns Hopkins University*

Geoffrey Howe, *Columbia University*

David H Jacobs, *University of Minnesota*

Suresh H Moolgavkar, *University of Washington*

Sverre Vedal, *University of British Columbia, HEI Health Review Committee*

Clarice Weinberg, *National Institute of Environmental Health Sciences*

Reanalysis Team

Daniel Krewski, *University of Ottawa*

Richard T Burnett, *Health Canada and University of Ottawa*

Mark S Goldberg, *University of Quebec and McGill University*

Kristin Hoover, *Hoover Consultants*

Jack Siemiatycki, *University of Quebec and McGill University*

Michael Jerrett, *McMaster University*

Michal Abrahamowicz, *McGill University and Montreal General Hospital*

Warren H White, *Washington University*

Gillian Bartlett, *McGill University*

Lynn Brodsky, *University of Ottawa*

Linda Calisti, *Calisti Consulting*

Yue Chen, *University of Ottawa*

Patrick De Luca, *McMaster University*

Roxane du Berger, *Montreal General Hospital*

Norm Finkelstein, *McMaster University*

Donna E Foliart, *Foliart and Associates*

Karen Fung, *University of Windsor*

Edward Hughes, *Infometrika*

Sally Kader, *University of Ottawa*

Ramzan Lakhani, *University of Quebec*

Xia Luo, *University of Ottawa*

Louise Nadon, *University of Quebec*

Renjun Ma, *University of Ottawa*

Ranjeeta Mallick, *Carleton University*

Frank Mo, *University of Ottawa*

Leslie Richardson, *University of Quebec*

Bret Schichtel, *Washington University*

Tom Schopflocher, *McGill University*

Yuanli Shi, *University of Ottawa*

Paul Villeneuve, *University of Ottawa*

Alette Willis, *University of Ottawa*

Original Investigators

Douglas W Dockery, *Harvard School of Public Health*

C Arden Pope III, *Brigham Young University*

Frank E Speizer, *Harvard Medical School and Channing Laboratories*

Michael J Thun, *American Cancer Society*

Continued

Particle Epidemiology Reanalysis Project

HEI Project Staff

Julia F Campeti, *Scientific Copy Editor*

Aaron J Cohen, *Senior Scientist*, ***Research Project Manager***

Sally Edwards, *Managing Editor*

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JoAnn Ten Brinke, *Staff Scientist*, ***Review Project Manager***

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Publication Assistance

John B Abbott, *Desktop Publishing Specialist*

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Genevieve MacLellan, *Scientific Editor*

Carol Moyer, *Scientific Copy Editor*

Susan L Shepherd, *Scientific Editor*

Quentin Sullivan, *Proofreader*

Gabe Weiss, *Desktop Publishing Specialist*

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INVESTIGATORS' REPORT

Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality

Daniel Krewski, Richard T Burnett, Mark S Goldberg , Kristin Hoover, Jack Siemiatycki, Michael Jerrett, Michal Abrahamowicz, and Warren H White

with Gillian Bartlett, Lynn Brodsky, Linda Calisti, Yue Chen, Patrick De Luca, Roxane du Berger, Norm Finkelstein, Donna E Foliart, Karen Fung, Edward Hughes, Sally Kader, Ramzan Lakhani, Xia Luo, Louise Nadon, Renjun Ma, Ranjeeta Mallick, Frank Mo, Leslie Richardson, Bret Schichtel, Tom Schopflocher, Yuanli Shi, Paul Villeneuve, and Alette Willis

Summary of Parts I and II

Daniel Krewski, Richard T Burnett, Mark S Goldberg , Kristin Hoover, Jack Siemiatycki, Michael Jerrett, Michal Abrahamowicz, Warren H White, and Others

PART I: REPLICATION AND VALIDATION

As part of the replication and validation effort, a quality assessment audit was conducted to confirm the integrity of the data provided to the Reanalysis Team. The audit of both the Harvard Six Cities Study (Dockery et al 1993) and the American Cancer Society (ACS)* Study (Pope et al 1995)† data was conducted in two phases: first, validation of the variables used in the original publication; and second, validation of those variables collected and coded by the Original Investigators, but not published. Formal study protocols were not available for either study.

SIX CITIES STUDY

Data Quality Audit

The audit of the Six Cities Study encompassed more than 21,750 morbidity and mortality data points for subjects in the six metropolitan areas (Harriman TN, Portage WI, Steubenville OH, St Louis MO, Topeka KS, and Watertown MA). Most of the original health and death certificate data were traceable via paper and electronic files. All analytic files and supporting documentation for health and mortality data were available and traceable during the audit. Some of the Original Investigators were present during the two weeks of audit and were available to clarify methods and verify documentation. Internal audits that had been conducted at the Harvard School of Public Health (HSPH) by the Original Investigators, beginning in 1981, were available for review by the Audit Team. These internal audits had tracked error rates by variable, as well as the corrective actions taken by the Original Investigators.

Questionnaires for a random sample of 250 subjects were selected for audit. One baseline questionnaire was missing, but the file folder and follow-up questionnaires for this subject were located. The primary finding was a computer programming problem that had resulted in early censorship of time-on-study data for some participants in some of the six cities. This had resulted in the loss of approximately 1% of the reported person-years. The loss of reported person-years was not equal in all six cities. The greatest censorship of data occurred for two cities with lower levels of pollutants, Portage and Topeka, whereas there was no censorship of data for Watertown.

Other questionnaire variables used in the analysis included information on sex, education, diabetes, hypertension, body mass index (BMI) derived from height and weight, smoking history, and occupational exposure to dusts or fumes. Few inconsistencies between the Original Investigators' analytic file and the questionnaires were noted, with the exception of information regarding occupational exposures (5% to 6% error rates). Most of the coding errors in the occupational exposure categories involved the earliest form of the baseline questionnaire, which had been used for Watertown, Harriman, and St Louis (Form 1-71). The format of Form 1-71 allowed for more variability in recorded information than occurred with these occupational variables in later, more structured forms of the questionnaire [Form 77(1-76)] used in Steubenville and for some subjects in Topeka, and an update, Form 78 (1-77) used for the remaining subjects in Topeka and all subjects in Portage).

A random sample of 250 death certificates were selected from the pool of known decedents whose death certificates had been obtained by the Original Investigators. Two (0.8%) death certificates in the audit sample were missing and few inconsistencies were noted in the remainder. Each death certificate in the audit sample was verified as belonging to a study participant. Two errors in date of death were found, one of which had been detected and corrected by the Orig-

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

† The original articles appear in their enirety at the end of this Special Report.

This is one section of an HEI Special Report that includes an HEI Statement about the research project, a Preface to the Particle Epidemiology Reanalysis Project, the Investigators' Report (Summary, Introduction, Part I, and Part II), a Commentary by the Institute's Health Review Committee, and the Original Articles and Comments on the Reanalysis from the Original Investigators. Correspondence concerning the Summary of Parts I and II may be addressed to Dr Daniel Krewski, Professor of Epidemiology & Statistics, Department of Epidemiology & Community Medicine, Room 3229C, 451 Smyth Road, University of Ottawa, Ottawa Ontario K1H 8M5, Canada.

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inal Investigators after the analytic file had been finalized. For two (0.8%) of the death certificates, the auditor selected a 4-digit *International Classification of Diseases,* Ninth Revision (ICD-9) code different from the code assigned by the study nosologist, which placed the death in a different analysis category. In six cases, the auditor's coding did not match the full four digits of the nosologist's code and in three of these, the differences did not affect the overall disease category. There was a 100% match between the nosologist's codes and the ICD-9 codes in the analytic file. The Statistical Application Software (SAS) program the Original Investigators used to group causes of death was consistent with their a priori disease categories.

Audit of the air quality data focused on the key explanatory variable identified in the epidemiologic analysis: the fine particle mass concentration. The dichotomous samplers used to collect fine and coarse particles were newly introduced instruments, and their field logs had recorded a number of significant operational difficulties. Moreover, in different years sample particle masses had been determined by two fundamentally different methods, carried out by different organizations, in different laboratories. Finally, the dichot analyses had not been challenged with blind audit samples as had the high-volume sampler analyses.

Three distinct audit objectives for the dichot sampler data were established: (1) verify the reduction of primary measurements to concentration data; (2) evaluate procedures for validating and archiving concentration data; and (3) clarify the derivation of published means, evaluating sensitivity to computational procedures and data selection criteria.

Delays in location of records in the archives and involvement of several laboratories limited the selection of dichot data for audit. Only data files that could be more readily obtained were reviewed. The Audit Team was able to verify the reduction of primary measurements to concentration data for the period November 1981 to January 1984, but not for the other study years because the work was performed by a US Environmental Protection Agency (EPA) laboratory and records were not available at HSPH. The EPA laboratory responsible for data reduction in those study years, however, was the leading practitioner of these methods at that time. For the audited dataset (St Louis, May through July 1983), recalculated and reported values for fine and coarse mass concentrations were quite similar.

The second audit objective was to reproduce the analysis dataset from the master database, verifying the criteria used to reject the data excluded from analysis. This objective could not be achieved because the original database no longer exists. No contemporary account of the criteria used to select data for analysis was located. However, some criteria could be inferred by comparing the reconstructed analytic file with earlier records, and it was clear that different criteria were applied to different years. One example is rejection of observations with coarse or fine mass ratios outside a restricted range during the years 1979–1981 and inclusion of such observations in the years 1982–1985. This restriction did not bias the data in a predictable manner, and the empirical effect of the coarse or fine mass ratio criterion on average concentrations was assessed by extending the criterion into the data for 1982 and later years when it had not been applied. For fine particle mass, this exercise showed generally similar results for all cities except Topeka, where the effect was greatest (15% bias).

The final audit objective was to rederive the means presented in the *New England Journal of Medicine* (NEJM) publication (Dockery et al 1993) and evaluate their sensitivity to different computational procedures and data selection criteria. One problem with this objective was that the Audit Team worked with a reconstructed data file that was derived specifically for the reanalysis to supply the air quality data necessary to arrive at the published values. Using the available information, including additional data that had been subsequently published by Schwartz and colleagues (1996), the Audit Team recalculated means for all observations, annually and quarterly, and compared them with the NEJM data. The 1979–1985 data used by Schwartz and colleagues (1996) had been compiled independently of those used in the NEJM analysis, selected according to different criteria, and did not yield the exact means presented in NEJM.

For particle data, even with the limitations imposed by a reconstructed electronic analytic file, lack of contemporary documentation about inclusion and exclusion criteria, and lack of access to the entire set of raw data, the Audit Team was able to generally verify the results presented in the NEJM publication with the previously described caveats. With the exception of sulfur dioxide (SO_2), the original and reconstructed data for the gaseous pollutants were in good agreement.

Validation of Original Analysis

The validation analysis conducted by the Reanalysis Team showed almost complete agreement with the original findings. Using the Cox proportional-hazards model (Cox 1972) to describe the mortality data for the cohort, the Reanalysis Team was able to reproduce the estimates [and associated confidence intervals (CIs)] of excess mortality due to exposure to fine particles.

Although the Reanalysis Team was satisfied that the original findings were reproducible, we noted some minor discrepancies. These included trivial differences in risk

estimates owing to the order in which the reanalysis calculations were completed. The Reanalysis Team considers such differences to be immaterial. As well, tobacco consumption within the group of former-smokers was originally reported as 10 pack-years, rather than 20 pack-years as calculated by the Reanalysis Team. This turned out to be a typographic error that the Original Investigators had noted at the time the NEJM article was published, but had been unable to correct before publication.

The Reanalysis Team also used a method of calculating confidence intervals for the mortality rate ratios for tobacco consumption among current-smokers and former-smokers that was less conservative than that used by the Original Investigators, producing somewhat narrower confidence intervals. This methodologic difference affects only the confidence intervals on the mortality rate ratios and not the point estimates of the ratios that were reproduced by the Reanalysis Team.

AMERICAN CANCER SOCIETY STUDY

Data Quality Audit

The ACS Study audit used methods similar to those applied to the Six Cities Study. Random samples were selected of 250 questionnaires and 250 death certificates. However, several important differences between the two studies limited the Audit Team's ability to use the same methods for both. First, the Six Cities Study had been designed specifically to answer the Original Investigators' hypotheses about the health effects of air pollution; ACS data had been gathered for other scientific objectives that did not involve questions related to air pollution. Data collection at HSPH had always been under the direct control of the Original Investigators, who were trained in studies of this type. Many of these scientists are still on staff at HSPH and were available to answer the Audit Team's questions. However, questionnaires in the ACS Study had been administered by volunteers, and data collection had not been under the control of the Original Investigators. Furthermore, staff turnover at the ACS was such that the Audit Team did not have access to scientists or volunteers who were involved in the main study, with the exception of one epidemiologist who had worked on computer programs near study termination.

The original analytic files and raw data on morbidity and mortality for the ACS Study were not available. Records were limited to microfilmed copies of death certificates and health questionnaires and to some computer programming documentation that allowed the electronic analytic file to be reconstructed and given to the Audit Team. All hard copy death certificates and questionnaires had been destroyed after microfilming, and follow-up documentation of vital status was lost when the ACS moved from New York to Atlanta. Three microfilmed questionnaires were missing. Little ancillary documentation was available that could be used by the Audit Team, such as the internal and external data audits, intermediate versions of programs, vital status postcards, subject tracking sheets, follow-up questionnaires, detailed coding information, and documentation of internally identified errors and corrective actions that were available for the Six Cities Study. When microfilm could not be located or was not readable, or when coding questions arose that could not be resolved by the remaining ACS contact, the Audit Team was limited in the possible steps that could be taken to follow up and resolve issues.

No raw data for air pollutants were available for the ACS Study. The only documentation of air pollutants was a report from Brookhaven National Laboratory (Lipfert et al 1988), which had not been under the control of the Original Investigators. Therefore, significantly fewer data points were available for audit in the ACS Study despite our original intention to audit these studies similarly. Many of the decisions on coding conventions had to be made through inference by the Audit Team.

The audit of the ACS Study was based on data from the cohort used by the Original Investigators. In developing this cohort, the Reanalysis Team started with the original American Cancer Society's Cancer Prevention Study II (CPS-II) cohort of 1.2 million and applied the same exclusions as had been indicated by the Original Investigators. During this reduction, it was noted that 7,706 female former-smokers and 5,421 female deaths occurring between September 1, 1988, and December 31, 1989, had not been included in the Original Investigators' cohort. The total number of deaths in the reduced cohort was found to be 56,558, rather than the 51,137 deaths reported in the published ACS Study. This discrepancy was due to two programming errors also noted by the ACS before the audit. A third programming error resulted in the exclusion of 83 asthma deaths in the summary category of cardiopulmonary deaths (these deaths had been, however, included in the category of all-cause mortality). The implications of these errors are discussed below.

Microfilm copies of questionnaires and death certificates were traceable with the exception of 1 (0.4%) of the questionnaires and 8 (3.2%) of the death certificates. Two more death certificates were traced but did not have legible information on cause of death.

The review of variables drawn from the questionnaire included study identification number, race, sex, age, smoking history (8 variables), passive smoke exposure (3

variables), alcohol consumption (3 variables), selected occupational exposures (6 variables), education, height and weight, time-on-study, vital status, and death month and year (when applicable). Few errors were noted, with many variables having no errors. The records of vital status follow up by ACS volunteers had been lost when ACS relocated to Atlanta. Therefore, the auditors recalculated time-on-study assuming that those individuals identified as alive in the vital status variable were alive until the end of the study. The vital status of the 250 subjects in the questionnaire sample was audited against three sources: a search of the National Death Index from 1982 to 1989, a review of participants in an American Cancer Society Nutrition Survey conducted after 1989, and a search of the Social Security Information database available via the Internet. No discrepancies in vital status were found.

The review of the random sample of death certificates found few inconsistencies. One (0.4%) of the 242 death certificates available for audit did not pertain to the study participant. Two certificates (0.8%) had errors in date of death. The ICD-9 code for cause of death had been collapsed into a more general, 2-digit code in the analytic file. Therefore, the audit of the ACS death certificates could not be performed at the same level of detail as for the Six Cities Study. In four (1.6%) of the certificates, the auditor's 4-digit ICD-9 code would place the death in a different analysis category as compared with the code assigned by the study nosologist. During the review of death certificates, another computer programming error was detected: the statistical program used to group causes of death placed two codes of cardiovascular deaths into the "other deaths" category. The ACS staff was notified of this programming error and the complete cohort of deaths was reviewed. The two codes accounted for only 71 deaths among the total cohort, and the reassignment of these deaths to the cardiovascular category would not affect the final results.

The audit of the air quality data was significantly more problematic than that of the other study variables for several reasons. No raw air pollution data had been gathered specifically for the ACS Study; accordingly, the Original Investigators had not controlled raw data acquisition or record management. They had designed this study in response to findings from previous studies that had been conducted with smaller cohorts or study areas. They had taken advantage of existing data from the large CPS-II population cohort by collating them with annual statistics on air quality obtained by routine monitoring in a large number of cities. The original monitoring data had come from a variety of sources that are now technologically difficult to access, and there had been little or no documentation of the data selection process, acquisition methods, or underlying coding conventions. Documentation of the statistical reduction procedures had been lost, so it was uncertain whether an exposure value represented data from all monitors or a subset of the monitors in a metropolitan area, or if means and medians had been adjusted for missing observations and seasonal patterns. The summary statistics for different groups of metropolitan areas had been derived by different investigators. Sulfate (SO_4^{2-}) values for some cities could have come from several different sources. No information was available on any trimming procedures that may have been applied to outliers. It was not possible to audit instrument operating logs, filter weights, or other raw records because these had never been collected from the diverse agencies that carried out the original measurements. Because the data for this study could not be meaningfully audited, the Reanalysis Team decided to create our own statistics for the metropolitan areas in this study using the EPA Aerometric Information Retrieval System (AIRS) and the Inhalable Particle Monitoring Network (IPMN) databases.

Validation of Original Analysis

The Reanalysis Team was able to reproduce essentially all of the findings reported in the ACS Study using the same analysis file as had been used by the Original Investigators. As in the Six Cities Study, however, the Reanalysis Team applied a different method of calculating confidence intervals for current-smokers, resulting in somewhat narrower confidence intervals than those reported by the Original Investigators. This methodologic difference did not affect the confidence intervals on the relative risks of mortality associated with fine particles and sulfate.

When reconstructing the cohort used in the ACS Study, the Reanalysis Team found that 7,706 female former-smokers who met the selection criteria had been excluded from the original analysis, as discussed previously. In addition, we found that 5,421 female deaths occurring between September 1, 1988, and December 31, 1989 (the date at which follow-up was terminated), had not been included in the original analysis. Inclusion of these additional female former-smokers and additional female deaths in the analysis slightly increased the mortality risk ratios for both fine particles and sulfate. For example, the mortality risk ratio among female ever-smokers for all causes of death increased from 1.14 (95% CI: 0.97–1.33) to 1.18 (95% CI: 1.04–1.35) for sulfate. The lower bound of the 95% confidence intervals on the risk ratio exceeded 1 when these subjects were included in the analysis. Similarly, among female ever-smokers, the risk ratios for cardiopulmonary mortality associated with fine particles increased from 1.27 (95% CI: 0.92–1.74) to 1.32 (95% CI: 1.01–1.72).

PART II: SENSITIVITY ANALYSES

Following the validation and replication of the Six Cities Study and the ACS Study, the Reanalysis Team conducted a series of comprehensive sensitivity analyses of the original findings using alternative analytic methods. These new analyses were augmented by new data taken from the original questionnaires. These new data were subjected to a rigorous audit and found to be of generally high quality by comparisons between values in the analytic files provided to the Reanalysis Team and values on the original questionnaires. Part II of the audit did identify a number of errors in occupational coding in the ACS Study, with an overall error rate in excess of 15%.

Sensitivity analyses focus primarily on mortality associated with fine particles or sulfate in both the Six Cities Study and the ACS Study. Unless otherwise specified, relative risks of mortality are based on the ratio of the mortality rate in the most-polluted city relative to the mortality rate in the least-polluted city.

The Reanalysis Team conducted a wide range of sensitivity analyses to explore the observed associations between exposure to fine particle or sulfate air pollution and mortality. In particular, we examined the impact of alternative risk models on estimates of risk. These alternative risk models involved covariates not included in the original analyses. In addition to providing a basis for assessing the robustness of the original risk estimates to alternative model specifications, these risk models provided a basis for identifying covariates that may confound or modify the association between fine particle or sulfate air pollution and mortality, and for identifying sensitive population subgroups.

The possibility of confounding due to occupational exposures was also investigated in detail. Specifically, members of the Reanalysis Team who have experience in occupational exposure assessment developed two new aggregate indices of occupational exposures, which were applied in both the Six Cities Study and the ACS Study. The first index provided a seven-category ordinal measure of the overall "dirtiness" of specific jobs and occupations of the study subjects; the second provided a binary indicator of ever or never having been exposed in the workplace to agents that are known to be associated with increased lung cancer risk.

The two studies possess complementary strengths that permitted different sensitivity analyses to be done within each study. In the Six Cities Study, the availability of data on study subjects at 3, 6, and 12 years after the collection of baseline data at the time of enrollment permitted an assessment of changes in key covariates, such as tobacco consumption, over time. The availability of detailed residence histories in this study also permitted an assessment of the impact of population mobility on estimates of risk. The ACS Study, which had involved 154 metropolitan statistical areas (generally referred to as cities by the Original Investigators) from across the United States, allowed for an assessment of the association between mortality in these cities and a number of auxiliary sociodemographic and environmental variables derived from publicly available data sources. Of particular interest in this analysis is the possibility that these ecologic covariates could modify or confound the association between fine particle or sulfate air pollution and mortality.

Because many of the ecologic covariates considered in the ACS Study demonstrated clear spatial patterns across the United States, the Reanalysis Team used spatial methods of analysis to investigate the association among these ecologic covariates, the pollutants of interest, and mortality. These spatial analytic methods take into account spatial autocorrelation in the data, which can affect the significance of statistical tests for associations between the covariates of interest and mortality.

ALTERNATIVE RISK MODELS

The Original Investigators in both the Six Cities Study and the ACS Study had examined the relation between fine particle or sulfate air pollution and mortality using the Cox proportional-hazards survival model. With this approach, the relative increase in the death rate at any point in time is assumed to be constant throughout the period of follow-up, but can be modulated by covariates such as smoking, education, and air pollution. Calendar year had been used as the time axis, and the effects of age at enrollment into the study and sex had been accounted for by stratifying the baseline hazard function by age (5-year groups) and sex. In addition to assessing all-cause mortality, the Original Investigators had considered deaths from cardiopulmonary diseases and lung cancer.

In order to evaluate the sensitivity of the risk estimates obtained by the Original Investigators, the Reanalysis Team considered alternative Cox proportional-hazards risk models of different specifications for the covariates as well as covariates not considered originally. The Reanalysis Team also considered models with age as the time axis, as this approach is thought to more fully account for confounding by age than the above-mentioned analyses. Finally, the Reanalysis Team considered mortality from other causes, including respiratory diseases, cardiovascular diseases, cancers other than lung, and all other causes (excluding cancers) combined.

The Reanalysis Team considered four alternative risk models (Base, Original, Full, and Extended). The Base

Model included air pollution and no other covariates. The Original Model was that followed by the Original Investigators. The Full Model included a much larger number of covariates than did the Original Model: for example, smoking status, duration and intensity of smoking, age started smoking, pipe or cigar smoking (available in the ACS Study only), passive smoking (ACS Study only), education, occupational exposure to dust or fumes (Six Cities Study only), exposure to air toxics (ACS Study only), BMI, marital status, and alcohol consumption. In addition to covariates in their original scale of measurement, we included quadratic terms for continuous covariates, such as number of cigarettes smoked, number of years of smoking, and BMI, in order to account for nonlinear effects on mortality. To describe the effects of educational attainment in more detail, we considered three levels: less than high school, high school, and more than high school. The Full Model also included interaction terms between each of these covariates and gender.

Using data for all causes of death, the Extended Model, a more parsimonious model involving fewer covariates than the Full Model, was developed using step-down regression techniques. The Extended Model was also used to evaluate mortality from specific causes (cardiopulmonary diseases, cardiovascular diseases, respiratory diseases, lung cancer, other cancers, and all other causes), as well as mortality from all causes.

Risk estimates for the four models are given in Summary Table 1 (Six Cities Study) and Summary Table 2 (ACS Study) by cause of death. Adjustment for covariates reduced the risk estimates for all causes of death and for both time axes (age and calendar year) relative to the Base Model (which included only air pollution). Similar relative risks of air pollution were obtained with the Original, Full, and Extended Models. No association between air pollution and mortality from (nonmalignant) respiratory diseases was found in either study; the highest risks were for cardiovascular mortality.

IDENTIFICATION OF SENSITIVE SUBGROUPS

In order to identify population subgroups that may be susceptible to the effects of fine particle or sulfate air pollution, the Reanalysis Team examined the extent to which risk estimates differed among different subgroups. In the ACS Study married persons appeared to be at less risk than nonmarried individuals for deaths related to air pollution; in the Six Cities Study similar risks were observed for married and nonmarried people. Gender did not modify the effect of fine particles in the ACS Study but did so in the Six Cities Study, with males (RR = 1.33, 95% CI: 1.08–1.63) showing a higher risk than females (RR = 1.20, 95% CI: 0.94–1.53). Air

Summary Table 1. Relative Risks of Mortality by Cause of Death Associated with an Increase in Fine Particles in Risk Models with Alternative Time Axes in the Reanalysis of the Six Cities Study[a]

	Time Axis	
Alternative Risk Model[b]	Calendar Year	Age
All Causes [100%]		
Base	1.33 (1.14–1.54)	1.33 (1.15–1.55)
Original	1.29 (1.11–1.50)	1.29 (1.11–1.50)
Full	1.27 (1.09–1.49)	1.27 (1.09–1.48)
Extended	1.28 (1.09–1.49)	1.27 (1.09–1.48)
Cardiopulmonary Disease [54%]		
Base	1.39 (1.13–1.70)	1.39 (1.14–1.71)
Original	1.35 (1.10–1.66)	1.34 (1.09–1.65)
Full	1.31 (1.06–1.62)	1.30 (1.05–1.60)
Extended	1.32 (1.07–1.63)	1.31 (1.06–1.61)
Cardiovascular Disease [47%]		
Base	1.43 (1.15–1.78)	1.44 (1.16–1.79)
Original	1.41 (1.13–1.76)	1.40 (1.12–1.74)
Full	1.38 (1.10–1.72)	1.35 (1.08–1.69)
Extended	1.39 (1.11–1.73)	1.37 (1.09–1.70)
Respiratory Disease [7%]		
Base	1.11 (0.62–1.97)	1.10 (0.63–1.95)
Original	0.93 (0.51–1.71)	0.95 (0.53–1.72)
Full	0.89 (0.47–1.67)	0.94 (0.51–1.73)
Extended	0.88 (0.47–1.64)	0.93 (0.51–1.69)
Lung Cancer [8%]		
Base	1.53 (0.91–2.55)	1.64 (0.99–2.72)
Original	1.31 (0.76–2.25)	1.53 (0.90–2.60)
Full	1.30 (0.76–2.23)[c]	1.42 (0.84–2.42)
Extended	1.29 (0.75–2.22)[c]	1.45 (0.85–2.47)
Other Cancers [20%]		
Base	1.05 (0.74–1.48)	1.04 (0.73–1.47)
Original	1.04 (0.73–1.47)	1.02 (0.72–1.45)
Full	1.11 (0.78–1.59)	1.09 (0.77–1.55)
Extended	1.10 (0.77–1.57)	1.08 (0.76–1.54)
Other Causes [18%]		
Base	1.19 (0.80–1.75)	1.15 (0.78–1.70)
Original	1.16 (0.79–1.72)	1.12 (0.76–1.65)
Full	1.16 (0.78–1.73)	1.10 (0.74–1.63)
Extended	1.15 (0.77–1.71)	1.10 (0.74–1.62)

[a] Relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city; in the Six Cities Study, this difference for fine particles was 18.6 $\mu g/m^3$. Causes of death are shown with percentage of all causes. Data are RRs with 95% CIs.

[b] See the Alternative Risk Models section under the Harvard Six Cities Study in Part II for definition of model specifications and Table 2 in Part II for a list of covariates included in each model.

[c] Used 5-year age groups for stratification of baseline hazard function due to unsuitable risk estimates resulting from low numbers of deaths and large numbers of covariates.

Summary Table 2. Relative Risks of Mortality by Cause of Death Associated with an Increase in Fine Particles or Sulfate in Risk Models with Alternative Time Axes in the Reanalysis of the ACS Study[a]

	Time Axis			
	Calendar Year		Age	
Alternative Risk Model[b]	Fine Particles	Sulfate	Fine Particles	Sulfate
All Causes [100%]				
Base	1.27 (1.18–1.37)	1.26 (1.19–1.33)	1.26 (1.17–1.35)	1.25 (1.18–1.32)
Original	1.18 (1.10–1.27)	1.16 (1.10–1.23)	1.18 (1.10–1.27)	1.16 (1.10–1.22)
Full	1.17 (1.09–1.26)	1.15 (1.08–1.21)	1.16 (1.08–1.25)	1.14 (1.07–1.20)
Extended	1.18 (1.09–1.26)	1.15 (1.09–1.21)	1.17 (1.09–1.25)	1.14 (1.07–1.20)
Cardiopulmonary Disease [50%]				
Base	1.41 (1.27–1.56)	1.39 (1.28–1.50)	1.41 (1.27–1.56)	1.38 (1.27–1.49)
Original	1.30 (1.18–1.45)	1.27 (1.17–1.38)	1.30 (1.18–1.45)	1.27 (1.17–1.37)
Full	1.28 (1.15–1.42)	1.25 (1.15–1.35)	1.28 (1.15–1.42)	1.24 (1.14–1.34)
Extended	1.30 (1.17–1.44)	1.25 (1.16–1.36)	1.29 (1.17–1.43)	1.25 (1.15–1.35)
Cardiovascular Disease [43%]				
Base	1.47 (1.32–1.65)	1.47 (1.35–1.60)	1.46 (1.31–1.63)	1.46 (1.34–1.59)
Original	1.36 (1.22–1.52)	1.36 (1.25–1.48)	1.36 (1.22–1.52)	1.35 (1.24–1.47)
Full	1.34 (1.20–1.49)	1.33 (1.22–1.45)	1.33 (1.19–1.48)	1.32 (1.21–1.43)
Extended	1.35 (1.21–1.51)	1.34 (1.23–1.46)	1.34 (1.20–1.50)	1.33 (1.22–1.44)
Respiratory Disease [7%]				
Base	1.07 (0.80–1.42)	0.94 (0.76–1.17)	1.09 (0.82–1.45)	0.95 (0.76–1.18)
Original	1.00 (0.76–1.33)	0.83 (0.67–1.04)	1.01 (0.76–1.34)	0.85 (0.68–1.05)
Full	0.96 (0.72–1.27)	0.81 (0.65–1.01)	0.99 (0.74–1.31)	0.82 (0.66–1.03)
Extended	0.98 (0.74–1.30)	0.82 (0.65–1.02)	1.00 (0.76–1.33)	0.83 (0.66–1.03)
Lung Cancer [8%]				
Base	1.23 (0.96–1.57)	1.63 (1.35–1.97)	1.21 (0.95–1.54)	1.62 (1.34–1.95)
Original	1.02 (0.80–1.29)	1.36 (1.13–1.65)	1.02 (0.80–1.30)	1.36 (1.12–1.64)
Full	0.99 (0.78–1.26)	1.32 (1.09–1.60)	0.98 (0.77–1.25)	1.31 (1.09–1.59)
Extended	1.00 (0.79–1.28)	1.33 (1.10–1.61)	0.99 (0.78–1.26)	1.32 (1.09–1.60)
Other Cancers [27%]				
Base	1.18 (1.03–1.36)	1.15 (1.03–1.28)	1.17 (1.02–1.34)	1.14 (1.02–1.26)
Original	1.14 (0.99–1.30)	1.10 (0.99–1.23)	1.13 (0.98–1.29)	1.10 (0.99–1.22)
Full	1.14 (1.00–1.31)	1.10 (0.99–1.23)	1.13 (0.98–1.29)	1.09 (0.98–1.21)
Extended	1.14 (0.99–1.31)	1.10 (0.99–1.22)	1.12 (0.98–1.29)	1.08 (0.97–1.21)
Other Causes [15%]				
Base	1.06 (0.88–1.27)	0.93 (0.81–1.08)	1.05 (0.88–1.26)	0.92 (0.80–1.06)
Original	1.01 (0.84–1.21)	0.88 (0.76–1.01)	1.01 (0.84–1.21)	0.87 (0.75–1.01)
Full	1.01 (0.84–1.21)	0.86 (0.75–1.00)	1.00 (0.83–1.20)	0.85 (0.74–0.99)
Extended	1.00 (0.84–1.21)	0.86 (0.75–1.00)	0.99 (0.83–1.19)	0.85 (0.74–0.99)

[a] Relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city; in the ACS Study, this difference for fine particles was 24.5 $\mu g/m^3$, and for sulfate was 19.9 $\mu g/m^3$. Causes of death are shown with percentage of all causes. Data are RRs with 95% CIs.

[b] See the Alternative Risk Models section under the ACS Study in Part II for a description of models and Table 19 in Part II for a list of covariates included in each model.

pollution risks were higher among subjects with preexisting heart or lung disease and low lung function in the Six Cities Study. Of all the modifying factors considered in this analysis of population subgroups, education was the only variable to show a statistically significant effect. As indicated in Summary Table 3, the relative risks of mortality found using the Extended Model declined with increasing educational attainment for most causes of death examined in the ACS Study, although this pattern was not as consistent in the Six Cities Study.

OCCUPATIONAL EXPOSURES

Occupational exposure may be an important confounder of the association between fine particle or sulfate air pollution and mortality. Confounding could occur if individuals who lived in areas with higher levels of air pollution also tended to work in jobs with exposure to hazardous agents in the workplace. This concern is reinforced by the epidemiologic evidence that certain occupational exposures can lead to increased mortality from lung cancer and other nonmalignant respiratory diseases.

Some information on potential workplace exposures was available in both studies. In the Six Cities Study, the Original Investigators had adjusted for occupation on the basis of self-reported exposures to dusts or fumes in the workplace. Further information on occupation and industry obtained in the baseline interview had not been used in the original analysis, other than through the creation of a simple variable indicating white-collar or blue-collar employment. In the ACS Study, the Original Investigators had used self-reported exposure to six occupational dusts or fumes. Further information obtained during the interview on current or last occupation, as well as the occupation of longest duration, had not been used in the original analyses. As self-report is an imperfect indicator of occupational exposure, the Reanalysis Team developed two new indicators of occupational exposure using the occupational and industrial history data from each study, additional information from the literature, and the Team members' expertise about the nature of industrial working environments. Although these indices are not based on detailed lifetime work histories and are crude simplifications of complex occupational exposure circumstances, they represent perhaps the best that can be done to control for occupational confounding in these two studies.

The first index was an indicator of occupational dirtiness based on the 442 occupational codes in the 1970 US Census classification system (Boffetta et al 1995) used to classify jobs in the Six Cities Study and the 68 job categories used in the ACS Study. This dirtiness index ranged from 0 (indicating a very clean work environment) to 6 (a very dirty environment). The second index was a binary indicator of ever or never having been exposed to known occupational lung carcinogens, a list obtained using information from the International Agency for Research on Cancer. The validity of the application of these indices was limited by the precision of the occupational classifications used by the Original Investigators; because the ACS Study used quite a crude classification system, the resulting indices were less reliable than those used in the Six Cities Study.

The inclusion of these two new occupational exposure indices had almost no impact on the association between air pollution and either all-cause mortality or cardiopulmonary mortality in either study. However, the increased lung cancer risk associated with exposure to sulfate in the ACS Study was attenuated somewhat when the new occupational exposure indices were included in the reanalysis. In both studies, the effects of air pollution tended to be stronger among subjects with higher occupational dirtiness scores, providing evidence of effect-modification by occupational dirtiness.

Although attempts to more fully control for occupational confounding through the use of these two occupational exposure indices were constrained by limitations in the quality of the data, the findings increase our confidence that the association between air pollution and all-cause as well as cardiopulmonary mortality observed in both studies is not due to uncontrolled occupational confounding. However, the possibility of residual confounding by occupation in the ACS Study cannot be ruled out in the case of the increase in lung cancer mortality associated with sulfate.

FLEXIBLE EXPOSURE-RESPONSE MODELS

The Original Investigators in both the Six Cities Study and the ACS Study had used the Cox proportional-hazards regression model to evaluate the relation between mortality and key covariates, including fine particle and sulfate air pollution. Under this model, a fixed increment in ambient pollutant levels has the same multiplicative effect on the mortality rate at any point in time, so that the hazard functions for mortality at two pollutant levels are proportional and invariant in time. In addition, the relative increase in mortality had been described by a specific parametric form, with the logarithm of the hazard rate being a linear function of the covariates.

To evaluate the applicability of this model in the two studies of interest, the Reanalysis Team considered flexible exposure-response models to describe the relation between fine particles and sulfate on mortality, using regression spline generalizations of the Cox model. With only six cities, the Six Cities Study afforded a limited opportunity to define the shape of the exposure-response curve. In the

Six Cities Study, this flexible modeling approach did not provide evidence against linearity for fine particles. For sulfate particles, however, there was some evidence of departures from linearity at both low and high sulfate concentrations. Consistent with the quadratic relation between BMI and mortality in our Extended Model for both studies, the flexible modeling approach suggested a U-shaped relation between BMI and mortality. Although the Cox proportional-hazards assumption did not appear to be inappropriate throughout most of the study period, there was some evidence that effects of both fine particles and sulfate varied somewhat with follow-up time.

Flexible analysis of the ACS data yielded some evidence of nonlinear exposure-response relations for both fine particles and sulfate. In particular, the exposure curve for sulfate was relatively shallow below about 10 to 15 $\mu g/m^3$, rising more steeply at higher exposures. As in the Six Cities Study, flexible modeling also revealed a nonlinear U-shaped relation between BMI and mortality. No clear evidence of time dependency in the effects of either fine particles or sulfate on mortality was observed in the ACS Study.

TIME-DEPENDENT COVARIATES

The Original Investigators in the Six Cities Study had demonstrated a positive association between fine particles and mortality. For an increase of fine particles of 18.6 $\mu g/m^3$, the associated relative risk of all-cause mortality had been estimated to be 1.26 (95% CI: 1.08–1.46), based on Cox regression after adjustment for age, sex, smoking, education, BMI, and occupation. In order to take into account changes in these covariates over time, the Reanalysis Team used Poisson regression methods to allow for temporal changes in smoking and BMI. As a verification of the method, using constant covariates, the Poisson regression modeling approach led to a comparable although slightly higher relative risk of mortality of 1.32 (95% CI: 1.13–1.53). Incorporation of time dependency in smoking and BMI using Poisson regression did not appreciably alter this latter risk estimate. However, incorporation of time dependency in city-specific annual averages of fine particles resulted in a somewhat reduced estimate of 1.16 (95% CI: 1.02–1.32), although the confidence intervals exhibited considerable overlap with those based on constant (long-term average) fine particle levels.

POPULATION MOBILITY

Population mobility had not been considered in the original analyses, although both of the studies had involved extended follow-up periods. Although longitudinal information on participants in the ACS Study had not been collected after enrollment (other than for determining vital status), participants in the Six Cities Study had been given supplementary questionnaires at 3, 6 and 12 years after enrollment, and their whereabouts and vital status had been tracked using annual letters, postcards, or phone calls. In order to evaluate the potential impact of population mobility on risk in the Six Cities Study, the Reanalysis Team used this information to develop residence histories for each of the study participants.

Analysis of these residential histories indicated that relatively few subjects (18.5%) moved from their original city of residence. Mobility was similar in all cities (12.7–19.0%) except Watertown (31.8%). This group of movers tended to be younger and better educated than the nonmovers. For fine particles the relative risk of mortality in the subcohort

Summary Table 3. Relative Risks of Mortality by Cause of Death Associated with an Increase in Fine Particles by Education Level in the Reanalysis of the Six Cities and ACS Studies[a]

	ACS Study			Six Cities Study		
Cause of Death	Less Than High School [11%]	High School [30%]	More Than High School [59%]	Less Than High School [28%]	High School [38%]	More Than High School [34%]
All causes	1.35 (1.17–1.56)	1.23 (1.07–1.40)	1.06 (0.95–1.17)	1.45 (1.13–1.85)	1.30 (0.98–1.73)	0.97 (0.71–1.34)
Cardiopulmonary disease	1.47 (1.21–1.78)	1.35 (1.11–1.64)	1.14 (0.98–1.34)	1.28 (0.92–1.77)	1.42 (0.98–2.08)	1.40 (0.88–2.23)
Cardiovascular disease	1.47 (1.19–1.82)	1.39 (1.13–1.72)	1.24 (1.05–1.47)	1.31 (0.92–1.87)	1.63 (1.10–2.42)	1.37 (0.84–2.22)
Respiratory disease	1.36 (0.80–2.32)	1.16 (0.69–1.95)	0.65 (0.42–1.02)	0.97 (0.38–2.46)	0.36 (0.09–1.39)	1.80 (0.26–12.35)
Lung cancer	1.41 (0.87–2.29)	1.39 (0.90–2.15)	0.66 (0.46–0.95)	2.69 (1.09–6.60)	0.50 (0.11–2.22)	1.08 (0.33–3.58)
Other cancers	1.20 (0.87–1.66)	1.12 (0.87–1.43)	1.14 (0.94–1.38)	1.33 (0.75–2.37)	1.48 (0.77–2.83)	0.53 (0.25–1.09)
Other causes	1.12 (0.76–1.64)	1.00 (0.71–1.41)	0.95 (0.73–1.24)	1.76 (0.93–3.33)	0.65 (0.29–1.44)	0.69 (0.31–1.55)

[a] Relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city; in the Six Cities Study, this difference for fine particles was 18.6 $\mu g/m^3$; in the ACS Study, this difference was 24.5 $\mu g/m^3$. Time axis was calendar year. Percentage of sample in educational group is given in square brackets. Data are RRs with 95% CIs.

that never moved from the original city of residence was 1.30 (95% CI: 1.10–1.54), similar to that in the entire cohort. However, the relative risk among movers was 1.08 (95% CI: 0.67–1.76), notably lower than among nonmovers. The relative risk of mortality declined with increasing educational attainment among both movers (RR = 1.41, 1.42, and 0.96 with less than high school, high school, and more than high school education, respectively) and nonmovers (RR = 1.56, 0.71, and 0.96).

The Reanalysis Team also conducted an analysis of population mobility in which subjects who moved out of the original city of residence were treated as lost to follow up. This analysis resulted in a relative risk of 1.23 (95% CI: 1.05–1.45), similar to the value of 1.26 (95% CI: 1.08–1.46) reported by the Original Investigators.

The Reanalysis Team also examined the effect of the number of years lived in the original city of residence prior to recruitment into the study on risk, and this did not appear to affect the mortality rate ratios. However, because most subjects had lived in the same city for quite some time prior to the start of the study (median of 28 years), the opportunity to identify a difference in risk as a function of preenrollment mobility was limited.

Finally, the Reanalysis Team conducted an analysis of the mover group using the long-term average exposures to fine particles, but ignoring follow-up data on these subjects prior to the time when they first moved from the city of enrollment. For all-cause mortality, this analysis produced a relative risk of 1.25 (95% CI: 0.75–2.10), similar to that in the entire sample (RR = 1.28), but greater than that in the mover group (RR = 1.08), based on full follow up of this group starting at the time of enrollment into the study. Although the confidence intervals on estimates of the relative risk in the mover group are wide because of the small size of this group, this analysis suggests that the mortality risk in the mover group is comparable to that in the entire sample. Our previous estimate of RR = 1.08 for the mover group based on full follow up may be low because some individuals who might have otherwise moved from the original city of residence may have died before they had the opportunity to do so.

ALTERNATIVE PARTICULATE AIR POLLUTION DATA

The Original Investigators in the Six Cities Study had used air pollution monitoring data from state and local agencies in the early years of the study, and later conducted their own measurements of total particle mass, inhalable particle mass, fine particle mass, sulfate, aerosol acidity, sulfur dioxide, nitrogen dioxide (NO_2), and ozone (O_3). This extensive air pollution database has been subjected to several independent audits, including the audit conducted in Part I of the reanalysis. However, the present audit was the first to examine the fine particles dichotomous sampler data used in the Six Cities Study.

Because the Original Investigators in the ACS Study had derived their air pollution data from secondary sources, the original records of air pollution data they used were not available for audit. In order to evaluate the sensitivity of the risk estimates obtained in the ACS Study, the Reanalysis Team developed a number of alternative indicators of exposure to fine particle and sulfate air pollution. Whereas the Original Investigators had relied on air pollution data collected in 1980, the reanalysis attempted to obtain additional air pollution data throughout the study's follow-up period (1980–1989).

Specifically, we obtained data from both IPMN and AIRS databases maintained by the EPA. Whereas the Original Investigators had reported fine particle data for 50 of the 154 cities they considered in the ACS Study, we were able to locate fine particle measurements within the IPMN for 63 of the 154 cities.

Sulfate data were available in AIRS for 132 of the cities included in the ACS Study in 1980, 124 cities in 1981, and a maximum of 60 cities in any given year in the period 1982–1989. Because of the marked reduction in sulfate monitoring in the later years, we restricted our attention to the cities for which sulfate data were available from AIRS in either 1980 or 1981. These data were supplemented with sulfate monitoring data from the IPMN, allowing us to obtain sulfate data for 144 of the 151 cities in the sulfate cohort considered by the Original Investigators. The sulfate measurements in AIRS that were obtained using high-volume samplers with glass-fiber filters are known to be subject to artifactual sulfate from the presence of sulfur dioxide. Adjustment for this artifact was modeled by comparing sulfate data from AIRS with data from IPMN, which employed Teflon filters that did not result in artifactual sulfate. This adjustment reduced the mean sulfate levels by almost 50%.

The relative risk of mortality from all causes, cardiopulmonary diseases, and lung cancer based on these alternative fine particle and sulfate air pollution measurements and our Extended Model are shown in Summary Table 4. The risk estimates based on the 50 cities in the fine particle cohort using median fine particle levels considered by Original Investigators [$PM_{2.5}$(OI MD)] and the Reanalysis Team [$PM_{2.5}$(DC MD)] are comparable for all three causes of death. Using mean rather than median values for fine particles in the 63 cities for which we were able to locate fine particle data from the IPMN produced similar estimates of risk.

Our unadjusted sulfate [$SO_4^{2-}{}_{(cb\text{-}unadj)}$] measurements for the 144 cities for which we could locate sulfate data

Summary Table 4. Relative Risks of Mortality from All Causes, Cardiopulmonary Disease, and Lung Cancer Associated with an Increase in Fine Particles or Sulfate Using Alternative Measures of Pollutants in the Reanalysis of the ACS Study[a]

		Cause of Death		
Pollutant[b]	Number of Cities	All Causes	Cardiopulmonary Disease	Lung Cancer
$PM_{2.5}$(OI MD)	50	1.18 (1.09–1.26)	1.30 (1.17–1.44)	1.00 (0.79–1.28)
$PM_{2.5}$(DC MD)	50	1.14 (1.06–1.22)	1.26 (1.14–1.39)	1.08 (0.88–1.32)
$PM_{2.5}$(DC)	63	1.12 (1.06–1.19)	1.26 (1.16–1.38)	1.08 (0.88–1.32)
SO_4^{2-}(OI)	151	1.15 (1.09–1.21)	1.25 (1.16–1.36)	1.33 (1.10–1.61)
$SO_4^{2-}{}_{(cb\text{-}unadj)}$	144	1.14 (1.07–1.20)	1.24 (1.15–1.35)	1.18 (0.97–1.44)
$SO_4^{2-}{}_{(cb\text{-}adj\ US)}$	144	1.18 (1.11–1.26)	1.31 (1.19–1.43)	1.18 (0.96–1.47)
$SO_4^{2-}{}_{(cb\text{-}adj\ region)}$	144	1.23 (1.16–1.30)	1.34 (1.23–1.45)	1.25 (1.03–1.52)

[a] Relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city; in the ACS Study, this difference for fine particles was 24.5 μg/m^3, and for sulfate was 19.9 μg/m^3. Analyses are based on the Extended Model; see Table 19 in Part II for a complete list of covariates. Data are RRs with 95% CIs.

[b] Refer to the Abbreviations and Other Terms section at the end of the Investigators' Report for the specific meanings of these pollutant terms and to Table 29 in Part II for the sources of pollutant data. All values are means unless indicated by MD (median).

produced risk estimates similar to the sulfate data [SO_4^{2-}(OI)] in the 151 cities used by the Original Investigators. Adjustment for the artifactual sulfate [$SO_4^{2-}{}_{(cb\text{-}adj\ US)}$] resulted in somewhat higher risk estimates, particularly for all-cause mortality (RR increased from 1.14 without adjustment to 1.18 with adjustment) and cardiopulmonary mortality (RR increased from 1.24 to 1.31). The alternative sulfate data assembled by the Reanalysis Team yielded the same risk of lung cancer (RR = 1.18) whether or not adjustment for artifactual sulfate was done at the national level. However, our regional adjustment [$SO_4^{2-}{}_{(cb\text{-}adj\ region)}$] led to a slightly higher risk (RR = 1.25) of lung cancer.

Further analysis conducted by the Reanalysis Team failed to reveal increased relative risk of mortality for inhalable particles (PM_{15}), the coarse fraction ($PM_{15-2.5}$), or total suspended particles (TSP) in the approximately 60 cities for which such data were available in the IPMN. As well, no associations with TSP were found in the 156 cities for which these data were available from AIRS.

ECOLOGIC COVARIATES

The Reanalysis Team also considered other unmeasured covariates at the metropolitan level that might affect the relation between fine particle or sulfate air pollution and mortality. This examination was restricted to the ACS Study because the Six Cities Study involved at most 5 *df* for incorporation of ecologic covariates.

The Reanalysis Team applied several criteria in selecting additional ecologic covariates for inclusion in the sensitivity analyses. First, a potential ecologic covariate had to represent a valid measure of group-level or city-level attributes. Second, there had to be a plausible biologic or social mechanism by which an ecologic covariate could affect mortality. And third, only those ecologic variables for which there were reliable data were included in the analysis.

After carefully examining 30 potential ecologic covariates, the Reanalysis Team selected 20 for inclusion in the sensitivity analyses (Summary Table 5). These variables represent potentially important demographic, socioeconomic, health services, climate, and environmental indicators that may affect the relation between fine particle or sulfate air pollution and mortality.

The Reanalysis Team considered several approaches to the incorporation of these auxiliary ecologic covariates into Cox regression. First, the relative risk of mortality associated with each ecologic covariate was estimated by removing the variable representing air pollution (sulfate or fine particle) from our Extended Model and including the ecologic covariate in its place. The relative risks of all-cause mortality associated with each of these ecologic covariates are shown in Summary Table 5. These analyses indicated that population change, income, income disparity, unemployment, education, hospital beds, temperature, variation in temperature, water hardness, sulfur dioxide, ozone, and nitrogen dioxide demonstrated some association with mortality in the sulfate cohort ($P < 0.05$). However, income disparity among the population and nitrogen dioxide levels were negatively correlated with mortality, and water hardness was positively correlated; therefore, these ecologic associations require careful interpretation.

To evaluate the impact of these ecologic covariates on the association between fine particle or sulfate air pollution and

mortality, the Reanalysis Team then incorporated each covariate individually into the Extended Models developed for fine particles and sulfate. This analysis provided estimates of the relative risk of mortality due to exposure to fine particle or sulfate air pollution, adjusted for any effects of the ecologic covariates on mortality. The inclusion of most of these ecologic covariates did not appear to have a marked impact on the relative risk of all-cause mortality for sulfate. However, the inclusion of population change, which is negatively correlated with sulfate ($r = -0.40$), reduced the relative risk of mortality from 1.15 to 1.06. Similarly, sulfur dioxide ($r = 0.48$) reduced the relative risk from 1.16 to 1.04.

Most of the ecologic covariates did not appear to have a marked impact on relative risk of cardiopulmonary mortality associated with sulfate, although adjustment for population change decreased the relative risk from 1.24 to 1.12. Population change, income, income disparity, unemployment, education, physician availability, hospital beds, temperature variation, relative humidity, water hardness, and sulfur dioxide appeared to be associated with cardiopulmonary mortality. Several ecologic covariates (relative humidity, altitude, and ozone) appeared to be associated with lung cancer mortality, although the etiology of these associations is not readily apparent. Nonetheless, adjustment for these ecologic covariates did not alter the original conclusions concerning the positive association between lung cancer mortality and sulfate exposure.

Similar ecologic analyses were carried out for the fine particle cohort. As with sulfate, the relative risk of all-cause mortality for fine particles was diminished after adjustment for population change or sulfur dioxide exposure. This same effect was observed for cardiopulmonary mortality. Since lung cancer mortality was not associated with fine particles, no adjustment for ecologic covariates was attempted in this case.

Further analyses of the ecologic covariates were conducted for two important reasons. First, statistical tests of significance are not reliable if the residuals of the models are not autocorrelated. Second, although we adjusted for 20 different ecologic covariates, spatial autocorrelation may be present as a result of some missing, unmeasured variable.

SPATIAL ANALYSES

Prior to conducting formal spatial regression analyses, the Reanalysis Team examined the spatial patterns in the data using cartographic methods. Sulfate and sulfur dioxide concentrations obtained by the application of spatial interpolation techniques to data for the 151 cities in the sulfate cohort of the ACS Study are shown in Summary Figure 1 and Summary Figure 2, respectively. Note that the majority of the cities fall in the Eastern US, where both sulfate and sulfur dioxide tend to be higher although the regional distinctions for sulfur dioxide are less pronounced. Because there were only 50 cities in the fine particle cohort, interpolation results are less stable. However, fine particle concentrations also appear to be highest in the East, particularly in the Ohio Valley (Summary Figure 3). All of the other ecologic covariates considered by the Reanalysis Team also demonstrated clear spatial patterns.

The Reanalysis Team developed a two-stage regression modeling procedure to take into account spatial patterns in the ACS Study data. In the first stage, the city-specific mortality rates were estimated by fitting the Extended Model, excluding fine particle and sulfate air pollution, with an indicator function for each city. In the second stage, we regressed the logarithms of the city-specific relative mortality rates on the ecologic covariates discussed above. We focused on four different two-stage regression models, affording progressively more control for spatial autocorrelation (Summary Table 6).

Independent Observations Model

Like the standard Cox model, the two-stage Independent Observations Model assumes that all observations are statistically independent. Relative risks are obtained by fitting the Cox model with an indicator variable for each city in the first stage, and then combining the city-specific relative risks in the second stage with weights proportional to the inverse of the standard errors of the mortality risk ratios in the second stage. This model provides a baseline against which the remaining three models can be compared.

Independent Cities Model

The Independent Cities Model allows for clustering in mortality rates by city using a random effects approach to describe between-city variation. The random effects approach avoids the assumption of independent observations by incorporating between-city variation into the weights in the second stage. However, this approach assumes that the city-specific mortality rates are statistically independent, thereby ignoring possible regional patterns in mortality that extend beyond metropolitan area boundaries.

Summary Table 5. Ecologic Covariates Used in the Sensitivity Analyses of the ACS Study

Ecologic Covariate	Number of Cities: Sulfate	Number of Cities: Fine Particles	Description	Relative Risk of All-Cause Mortality in the Sulfate Cohort
Demographic Factors				
Population change	139	48	Percentage of net change in number of residents between 1980 and 1986	0.85 (0.81, 0.89)
Whites	151	50	Percentage of persons in the USA in 1980 who classified themselves as being of white race	1.02 (0.98, 1.06)
Blacks	151	50	Percentage of persons in 1980 who classified themselves as being of black race	1.01 (0.96, 1.06)
Socioeconomic Factors				
Income	151	50	Mean annual per capita income in US dollars for 1979	0.93 (0.88, 0.97)
Poverty	151	50	Percentage of individuals in 1979 who were classified as living below the poverty level specific to their family size, age, and number of dependents	0.95 (0.91, 1.00)
Income disparity	151	50	Gini coefficient (see Selection of Ecologic Covariates section in Part II and Appendix E[a] for description) calculated from income group data for 1979 as outlined in Shyrock et al 1976	0.88 (0.84, 0.93)
Unemployment	151	50	Percentage of total civilian labor force who were unemployed in 1986	1.12 (1.06, 1.19)
Education	151	50	Percentage of the number of persons 25 years of age or older who indicated they had completed 4 years of high school or some years of college divided by the total number of persons 25 years and older	0.91 (0.86, 0.96)
Health Services				
Physicians	138	48	Number of professionally active, non-Federal physicians with known addresses per 100,000 residents as of July 1, 1985	0.95 (0.89, 1.01)
Hospital beds	139	48	Number of hospital beds per 100,000 residents as of July 1, 1985	1.13 (1.06, 1.21)
Climate				
Temperature	135	46	Maximum daily temperature (°F) averaged by month for 1980 through 1989	0.88 (0.85, 0.92)
Temperature variation	135	46	Variation in maximum daily temperature (°F) averaged by month for 1980 through 1989	1.18 (1.11, 1.24)
Relative humidity	95	37	Minimum daily relative humidity (%) averaged by month for 1984 through 1989	1.05 (0.99, 1.12)
Relative humidity variation	95	37	Variation in minimum daily relative humidity (%) averaged by month for 1984 through 1989	0.96 (0.90, 1.02)
Physical Environment				
Altitude	110	38	Measured as meters above sea level	1.05 (0.99, 1.12)
Water hardness	109	49	Concentration of $CaCO_3$ (ppm) in drinking water, measured ca 1970	1.08 (1.02, 1.13)
Gaseous Copollutants				
CO	107	44	Daily average concentrations averaged by year for 1980; from residential, commercial, or mobile monitors	0.98 (0.92, 1.03)
NO_2	74	33	Daily average concentrations averaged by year for 1980; from residential, commercial, or mobile monitors	0.93 (0.89, 0.98)
O_3	117	45	Daily 1-hour maximum concentrations	0.93 (0.87, 0.99)
SO_2	113	38	Daily average concentrations averaged by year for 1980; from residential, commercial, or mobile monitors	1.30 (1.23, 1.38)

[a] Appendix E to Part II is available on request from Health Effects Institute.

Regional Adjustment Model

To allow for the possibility of such regional effects, we conducted further analyses in which an indicator variable was used to represent each of the seven regions in the US developed for use in National Morbidity, Mortality, and Air Pollution Study (Samet et al 2000) sponsored by the Health Effects Institute. These estimates were then combined in the second stage, allowing for residual between-city variation.

Spatial Filtering Model

The model shown in Summary Table 6 uses spatial filtering techniques to remove regional patterns in the data before applying the two-stage random effects regression methods. In this analysis, regional patterns in both mortality and the ecologic predictors of mortality are removed by spatial filtering prior to regression analysis. In contrast, the previous Regional Adjustment Model adjusted for spatial patterns in mortality, but not in the ecologic covariates used to predict mortality. The spatial filtering approach compares the relative risk for a city with the risks for cities within a specified distance for that city. The distance (600 km) was selected such that the residual spatial autocorrelation was minimized.

Results of Spatial Analyses

The results of applying the four different two-stage regression methods to the sulfate and fine particle cohorts of the ACS Study are summarized in Summary Table 6. Under the Independent Observations Model, the relative risk of mortality from all causes was estimated to be 1.17, similar to the estimate of 1.15 based on Cox regression. Allowing for clustering by city in the Independent Cities Model led to higher estimates of the relative risk of mortality from all causes due to exposure to sulfate than in the Independent Observations Model, because of the allowance for between-city heterogeneity in the weights used in the second stage. However, as in the Independent Observations Model, the association between sulfate and mortality was markedly reduced after adjustment for exposure to sulfur dioxide. (In both analyses, sulfur dioxide was associated with an increased risk of mortality from all causes.)

Adjusting for spatial clustering in city-specific mortality rates within the seven regions led to relative risk estimates closer to those obtained with the Independent Observations Model, although with somewhat wider confidence intervals. This reduction in risk following the Regional Adjustment Model suggests that part of the apparent sulfate effect observed with the Independent Cities Model is due to broad spatial concordance between mortality and air pollution. The final analysis involves the removal of regional trends both in mortality and in each of the ecologic covariates considered using spatial filtering techniques prior to regression analysis (see Summary Table 6). This analysis provides a more complete adjustment for regional patterns in the data without the need to specify arbitrary regional boundaries as in the previous analysis. Spatial filtering resulted in relative risks of all-cause mortality due to sulfate exposure that were lower than those in the Regional Adjustment Model.

To evaluate the stability of the sulfate effect to adjustment for the effects of multiple ecologic covariates, three other models involving multiple covariates were fit. The first model included all four gaseous copollutants (CO, NO_2, O_3, and SO_2) in addition to sulfate. The second included all of the ecologic covariates described as demographic (population change) and socioeconomic (educational attainment, income, poverty rate, income disparity, and unemployment rate). The third model included all ecologic covariates that individually were found to produce a 25% change in the relative risk associated with sulfate.

Because the only gaseous copollutant that appeared to be strongly associated with all-cause mortality was sulfur dioxide, simultaneous adjustment for all four gaseous copollutants led to sulfate relative risks that were somewhat comparable to those obtained by adjusting for sulfur dioxide alone. Adjusting for all demographic and socioeconomic variables simultaneously did not have a marked impact on the association between sulfate and all-cause mortality. Simultaneous adjustment for all ecologic covariates that individually resulted in a change of 25% or more in the relative risk of mortality associated with sulfate exposure tended to diminish the relative risk of sulfate, in large part because of the inclusion of sulfur dioxide in this multiple covariate analysis.

The general pattern of two-stage regression results for cardiopulmonary mortality was similar to that for all-cause mortality. The relative risk of lung cancer mortality associated with exposure to sulfate remained elevated after adjustment for multiple covariates. Because lung cancer exhibits a high degree of spatial heterogeneity, no attempt was made to remove spatial autocorrelation in the data using either the Regional Adjustment Model or the Spatial Filtering Model.

Exposure to fine particles was associated with all-cause mortality under the Independent Observations Model (RR = 1.18). The relative risk increased to 1.29 under the Independent Cities Model and dropped to 1.16 following the Regional Adjustment Model. It was not possible to apply the Spatial Filtering Model, because of the limited number of cities (50) in the fine particle cohort.

As in the sulfate cohort, sulfur dioxide appeared to be strongly associated with all-cause mortality. Adjustment for exposure to sulfur dioxide greatly diminished the relative

risk of sulfate in the Independent Observations Model, although the relative risk of all-cause mortality associated with exposure to fine particles remained elevated, if not significant, in the Independent Cities Model and Regional Adjustment Model. The relative risk of all-cause mortality due to sulfate exposure was not greatly altered following adjustment for all demographic and socioeconomic covariates, although the relative risk was notably reduced in multiple covariate models that include sulfur dioxide.

Fine particles alone were associated with cardiopulmonary mortality under all three models considered, with relative risks of 1.30, 1.38, and 1.24 under the Independent Observations, Independent Cities, and Regional Adjustment Models, respectively. Although sulfur dioxide was strongly associated with cardiopulmonary mortality, the sulfate effect on cardiopulmonary mortality was not eliminated by adjustment for sulfur dioxide exposure.

Because no association between fine particles and lung cancer mortality was detected using Cox regression, further spatial analyses were not conducted in this case.

CONCLUSIONS

Both time-series and cohort studies have shown associations between exposure to fine particles and sulfate in ambient air and morbidity and mortality. The two cohort studies of present interest, the Six Cities Study and the ACS Study, are of particular significance in that their results were instrumental in establishing the first US National Ambient Air Quality Standards for fine particles. The importance of these two studies in the development of regulatory standards for particulate matter in the US led to the independent audit and reanalysis described in this report.

Part I of the reanalysis focused on validation of the data used by the Original Investigators in both studies and replication of the original findings. In this first phase, we were able to establish the integrity of most of the data in both studies, the exception being the air pollution monitoring data used in the ACS Study, which were obtained from third party sources. (This limitation was addressed in Part II of the Ranalysis Project through the use of alternative air pollution data derived from original sources, described in Part II of the Investigators' Report.) Although some data discrepancies were noted in both studies, these did not materially affect the conclusions reached by the Original Investigators.

The objective of Part II of the reanalysis was to evaluate the sensitivity of the original findings to alternative analytic methods. In addition, we extended our data audit to the new set of variables considered in the sensitivity analyses and found that, except for occupational codes in the ACS Study, all new variables on the electronic data files accurately reflected the original information obtained from subjects. The Reanalysis Team applied a wide range of alternative analytic approaches in the sensitivity analyses, including two-stage random regression models and spatial filtering techniques. We also examined additional covariates from the original questionnaires not included in the original analyses, as well as a series of ecologic covariates developed from publicly available records and the scientific literature for the cities in the ACS Study.

The risk estimates reported by the Original Investigators were remarkably robust to alternative risk models. Specifically, for all alternative risk models considered by the Reanalysis Team within the family of Cox proportional-hazards regression models, the relative risk of all-cause mortality in the Six Cities Study was close to the mortality rate ratio of 1.26 reported by the Original Investigators. Similar results were obtained using either calendar year or age as the time axis. Relative risks of mortality from cardiopulmonary disease and lung cancer were also similar to the mortality rate ratios reported by the Original Investigators, with cardiopulmonary disease mortality, but not lung cancer mortality, significantly associated with fine particles. Relative risks of mortality from cardiovascular disease (RR = 1.41, 95% CI: 1.13–1.76, based on the Original Model specification with calendar year as the time axis) were comparable to the mortality rate ratio for cardiopulmonary disease (1.35, 95% CI: 1.10–1.66) calculated using the Original Model. The relative risks of mortality from respiratory diseases and nonpulmonary cancer were not significantly different from unity.

The Original Investigators in the ACS Study estimated the relative risk of all-cause mortality to be about 1.18 for an increase of 24.5 $\mu g/m^3$ in particulate matter 2.5 μm or smaller in aerodynamic diameter ($PM_{2.5}$). Similar estimates were obtained with all of the alternative risk models considered by the Reanalysis Team. The relative risks of cardiopulmonary and cardiovascular mortality were comparable to those in the Six Cities Study, and robust against specification of the statistical model. Lung cancer mortality was associated with sulfate but not fine particles, and also largely independent of model specification. As in the Six Cities Study, there was no clear evidence of associations between respiratory mortality or deaths from nonpulmonary cancer in the ACS Study.

The Reanalysis Team found some evidence of variation in risk among population subgroups in both studies. In the Six Cities Study, the association between fine particles and mortality was insensitive to lung function performance as measured by spirometric techniques. Of all the modifying factors considered in the reanalysis of both the Six Cities Study and the ACS Study, education was the only covariate

demonstrating a statistically significant effect, with the air pollution risk decreasing notably with increasing educational attainment.

Because of the potential for confounding by occupation, the Reanalysis Team conducted extensive analysis of the effects of occupation on the relation between fine particles or sulfate air pollution and mortality. However, analyses using two aggregate indicators of occupational dirtiness and exposure to agents in the workplace known to be associated with increased lung cancer risk increased our confidence that the association between fine particles and all-cause or cardiopulmonary mortality was not due to uncontrolled occupational confounding. However, the possibility of residual confounding by occupation in the ACS Study with respect to the association between lung cancer mortality and sulfate cannot be ruled out.

Flexible spline regression risk models were also applied in the reanalysis to evaluate the validity of the Cox proportional-hazards assumption underlying the original Cox regression model, and the assumed linear relation between covariates in the Cox model and the logarithm of the hazard rate. In the Six Cities Study, this flexible modeling approach revealed evidence of nonlinear effects of sulfate, but not fine particles. There was also some evidence that the effects of both fine particles and sulfate may vary somewhat with time. In the ACS Study, flexible modeling yielded some evidence of nonlinear exposure-response relations for both fine particles and sulfate, particularly in the exposure-response curve for sulfate. However, no clear evidence of time dependency in the effects of either fine particles or sulfate on mortality was observed in the ACS Study. In both studies, flexible modeling also revealed a nonlinear U-shaped relation between BMI and mortality.

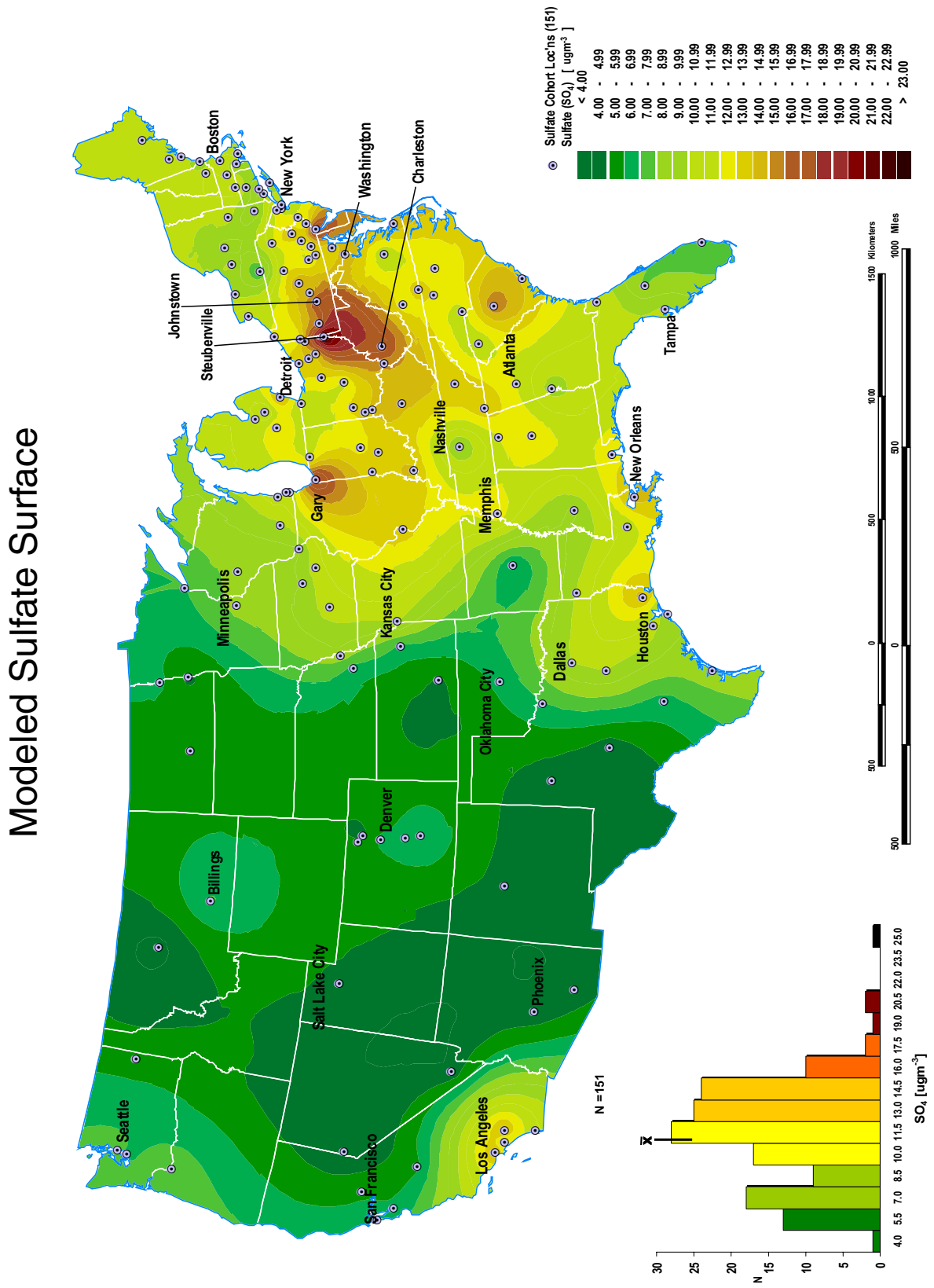
In the Six Cities Study, analysis of changes in BMI and smoking, determined from supplementary questionnaires administered during the follow-up period did not appreciably alter the relative risk of all-cause mortality for fine particles. However, allowing for the general decline in fine particles and sulfate resulted in a slight reduction in the mortality rate ratio, suggesting that the relative risk may change somewhat with time.

Examination of the postenrollment residence histories in the Six Cities Study revealed low mobility, with only 18.5% of subjects leaving the original city of enrollment during the follow-up period. Although risk estimates within the subcohort of nonmovers were comparable to those in the full cohort, the smaller subcohort of movers did not demonstrate an excess risk overall. However, risk declined with increasing educational attainment in both the mover and the nonmover subcohorts.

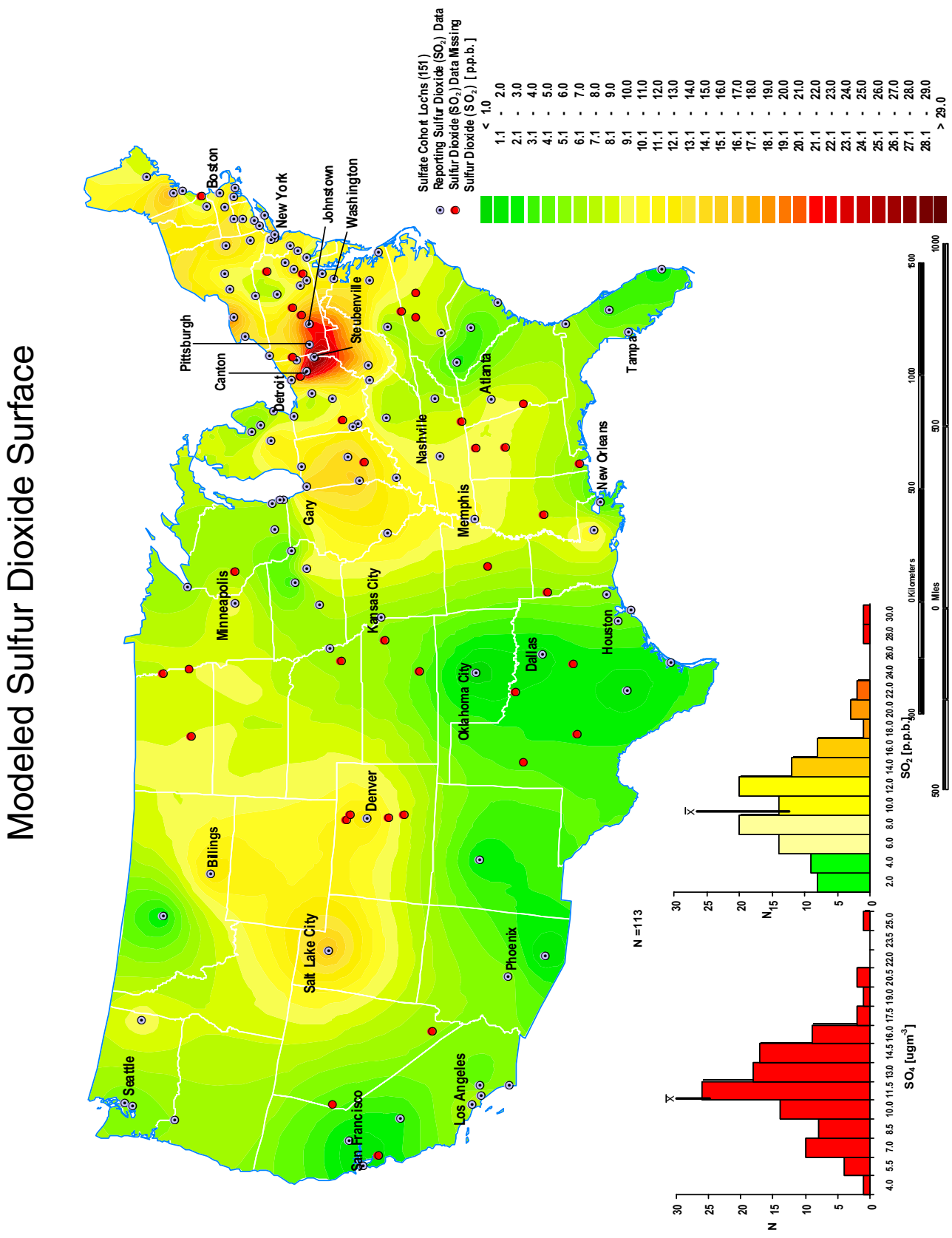
The Reanalysis Team considered a number of alternative indicators of fine particle and sulfate air pollution in the ACS Study. Our measures of fine particles and sulfate were highly correlated with those used by the Original Investigators, and led to comparable mortality risk ratios for all-cause, cardiopulmonary, and lung cancer mortality. However, adjustment for a known artifact in the sulfate measurements reduced the indicators of sulfate exposure by about 50%, resulting in an increase in the mortality risk ratios using the adjusted sulfate levels. Because of our inability to audit the original air pollution data used by the Original Investigators in the ACS Study in Part I, this analysis increased our confidence in the validity of the original air pollution data and in risk estimates based on those data.

In summary, the Reanalysis Team reached a number of important conclusions.

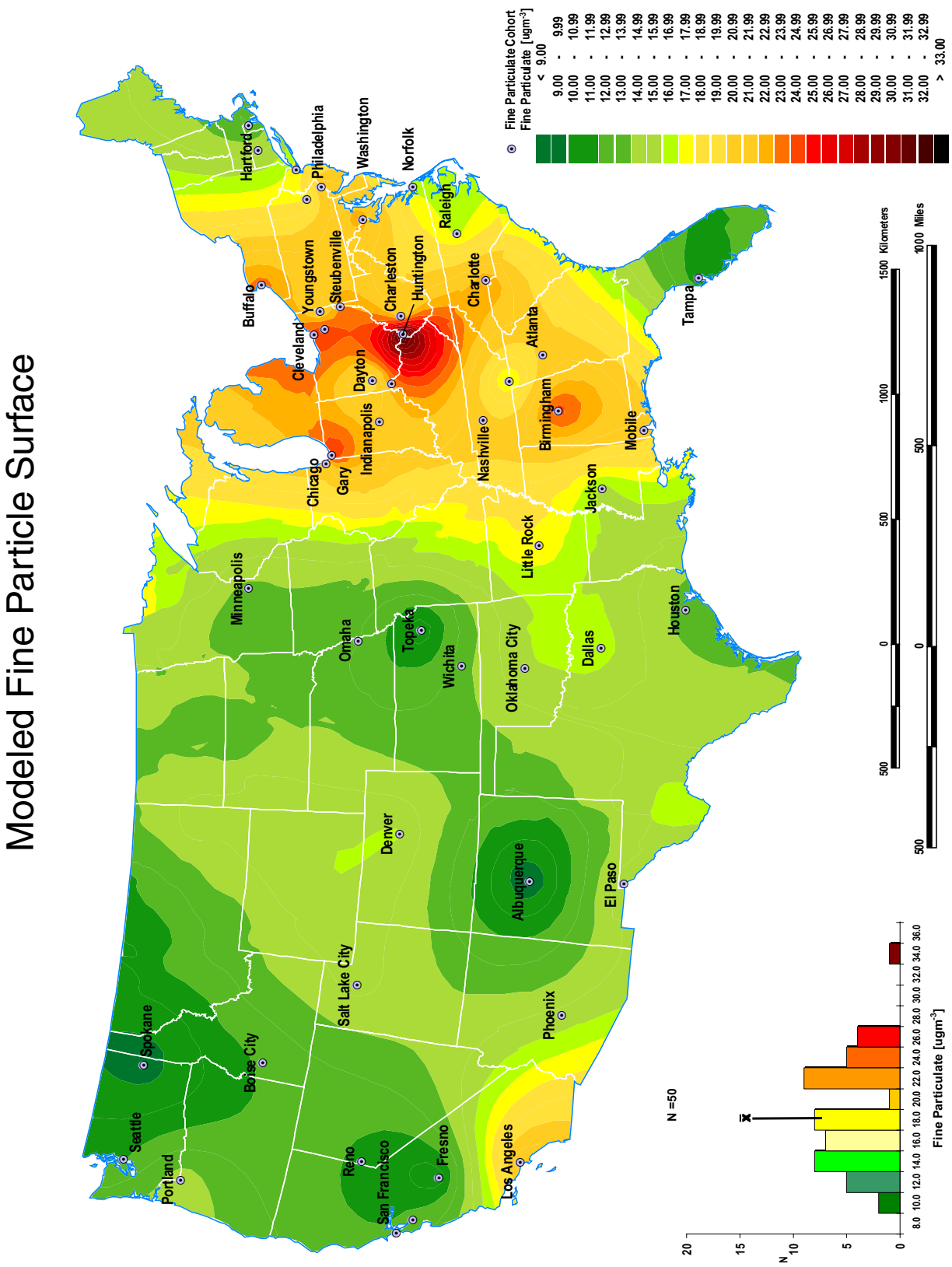
- With two exceptions, our audit demonstrated that the data used in both the original analyses and reanalyses were of high quality. Although we were unable to audit the air pollution data in the ACS Study, as noted above, our reconstruction of the air pollution data from the AIRS and IPMN databases confirmed the validity of the air pollution data used by the Original Investigators. Our audit did demonstrate appreciable error rates in the coding of jobs and occupations, particularly in the ACS Study, although the extent to which such errors compromise the utility of our aggregate indices of occupational exposure is not clear.
- Using the same data and methods of analysis, we were able to reproduce the risk estimates reported by the Original Investigators. Although the audit of both studies did identify that some subjects had been omitted from follow up, correction of these errors did not materially affect the original risk estimates.
- Our sensitivity analyses showed the mortality risk estimates for fine particle and sulfate air pollution reported by the Original Investigators in both the Six Cities Study and the ACS Study to be highly robust against alternative risk models of the Cox proportional-hazards family, including models with additional covariates from the original questionnaires not included in the original published analyses.
- Our detailed investigation of covariate effects revealed a significant modifying effect of education in both studies, with relative risk of mortality associated with fine particles declining with increasing educational attainment. Although the interpretation of this finding is unclear, it is possible that educational attainment is a marker for socioeconomic status, which is known to be correlated with health status.



Summary Figure 1. Spatial distribution of sulfate.



Summary Figure 2. Spatial distribution of sulfur dioxide.



Summary Figure 3. Spatial distribution of fine particles.

Summary Table 6. Impact of Selected Ecologic Covariates on the Relative Risks of Mortality Associated with an Increase in Sulfate or Fine Particles Using Spatial Analytic Methods (Two-Stage Regressions) and the ACS Study Data[a]

	Sulfate				Fine Particles		
		Random Effects				Random Effects	
Ecologic Covariate[b]	Independent Observations	Independent Cities	Regional Adjustment	Spatial[c] Filtering	Independent Observations	Independent Cities	Regional Adjustment
All-Cause Mortality							
Pollutant alone	1.17 (1.07–1.27)	1.25 (1.13–1.37)	1.19 (1.06–1.34)	1.09 (1.01–1.19)	1.18 (1.03–1.35)	1.29 (1.12–1.48)	1.16 (0.99–1.37)
SO_2	1.05 (0.98–1.12)	1.13 (1.02–1.25)	1.10 (0.97–1.24)	1.05 (0.97–1.14)	1.03 (0.95–1.13)	1.14 (0.98–1.32)	1.11 (0.93–1.33)
Gaseous copollutants	1.06 (0.98–1.14)	1.05 (0.93–1.18)	1.06 (0.90–1.26)	1.05 (0.96–1.14)	1.06 (0.95–1.18)	1.11 (0.95–1.29)	1.09 (0.92–1.29)
Socioeconomic status	1.10 (1.02–1.18)	1.17 (1.05–1.31)	1.21 (1.06–1.38)	1.11 (1.01–1.21)	1.15 (1.03–1.27)	1.23 (1.02–1.48)	1.15 (0.96–1.39)
25%[d]	1.18 (1.07–1.30)	1.10 (0.99–1.22)	1.10 (0.97–1.24)	1.09 (0.94–1.26)	1.12 (0.96–1.31)	1.06 (0.89–1.26)	1.05 (0.85–1.30)
Cardiopulmonary Disease Mortality							
Pollutant alone	1.25 (1.12–1.39)	1.29 (1.15–1.46)	1.19 (1.06–1.34)	1.13 (1.01–1.27)	1.30 (1.11–1.53)	1.38 (1.17–1.62)	1.24 (1.01–1.52)
SO_2	1.13 (1.03–1.24)	1.18 (1.04–1.34)	1.12 (0.96–1.32)	1.10 (0.99–1.22)	1.17 (1.03–1.33)	1.25 (1.05–1.49)	1.23 (0.97–1.55)
Gaseous copollutants	1.11 (0.99–1.24)	1.11 (0.97–1.27)	1.15 (0.93–1.42)	1.10 (0.99–1.23)	1.22 (1.05–1.42)	1.28 (1.05–1.57)	1.26 (0.96–1.66)
Socioeconomic status	1.15 (1.04–1.28)	1.18 (1.02–1.37)	1.21 (1.01–1.44)	1.12 (0.99–1.27)	1.16 (1.00–1.35)	1.19 (0.98–1.45)	1.13 (0.91–1.40)
25%[e]	1.02 (0.84–1.25)	1.07 (0.93–1.24)	1.12 (0.96–1.32)	1.20 (1.01–1.43)	1.18 (1.00–1.40)	1.10 (0.91–1.34)	1.23 (0.97–1.55)
Lung Cancer Mortality							
Pollutant alone	1.31 (1.05–1.65)	1.39 (1.09–1.75)					
SO_2	1.37 (1.08–1.73)	1.39 (1.08–1.81)					
Gaseous copollutants	1.61 (1.21–2.15)	1.63 (1.19–2.23)					
Socioeconomic status	1.14 (0.89–1.45)	1.23 (0.90–1.68)					
25%[f]	1.39 (0.98–1.99)	1.39 (0.97–2.01)					

[a] Relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city; in the ACS Study, this difference for fine particles was 24.5 $\mu g/m^3$, and for sulfate was 19.9 $\mu g/m^3$.

[b] The models for rows marked 25% incorporated all the ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the relative risk associated with the pollutant of interest. The covariates included in each model are reported in the Part II tables indicated.

[c] Used Filtered Both Sides Model.

[d] Part II Tables 40 and 41 for sulfate; Tables 46 and 47 for fine particles.

[e] Part II Tables 42 and 43 for sulfate; Tables 48 and 49 for fine particles.

[f] Part II Tables 44 and 45 for sulfate.

- We also found evidence that the relative risk of mortality for fine particles may have changed somewhat with time in both the Six Cities Study and the ACS Study. Resolution of the extent to which risk may be changing with time will require additional analyses, ideally involving further follow up of both cohorts.
- With some exceptions, the inclusion of additional ecologic covariates reflecting established determinants of health (including socioeconomic variables, demographic factors, environmental variables, and indicators of access to health services) in the ACS Study did not have a marked impact on the association between fine particles or sulfate and mortality. (The impact of ecologic covariates such as population change was reduced after allowing for spatial autocorrelation in the data, as discussed below.)
- The risk estimates in the ACS Study were somewhat sensitive to the cities included in the analysis, as demonstrated by our analysis of ecologic covariates restricted to those cities for which data on those covariates were available.
- Because of clear evidence of spatial patterns in the data leading to significant spatial autocorrelation, the Reanalysis Team developed and applied to the ACS Study data new spatial analytic methods as part of the reanalysis. Overall, the results from these analyses, which allow for varying levels of spatial autocorrelation in the data, support the associations between fine particles or sulfate and mortality reported by the Original Investigators. However, the spatially adjusted risk estimates are subject to somewhat greater uncertainty than the original risk estimates as a consequence of the presence of significant spatial autocorrelation in the ACS Study data.

- Our spatial analyses also demonstrated a significant association between sulfur dioxide and mortality. Further, this association appeared to be robust against adjustment for other ecologic covariates, including fine particles and sulfate, the covariates of primary interest in this report. However, this analysis revealed no association between mortality and the other gaseous copollutants (NO_2, O_3, and CO) that we examined.
- In contrast, the inclusion of sulfur dioxide in our spatial regression analyses resulted in a reduction in the mortality risk associated with both fine particles and sulfate. Nonetheless, both fine particles and sulfate continued to demonstrate a positive association with mortality even after adjustment for the effects of sulfur dioxide in our spatial regression analyses.

Collectively, our reanalyses suggest that mortality may be attributed to more than one component of the complex mixture of ambient air pollutants in urban areas in the US. For most of the individual pollutants measured in the Six Cities Study, associations with mortality were comparable in magnitude owing to the strong correlations among pollutants in these six cities. In the ACS Study, where the data afforded a greater opportunity to examine the joint effects of components of the pollutant mixture because of the greater variation in exposure profiles among the 154 cities involved, our analyses showed an association with mortality for sulfur dioxide in addition to that for fine particles and sulfate. It is important to bear in mind that the results of our reanalysis alone are insufficient to identify causal associations with mortality; rather, we can only conclude that urban air pollution is associated with increased mortality in these two important epidemiologic investigations.

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Introduction to Parts I and II

Daniel Krewski, Richard T Burnett, Mark S Goldberg , Kristin Hoover, Jack Siemiatycki, Michael Jerrett, Michal Abrahamowicz, Warren H White, and Others

BACKGROUND

The reanalysis of the Harvard Six Cities Study (Dockery et al 1993) and the American Cancer Society (ACS)* Study (Pope et al 1995)† is one contribution in a long history of research into the effects of air pollution on human health. Research in this field arguably began with an air pollution episode in London in the winter of 1952, which demonstrated conclusively that very high levels of ambient particulate air pollution can cause immediate and dramatic increases in mortality (Logan 1953). This episode was caused by cold stagnant weather conditions that trapped combustion products (particles and gases) at ground level. The resulting smog was strongly associated with increased mortality from respiratory and cardiovascular complications, especially in elderly members of the population. Other major air pollution episodes in the Meuse Valley in Belgium (Firket 1936) and in Donora PA in the US (Ciocco and Thompson 1961) were associated with health effects similar to those that occurred in London.

In the 1950s, levels of air pollution in most North American and European cities were 10 to 50 times higher than those found today. New emissions control technologies, such as catalytic converters on automobiles, have contributed to reducing levels of particles and other pollutants over the years despite increases in emissions from industrial, commercial, and personal activities. For example, in the US during the period 1988 through 1995, mean annual emissions and mean ambient concentrations of particles with a mass median aerodynamic diameter under 10 μm (PM_{10}) decreased by 22% and 17%, respectively (US Environmental Protection Agency [EPA] 1995). During this period, annual mean emissions and ambient concentrations of sulfur dioxide (SO_2) also decreased by 18% and 37%, respectively.

Associations between short-term elevations of particulate matter in ambient air and a host of adverse health outcomes have been reported at concentrations much lower than those previously thought to have an effect. In 1970, Lave and Seskin reported a relation between city-specific mortality rates and air pollution levels, including particulate matter. Bates and colleagues in 1985 reported an association between increased hospital admissions for respiratory diseases and elevated levels of sulfate. Increased short-term levels of particulate matter smaller than 2.5 μm in mass median aerodynamic diameter ($PM_{2.5}$) also have been associated with lung function decrements in asthmatic and healthy children (Dockery et al 1992; Dockery 1993; Koenig et al 1993, 1998; Schwartz 1994). Subsequent time-series studies of hospital admissions and air pollutants conducted in a number of countries have confirmed these early findings of an association between increased morbidity and mortality and ambient concentrations of particulate matter and gaseous pollutants such as ozone (O_3) (Burnett et al 1997). In particular, recent studies have shown that concentrations of ambient air particles are associated with (1) increased hospitalization for respiratory disease (Burnett and Krewski 1994; Burnett et al 1995); (2) a greater number of emergency department visits for respiratory illness (Delfino et al 1997); (3) exacerbated episodes of asthma (Roemer et al 1993); (4) increased incidence and duration of respiratory symptoms (Hoek and Brunekreef 1993); (5) decrements in lung function (Hoek and Brunekreef 1994); (6) restricted activities for adult workers; (7) increased absences of children from elementary school (Ransom and Pope 1992); and (8) increased daily mortality (Schwartz 1991, 1994). Studies of these acute effects have been used, in part, to inform new regulations and 24-hour air quality standards for fine particles.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

† The original articles appear in their entirety at the end of this Special Report.

This is one section of an HEI Special Report that includes an HEI Statement about the research project, a Preface to the Particle Epidemiology Reanalysis Project, the Investigators' Report (Summary, Introduction, Part I, and Part II), a Commentary by the Institute's Health Review Committee, and the Original Articles and Comments on the Reanalysis from the Original Investigators. Correspondence concerning the Introduction to Parts I and II may be addressed to Dr Daniel Krewski, Professor of Epidemiology & Statistics, Department of Epidemiology & Community Medicine, Room 3229C, 451 Smyth Road, University of Ottawa, Ottawa Ontario K1H 8M5, Canada.

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In addition, three large prospective cohort studies have followed thousands of subjects (Dockery et al 1993; Pope et al 1995; Abbey et al 1999). Abbey and associates (1999) reported on the relation between long-term ambient concentrations of particulate air pollution and mortality in a cohort of over 6,000 nonsmoking, non-Hispanic white Seventh-Day Adventists who lived in one of the three California air basins. From 1973 through 1992, the researchers estimated monthly ambient concentrations of PM_{10}, ozone, sulfur dioxide, and nitrogen dioxide (NO_2) using 348 fixed-site monitoring stations, and gathered mortality data from 1977 through 1992. Statistically significant associations were observed between PM_{10} and mortality from nonmalignant respiratory disease in both sexes and between PM_{10} and lung cancer mortality in males. Ozone and sulfur dioxide also were associated with lung cancer mortality in males, but because of close correlation among PM_{10}, ozone, and sulfur dioxide, the authors were unable to clearly distinguish among the effects of these three pollutants. None of the pollutants demonstrated an association with cardiopulmonary mortality in either males or females.

The other two of these three cohort studies, the Harvard Six Cities Study (Dockery et al 1993) and the ACS Study (Pope et al 1995), have been the focus of the Reanalysis Project. Both reported increases in mortality associated with long-term levels of fine particles and sulfate.

THE HARVARD SIX CITIES STUDY

The Six Cities Study is a unique, long-term, longitudinal cohort study of the health effects associated with airborne pollutants. Subjects were selected randomly from six US cities that had a wide range of levels of ambient particles and gaseous pollutants. The original investigation (which began in 1974) focused on changes in pulmonary symptoms and lung function. Because vital status had been obtained for study subjects, it was feasible later to conduct a follow-up study to determine whether mortality rates in the six cities varied as levels of air pollution changed (this follow-up study, as reported in Dockery et al 1993, is the subject of the Reanalysis Project).

For the original investigation, subjects were enrolled from Watertown MA (in 1974), Harriman TN (1975), St Louis MO (1975), Steubenville OH (1976), Portage WI (1976), and Topeka KS (1977). A series of questionnaires administered at the time of enrollment and at subsequent intervals (3, 6, and 12 years after enrollment) elicited information on age, sex, weight, and height; educational level; smoking history; occupational exposure to dusts, gases, and fumes; and medical history.

The analysis of mortality and air pollution had been restricted to a subcohort of 8,111 Caucasian subjects (see Introduction Table 1 for a summary of population characteristics) who had been between 25 and 74 years of age at the time of enrollment. Vital status was assessed through active follow-up and from a record linkage to the National Death Index (1979–1989); 1,430 deaths were uncovered, for which 1,401 death certificates were obtained. Calculated from the size of the subcohort and the years of death or the end of the observation period, the person-years of observation used in the analyses totaled 111,076. Causes of death were coded by a certified nosologist according to the *International Classification of Diseases, Ninth Revision* (ICD-9; codes 400–440 and 485–496 for cardiopulmonary disease and code 162 for lung cancer) (World Health Organization 1975).

As part of the longitudinal study, the investigators measured levels of ambient air pollutants. Centrally located monitors in each city collected data for concentrations of total suspended particles (TSP), sulfur dioxide, ozone, and suspended sulfate (SO_4^{2-}). In the late 1970s, they began to collect data on inhalable and fine particles. In the mid-1980s, acid aerosols (H^+) were measured. Data from different time periods were used to calculate mean levels of air pollutants: 1977 through 1985 for TSP, sulfur dioxide, nitrogen dioxide, and ozone; 1979 through 1985 for inhalable and fine particles; 1979 through 1984 for sulfate particles; and 1985 through 1988 for acid aerosols.

The principal statistical analyses of all-cause mortality and cause-specific mortality were derived from Cox proportional-hazards regression models, stratified by sex and 5-year age groups, and adjusted for cigarette smoking, level of education, body mass index, and occupational exposure to dusts, gases, and fumes.

The principal results of these analyses were that all-cause mortality increased in association with concentrations of inhalable particles, fine particles, and sulfate. The excess mortality risk was about 26% when the Original Investigators compared the city with the highest levels of particles (Steubenville) to the city with the lowest levels (Portage). The concentration ranges between these two cities were 18.2–46.5 $\mu g/m^3$ for inhalable particles, 11.0–29.6 $\mu g/m^3$ for fine particles, and 4.8–12.8 $\mu g/m^3$ for sulfate. Mortality rate ratios were relatively invariant with respect to smokers and nonsmokers and to persons with and without occupational exposures to dusts, gases, or fumes. Mortality from cardiopulmonary disease also was associated with fine particles in the Six Cities Study, although mortality from lung cancer was not. Death certificates were obtained for approximately 98% of deaths.

Introduction Table 1. Comparison of Population and Pollutant Characteristics in the Six Cities Study and the ACS Study

		American Cancer Society Study[b]	
	Harvard Six Cities Study[a]	Sulfate Cohort	Fine Particle Cohort
Number of cities	6[c]	151[d]	50[d]
Number of subjects (all adults)	8,111	552,138	295,223
Number of deaths	1,430	38,963	20,765
Mean age at enrollment	49.7	58.5	58.6
Percentage of women	54.8	58	35.9
Race			
Percentage white	100%	94.2	94.0
Percentage black		4.1	4.1
Percentage other		1.7	1.9
Source of population	Harvard Six Cities Study of the health effects of air pollution; random population sample prospectively followed starting in 1974, ending in 1989	ACS Cancer Prevention Study II (total study population of ~1.2 million); population enrolled by ACS volunteers and prospectively followed starting in 1982, ending in 1989	
Total years of follow-up	14 to 16	About 7	
Total person-years of follow-up	111,076	2,112,239[e]	3,950,963[e]
Source of air quality data	Study-based air quality monitors in each of the six cities	EPA National Aerometric Database and EPA Aerometric Information Retrieval System	
Fine particles[f]	18.6 (11.0–29.6)		24.5 (9.0–33.5)
Sulfate[f]	8.0 (4.8–12.8)	19.9 (3.6–23.5)	

[a] All values are taken from the text or calculated from Table 1 in Dockery et al 1993.

[b] Unless otherwise noted, all values are taken from the text and Tables 1 and 2 of Pope et al 1995.

[c] Harriman TN, Portage WI, Steubenville OH, St Louis MO, Topeka KS, and Watertown MA.

[d] All but 3 of these cities were the same, which resulted in a total of 154 cities.

[e] Calculated by the Reanalysis Team.

[f] Difference between the mean concentrations for the most-polluted city and the least-polluted city with range in parentheses; given in $\mu g/m^3$.

As a result of these findings in a limited population base, the Original Investigators considered a similar analysis using a larger study population. In collaboration with the ACS, they used the database from the ACS's Cancer Prevention Study II (CPS-II) to analyze mortality and particulate air pollution across the US (Pope et al 1995).

THE AMERICAN CANCER SOCIETY STUDY

The original prospective cohort CPS-II was initiated in 1982 and included approximately 1.2 million men and women recruited from all 50 US states, the District of Columbia, and Puerto Rico. Subjects were individuals 30 years of age or older who were living in a household with at least one person who was 45 years or older. The participants in CPS-II were enrolled by approximately 77,000 volunteers; consequently, the study population consisted mainly of relatives, friends, neighbors, or acquaintances of the volunteers. Each participant completed a self-administered questionnaire that requested information on age, sex, weight, height, demographic characteristics, family history of cancer, disease history, use of medication and vitamins, occupational exposures, dietary habits, use of alcohol and tobacco, and various aspects of exercise and health-related behavior. Vital status of participants was assessed by the volunteers, who made inquiries directly to participants or

their families in 1984, 1986, and 1988. In addition, a record linkage to the US National Death Index (1982–1989) was maintained to obtain vital status for subjects lost to follow-up. Death certificates were obtained subsequently from state health departments and coded by a nosologist according to a simplified system based on the ICD-9 (World Health Organization 1975).

The analysis of the relation between mortality and ambient air pollution was restricted to a subset of adults who lived in areas of the US for which data on sulfate or fine particle air pollution were available. In addition, only those subjects who had completed questionnaires and those decedents for whom death certificates had been obtained were included in the analyses. Thus, the investigators included 552,138 adult subjects who resided in 151 US metropolitan areas for which sulfate data had been regularly collected in 1980 and 1981 and 295,223 adult subjects who lived in the 50 metropolitan areas for which fine particle data were available (collected from 1979 through 1983). A total of 38,963 and 20,765 deaths were recorded for these two cohorts, respectively. Loss to follow-up between 1982 and 1988 was approximately 2% of participants. Death certificates were obtained for approximately 96% of deaths. (This study of the association between mortality and air pollution indices in a subset of the CPS-II population, as reported in Pope et al 1995, is hereafter referred to as the ACS Study and is the subject of the Reanalysis Project.)

For 50 metropolitan areas, fine particles had been measured by the EPA's Inhalable Particle Monitoring Network (IPMN), which operated between 1979 and 1983 (Lipfert et al 1988). The average median fine particle concentration across the 50 metropolitan areas was 18.2 $\mu g/m^3$ (range: 9.0–33.5 $\mu g/m^3$). Sulfate concentrations in the 151 metropolitan areas were assembled from multiple sources. The bulk of the data had been derived from Özkaynak and Thurston (1987). That database had been further augmented with data from the IPMN and with data from EPA's high-volume samplers in metropolitan areas that did not meet the National Ambient Air Quality Standard. The arithmetic average of 24-hour sulfate concentrations for the year 1980 was 11 $\mu g/m^3$ (range: 3.6–23.5 $\mu g/m^3$).

Subjects were assigned to metropolitan areas according to their three-digit ZIP code at the time they completed the initial questionnaire. The mean concentration of sulfate (for 1980) and the median concentration of fine particles (for 1979–1983) in each metropolitan area just before the cohort was enrolled were used as the indices of air pollution. Using Cox proportional-hazards models, stratified by sex, race, and 5-year age groups, risk ratios of all-cause and cause-specific mortality (lung cancer [ICD-9 code 162] and cardiopulmonary disease [ICD-9 codes 401–440 and 460–519]) were estimated in relation to each air pollutant in each metropolitan area after adjusting for selected individual risk factors (smoking, education, body mass index, alcohol consumption, and self-reported occupational exposure to a number of substances) and differences among metropolitan areas in climate (relatively hot or cold conditions).

The principal results of these analyses showed that, for both men and women, higher mean levels of sulfate were significantly associated with increased mortality from all causes, lung cancer, and cardiopulmonary disease. The association for women with lung cancer, although elevated and similar in magnitude to the association found for men, had a 95% confidence interval that included unity, which means it was not statistically significant. Median fine particle concentrations were associated with increased mortality from all causes and cardiopulmonary disease in both men and women; an association between fine particles and lung cancer was not apparent. In addition, the effects found for never-smokers, former-smokers, and current-smokers were similar.

THE REANALYSIS PROJECT

The findings of the Six Cities Study and the ACS Study have been the subject of debate regarding the following factors: possible residual confounding by individual risk factors (eg, sedentary lifestyle, active or passive cigarette smoke exposure) or ecologic risk factors (eg, aspects of climate or social milieu); inadequate characterization of the long-term exposure of study subjects; different kinds of bias in allocating exposure to separate cities; and robustness of the results to changes in the specification of statistical models.

Because the EPA and other regulatory agencies have relied, in part, on these two studies in setting standards for particulate matter in ambient air, issues regarding the analysis of the data and the interpretation of these two studies needed to be resolved. Representatives of industry, members of the US Congress, and other scientists urged the EPA who, in turn, urged Harvard University and the American Cancer Society to make the original data from these studies available to other analysts. In response, Harvard University requested that the Health Effects Institute organize an independent reanalysis of these studies and, shortly thereafter, the American Cancer Society followed suit. The process by which HEI responded to these requests and established the Reanalysis Project is described in detail in the Preface to this HEI Special Report.

The Reanalysis Project was carried out in two phases to accomplish these objectives:

- to replicate and validate the original published analyses by conducting a quality assurance audit of the original data and reproducing the original numerical results; and
- to conduct comprehensive sensitivity analyses to test the robustness of the original findings and interpretations to alternative analytic approaches.

As part of the replication and validation effort, we conducted quality assurance audits to confirm the integrity of the data used by the Original Investigators. In Phase I, we validated the variables used in the original analyses; and in Phase II, we verified data that had been collected and coded by the Original Investigators but not used in their original published analyses.

For Phase I, we designed the data audits to retrospectively determine whether each study had been consistently conducted and whether the data files were complete and accurate in accordance with information contained from questionnaires and death certificates. Audits for both studies carefully examined a random sample of 250 questionnaires and a separate random sample of 250 death certificates and focused on detecting errors. The sample size of 250 would be sufficiently large to allow us to (1) almost certainly identify some errors if the underlying error rate were 5%, (2) distinguish between error rates of 1% or less and 5% or more with high confidence, and (3) estimate error rates to within about two percentage points of their true values.

The audit also permitted the Reanalysis Team to assess study documentation, computer programs, coding conventions, record keeping procedures, and internal error detection; to recode the causes of death recorded on death certificates to determine that the correct codes and categories had been reported; and to review previous internal and external audits.

The original air quality data files were not readily available for the Six Cities Study, so that audit used electronic data files reconstructed by the Original Investigators. The air quality data for the ACS Study had been updated after the termination of the published study because the data continue to be used; therefore, the ACS reconstructed data files to reflect their status at the time of the original analyses. Nevertheless, we could not audit the actual air quality data used for the ACS Study because documentation for these data is no longer accessible.

For Phase II, we conducted a series of comprehensive sensitivity analyses of the original findings using alternative statistical models and, in some cases, new data from the original questionnaires. In particular, we examined the impact of alternative models on estimates of risk. These models used additional covariates that had not been included in the original analyses. In addition to assessing the robustness of the original risk estimates to alternative model specifications, we used these models to identify covariates that may confound or modify the association between particulate air pollution and mortality and to identify sensitive population subgroups.

Furthermore, we investigated the possibility that the original results had been confounded by occupational exposures. Specifically, the Reanalysis Team developed two new aggregate indices of occupational exposures and applied them to the data from both studies. The first index was a seven-category ordinal measure of the overall "dirtiness" of specific jobs and occupations for each study subject; the second was a binary indicator of having ever/never been exposed in the workplace to agents known to be associated with increased lung cancer risk.

The complementary strengths of the two original studies allowed the Reanalysis Team to perform additional sensitivity analyses. In the Six Cities Study, follow-up data on study subjects at 3, 6, and 12 years after enrollment permitted us to assess changes in key covariates (such as tobacco consumption) over time. Furthermore, detailed residence histories for these subjects allowed us to assess the impact of population mobility on estimates of risk. The ACS Study, which involved 154 metropolitan areas across the US, allowed us to assess the association between mortality in these cities and a number of auxiliary sociodemographic and environmental variables (referred to as ecologic covariates) derived from publicly available data sources. Of particular interest in this set of analyses was the possibility that these ecologic covariates could modify or confound the association between particulate air pollution and mortality.

Many ecologic covariates the Reanalysis Team considered in reanalyzing the ACS Study data, including mortality and particulate air pollution, demonstrated clear spatial patterns across the US; therefore, we used spatial methods of analysis to investigate the association between these ecologic covariates and mortality. The spatial analytic methods took into account the possibility that, for some covariates, data may correlate automatically because of their spatial relationship; this autocorrelation could affect the statistical significance level of tests for associations between the covariates of interest and mortality.

The rationale, methods, and results for all of the audit tasks and sensitivity analyses described briefly here are presented in detail in Parts I and II of the following Investigators' Reports.

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BACKGROUND

Epidemiologic work conducted over several decades has suggested that long-term residence in cities with elevated ambient levels of air pollution from combustion sources is associated with increased mortality. Subsequently, two prospective cohort studies, the Six Cities Study (as reported in Dockery et al 1993) and the American Cancer Society (ACS)* Study (as reported in Pope et al 1995)† estimated that annual average all-cause mortality increased in association with an increase in fine particles (all particles less than 2.5 μm in median aerodynamic diameter [$PM_{2.5}$]).

As part of the Six Cities Study, Dockery and colleagues (1993) had prospectively followed a cohort of 8,111 adult subjects in northeast and midwest United States for 14 to 16 years beginning in the mid-1970s. The authors found that higher ambient levels of fine particles and sulfate (SO_4^{2-}) were associated with a 26% increase in mortality from all causes when comparing the most-polluted to the least-polluted city, and that an increase in fine particles was also associated with increased mortality from cardiopulmonary disease. The relative risks in all-cause mortality were associated with a difference (or range) in ambient fine particle concentrations of 18.6 μg/m^3 and a difference of ambient sulfate concentrations of 8.0 μg/m^3, comparing the least-polluted city to the most-polluted city.

In the much larger ACS Study, Pope and colleagues (1995) followed 552,138 adult subjects in 154 US cities beginning in 1982 and ending in 1989 (3 cities did not overlap between the 151 and 50 cities studied, resulting in a total of 154 cities). Again, higher ambient levels of fine particles were associated with increased mortality from all causes and from cardiopulmonary disease in the 50 cities for which fine particle data were available (sampled from 1979 to 1983). Higher ambient sulfate levels were associated with increased mortality from all causes, cardiopulmonary disease, and lung cancer in the 151 cities for which sulfate data were available (sampled from 1980 to 1982). The difference between all-cause mortality in the most-polluted city and the least-polluted city was 17% and 15% for fine particles and sulfate, respectively (the pollutant range among the cities was 24.5 μg/m^3 for fine particles and 19.9 μg/m^3 for sulfate).

Although these two studies produced similar results, they differed in design and limitations. Important strengths of the Six Cities Study included random selection of study subjects, response rates exceeding 70%, personal interviews with respondents at the time of enrollment, subsequent follow-up at intervals of 3, 6, and 12 years, lung function measurements at baseline, and residential histories. The air pollution data were measured by the Original Investigators, who designed the Six Cities Study to cover a range of air pollution levels across cities nearly as large as that found in the ACS study. A limitation was that air pollution exposure was represented by one average figure for each city, so that only 6 air pollutant data points were used.

Important strengths of the ACS Study were the 154 cities, the very large cohort of subjects, and the extensive information on health status, demographic characteristics, smoking history, alcohol use, and occupational exposures. A limitation was that these subjects were enrolled by volunteers from among their friends and relatives so it is likely that the subjects probably were not representative

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

† The original articles (Dockery et al 1993 and Pope et al 1995) appear in their entirety at the end of this Special Report.

The 2-year *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality* conducted by the Reanalysis Team led by Dr Daniel Krewski began in July 1998 with total expenditures of $899,046. The Part I Investigators' Report from Dr Krewski and colleagues was received for review in August 1999 and the Part II Investigators' Report in December 1999. The revised Part I report was received in January 2000 and accepted for publication in February 2000; the revised Part II was received in March 2000 and accepted in April 2000. During the review process, the Special Panel of the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in the Investigators' Report and in the Review Committee's Commentary.

of the general population within each city. Finally, the air quality measures were not designed for this study: they were obtained from monitors set up previously by the US Environmental Protection Agency (EPA).

Both of these studies came under intense scrutiny in 1997 when the EPA used the results to support new National Ambient Air Quality Standards for fine particles and to maintain the standards for particles less than 10 µm in median aerodynamic diameter (PM_{10}) already in effect. Members of Congress and industry, the scientific community and others interested in regulation of air quality scrutinized the studies' methods and their results. Some insisted that any data generated using federal funding should be made public. Others argued that these data had been gathered with assurances of confidentiality for the individuals who had agreed to participate and that the concept of public access to federally funded data did not take into account the intellectual property rights of the investigators and their supporting institutions. To address the public controversy, Harvard University and the ACS requested that the Health Effects Institute organize an independent reanalysis of the data from these studies. Both institutions agreed to provide access to their data to a team of analysts to be selected by HEI through a competitive process.

The overall objective of the Particle Epidemiology Reanalysis Project was to conduct a rigorous and independent assessment of the findings of the Six Cities and ACS Studies of air pollution and mortality. This objective was met in two parts. In *Part I: Replication and Validation*, the Reanalysis Team sought to replicate the original studies via a quality

BACKGROUND CONCEPTS

ASSOCIATION VERSUS CAUSATION

Epidemiologists rely on several guidelines to assess whether an association between a risk factor and an adverse outcome can credibly be interpreted as one of cause and effect. For example, strong associations are difficult to ascribe to confounding by covariates with weak associations. An association that is consistently found in different settings and via different analytic methods is less likely to be the result of chance or data collection bias. A causal relation is also more likely when the data show evidence of a dose-response effect (ie, variation in risk factor matches variation in the outcome). In this association, eliminating the apparent cause should eliminate (or reduce) the effect. Finally, some biological explanation should be plausible, and other plausible explanations should be ruled out. No one of these guidelines is necessary or sufficient to establish cause, but as evidence mounts for each the credibility of the suggested cause and effect is strengthened.

On the other hand, noncausal explanations for such an association also need to be investigated. The association may be one of chance or random variation among the risk factors and outcomes. Systematic measurement errors may bias the evidence toward or away from an association. Extraneous factors found to be associated with both the risk factor and the outcome may confound the association being investigated. Finally, the methods of specifying analytic models, or the basis on which variables are included or excluded, may yield different associations. All of these possibilities are particularly important in observational studies, like the Six Cities and ACS Studies, in which the investigators have no control over who is and who is not exposed to the risk factor.

RELATIVE RISKS, POINT ESTIMATES, CONFIDENCE INTERVALS, AND STATISTICAL SIGNIFICANCE

The association between air pollutants and mortality was described by the Reanalysis Team in terms of *relative risk*, which is the increase in risk of an adverse outcome (death) given the presence of some risk factor (air pollutant), across some range of pollutant concentrations, for residents in the most-polluted city relative to residents in the least-polluted city. Although investigators from the ACS study refer to the mortality risk ratio, and investigators from the Six Cities study refer to the mortality rate ratio, both terms indicate that the relative risk was calculated using the ratio of mortality rates, which compares the age-adjusted rates of death across the observed range of pollution levels (most-polluted to least-polluted).

A relative risk is a *point estimate*, a single numerical value used to estimate a measure of effect from a sample of observations. When evaluating a point estimate, investigators take into account the precision, or *confidence interval*. The confidence interval is that range of values, indicated by a lower bound and an upper bound, that

assurance (QA) audit of a sample of the original data and to validate the original numeric results. In *Part II: Sensitivity Analyses*, they tested the robustness of the original analyses to alternate risk models and analytic approaches.

The Particle Epidemiology Reanalysis Project was designed to investigate and test the strengths and limitations of these substantial epidemiologic studies. By its nature, epidemiology is the study of the distribution and determinants of health-related conditions in human populations and the application of study findings to control health problems. Several issues inherent to epidemiology provide a challenge to interpreting associations between mortality and air pollutants in the work reported here. First, no single study can definitively answer questions regarding cause. Second, to evaluate the importance of reported associations, both a single value estimating risk, or point estimate, and confidence intervals about the point estimate need to be considered. Third, identifying which pollutant may be associated with a specific outcome is extremely difficult because humans are exposed to a complex mixture of airborne particles, gases, and other unmeasured components. Fourth, assessing associations among pollutants and outcomes by applying a variety of analytic models can result in some significant associations being observed by chance alone. As the number of analyses increases, the chance of erroneously identifying random associations as being significant also increases. These issues need to be considered when evaluating the final conclusions of any epidemiologic study (see sidebar for further elaboration of these issues).

with high probability (typically 95%) contains the true parameter (represented by the observed point estimate). The confidence interval is based on the variance and sample size (n) of the data: the larger the variance, the wider the interval and the less the precision. Confidence intervals around a point estimate that include 1.0 (where one boundary is above 1.0 and one boundary is below 1.0) are not *statistically significant* (ie, the results may have occurred by chance alone).

Formal statistical significance is based on confidence intervals that do not cross 1.0; however, what if the lower bound of an interval is 0.99? Most scientists consider the pattern of their findings when summarizing their results, rather than commenting only on statistical significance. Any single result (point estimate, confidence interval, significance) should therefore be interpreted in the context of other findings.

COLLINEARITY

A serious hindrance in interpreting epidemiologic data is the high degree of correlation among major air pollutants which have common sources. If mortality data are found to be correlated with each of five or six pollutants and the concentrations of those pollutants tend to rise and fall together, it may be difficult or impossible to tell from epidemiologic data alone whether the correlation with mortality is caused by some specific pollutant in the mixture, the mixture as a whole, or even some other, unmeasured component. Collinearity complicates the study of air pollutants because levels of several pollutants (eg, $PM_{2.5}$, SO_4^{2-}, SO_2, and NO_x) tend to be positively correlated and one (ozone) is often negatively correlated with the others. Consequently, no analysis can determine with precision how much one or another specific air pollutant contributes to some health outcome. Findings of associations can be strengthened if the same general result is found in multiple studies and if the same associations also are identified in other kinds of investigations (such as laboratory studies).

MULTIPLE TESTING

In the search for significant effects of air pollution on health, statistical analyses must be designed to guard against two kinds of errors: reporting that a relation exists when it is merely a reflection of chance variations in the data (a Type I error), and failing to find a relation when one does, in fact, exist (a Type II error). The first is controlled to the level specified for significance in the familiar P values of ordinary statistical testing. However, testing regression coefficients at the usual 5% level of significance produces, on average, one statistically significant result for each 20 tests even when no association is present. When numerous tests are performed, therefore, the chance becomes quite large of finding at least one statistically significant result where no true effect is present. For example, of the 20 ecologic covariates tested in single-pollutant models in the current study, one ecologic covariate could have demonstrated significant results by chance. This problem of multiple comparisons can be partially reduced by using more stringent critical values (for example, P less than 1% rather than 5%) and by looking for suggestive patterns in how the significant values are distributed across the data.

Table 1. Relative Risks of Mortality from Various Causes Associated with an Increase in Fine Particles: A Comparison of Results from the Original Six Cities Study, the ACS Study, and the Particle Epidemiology Reanalysis Project[a]

	Six Cities Study			ACS Study			
	All Causes	Cardiopulmonary Disease	Lung Cancer	All Causes	Cardiopulmonary Disease	Lung Cancer	Source
Original Investigators	1.26 (1.08, 1.47)	1.37 (1.11, 1.68)	1.37 (0.81, 2.31)	1.17 (1.09, 1.26)	1.31 (1.17, 1.46)	1.03 (0.80, 1.33)	c
Part I: Replication and Validation							
Reanalysis Validation[b]	**1.28 (1.10, 1.48)**	**1.38 (1.12, 1.69)**	**1.43 (0.85, 2.41)**	**1.18 (1.10, 1.27)**	**1.32 (1.19,** 1.46**)**	**1.02** (0.80, **1.30**)	Tables 21c, 27c
Part II: Alternative Risk Models[d]							
Base	1.33 (1.14, 1.54)	1.39 (1.13, 1.70)	1.53 (0.91, 2.55)	1.27 (1.18, 1.37)	1.41 (1.27, 1.56)	1.23 (0.96, 1.57)	Summary Tables 1, 2
Original	1.29 (1.11, 1.50)	1.35 (1.10, 1.66)	1.31 (0.76, 2.25)	1.18 (1.10, 1.27)	1.30 (1.18, 1.45)	1.02 (0.80, 1.29)	
Full	1.27 (1.09, 1.49)	1.31 (1.06, 1.62)	1.30 (0.76, 2.23)	1.17 (1.09, 1.26)	1.28 (1.15, 1.42)	0.99 (0.78, 1.26)	
Extended	1.28 (1.09, 1.49)	1.32 (1.07, 1.63)	1.29 (0.75, 2.22)	1.18 (1.09, 1.26)	1.30 (1.17, 1.44)	1.00 (0.79, 1.28)	
Population mobility							
Nonmovers	1.30 (1.10, 1.54)						pages 145–146
Movers[e]	1.25 (0.75, 2.10)						
Time-Dependence							
Without	1.31 (1.13, 1.52)						Table 14
With	1.16 (1.02, 1.32)						
Occupational exposure	1.28 (1.09, 1.50)	1.35 (1.08, 1.68)	1.05 (0.59,1.89)	1.15 (1.07, 1.24)	1.28 (1.14, 1.43)	0.99 (0.77, 1.28)	Tables 7, 24
Exercise				1.13[f]			page 159
FVC	1.19 (1.11, 1.52)						page 136
FEV_1	1.27 (1.09, 1.49)						
Education level[g]							
Less than high school	1.45 (1.13, 1.85)	1.28 (0.92, 1.77)	2.69 (1.09, 6.60)	1.35 (1.17, 1.56)	1.47 (1.21, 1.78)	1.41 (0.87, 2.29)	Table 52
More than high school	0.97 (0.71, 1.34)	1.40 (0.88, 2.23)	1.08 (0.33, 3.58)	1.06 (0.95, 1.17)	1.14 (0.98, 1.34)	0.66 (0.46, 0.95)	
Part II: Alternative Analytic Approaches							
Alternative Air Quality Dataset							
$PM_{2.5}$(DC)[h]				1.12 (1.06, 1.19)	1.26 (1.16, 1.38)	1.08 (0.88, 1.32)	Table 31
Ecologic Covariates							
Population change				1.07 (0.99, 1.17)	1.12 (0.99, 1.27)		Tables 37, 38
SO_2				1.03 (0.95, 1.13)	1.17 (1.03, 1.33)		
Spatial Analyses							
Independent Cities Model							
$PM_{2.5}$ alone				1.29 (1.12, 1.48)	1.38 (1.17, 1.62)		Tables 46, 48
Population change				1.19 (1.01, 1.39)	1.19 (1.00, 1.43)		
SO_2				1.14 (0.98, 1.32)	1.25 (1.05, 1.49)		
Regional Adjustment Model							
$PM_{2.5}$ alone				1.16 (0.99, 1.37)	1.24 (1.01, 1.52)		Tables 46, 48
Population change				1.18 (0.97, 1.42)	1.20 (0.95, 1.51)		
SO_2				1.11 (0.93, 1.33)	1.23 (0.97, 1.55)		

(Footnotes on page following Table 2)

Table 2. Relative Risks of Mortality from Various Causes Associated with an Increase in Sulfate: A Comparison of Results from the Original Six Cities Study, the ACS Study, and the Particle Epidemiology Reanalysis Project[a]

	Six Cities Study			ACS Study			
	All Causes	Cardiopulmonary Disease	Lung Cancer	All Causes	Cardiopulmonary Disease	Lung Cancer	Source
Original Investigators	1.26 (1.08, 1.47)			1.15 (1.09, 1.22)	1.26 (1.16, 1.37)	1.36 (1.11, 1.66)	c
Part I: Replication and Validation							
Reanalysis Validation[b]				**1.16 (1.10, 1.23)**	**1.28 (1.19, 1.40)**	1.36 (**1.13, 1.65**)	Table 26c
Part II: Alternative Risk Models[d]							
Base				1.26 (1.19, 1.33)	1.39 (1.28, 1.50)	1.63 (1.35, 1.97)	Summary Table 2
Original				1.16 (1.10, 1.23)	1.27 (1.17, 1.38)	1.36 (1.13, 1.65)	
Full				1.15 (1.08, 1.21)	1.25 (1.15, 1.35)	1.32 (1.09, 1.60)	
Extended				1.15 (1.09, 1.21)	1.25 (1.16, 1.36)	1.33 (1.10, 1.61)	
Occupational exposure				1.14 (1.08, 1.21)	1.25 (1.15, 1.35)	1.32 (1.09, 1.60)	Table 25
Exercise				1.11 (1.05, 1.18)			page 159
Education[g]							
Less than high school	1.47 (1.14, 1.89)	1.28 (0.91, 1.79)	2.82 (1.15, 6.90)	1.27 (1.13, 1.42)	1.39 (1.20, 1.62)	1.49 (1.02, 2.18)	Table 52
More than high school	0.99 (0.72, 1.36)	1.47 (0.90, 2.24)	0.91 (0.27, 3.02)	1.05 (0.96, 1.14)	1.11 (0.98, 1.25)	1.19 (0.89, 1.59)	
Part II: Alternative Analytic Approaches							
Alternative Air Quality Dataset							
$SO_4^{2-}{}_{(cb\text{-}adj\ US)}$[i]	1.27 (1.09, 1.48)	1.30 (1.05, 1.59)	1.14 (0.66, 1.96)	1.18 (1.11, 1.26)	1.31 (1.19, 1.43)	1.18 (0.96, 1.47)	Tables 16, 31
Ecologic Covariates							
Population change				1.06 (0.99, 1.13)	1.12 (1.03, 1.23)	1.30 (1.05, 1.61)	Tables 34, 35, 36
SO_2				1.04 (0.98, 1.11)	1.14 (1.04, 1.25)	1.36 (1.08, 1.72)	
Spatial Analyses							
Independent Cities Model							Tables 40, 42, 44
SO_4^{2-} alone				1.25 (1.13, 1.37)	1.29 (1.15, 1.46)	1.39 (1.09, 1.75)	
Population Change				1.16 (1.05, 1.29)	1.17 (1.03, 1.33)	1.36 (1.04, 1.77)	
SO_2				1.13 (1.02, 1.25)	1.18 (1.04, 1.34)	1.39 (1.08, 1.81)	
Regional Adjustment Model							
SO_4^{2-} alone				1.19 (1.06, 1.34)	1.19 (1.06, 1.34)		
Population change				1.17 (1.02, 1.33)	1.16 (0.98, 1.37)		
SO_2				1.10 (0.97, 1.24)	1.12 (0.96, 1.32)		
Spatial Adjustment Model							
SO_4^{2-} alone				1.09 (1.01, 1.19)	1.13 (1.01, 1.27)		
Population change				1.10 (1.00, 1.20)	1.12 (1.00, 1.25)		
SO_2				1.05 (0.97, 1.14)	1.10 (0.99, 1.22)		

(Footnotes on following page)

Footnotes to Tables 1 and 2

[a] For Part II: Alternative Risk Models, relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. In the Six Cities study, this difference for fine particles was 18.6 $\mu g/m^3$, and for sulfate was 8.0 $\mu g/m^3$. In the ACS study this difference for fine particles was 24.5 $\mu g/m^3$, and for sulfate was 19.9 $\mu g/m^3$. For Part II: Alternative Analytic Approaches, effects were evaluated for the respective range of fine particles and sulfate from Table 30 (Part II), and for the respective range of each ecologic covariate specified in Appendix G (Part II), which is available upon request from Health Effects Institute.

[b] **Bold type** indicates relative risks calculated by the Reanalysis Team after resolving errors discovered through the quality assurance audit.

[c] Dockery et al 1993; Pope et al 1995.

[d] Base, Original, Full, and Extended Models are defined in the Commentary section Technical Evaluation of Methods. Unless otherwise indicated, Part II effects were estimated using the Extended Model with calendar year as the time axis.

[e] Rate among people who left the city of enrollment during follow-up.

[f] Confidence interval was not given in the Investigators' Report.

[g] Source table contains a third category ("high school") that is not reported here.

[h] $PM_{2.5}$(DC) = mean fine particle fraction from dichotomous samplers (based on IPMN 1979–1983).

[i] $SO_4^{2-}{}_{(cb\text{-}adj\ US)}$ = sulfate data for 1980–1981 inclusive, with US-specific adjustment for artifactual sulfate.

PART I: REPLICATION AND VALIDATION

TECHNICAL EVALUATION OF METHODS

As part of the replication and validation effort, a quality assurance audit was conducted to assess whether the data on subjects and the air quality data collected throughout the studies were the actual data used in analyses of mortality and air pollution. The audit was conducted by an independent team of auditors selected by HEI via a competitive process. The audit was designed to determine retrospectively whether the data files were complete and accurate records of information gathered via questionnaires, death certificates, and air quality monitors or databases.

For each study population, the Audit Team randomly selected 250 questionnaires and 250 death certificates to examine. They defined an error rate of less than 5% as acceptable for each variable. The audit of air quality data focused on two issues: the quality of the original data (eg, measurement methods, potential artifacts), and the criteria applied to include or exclude original data.

Using the records of the Six Cities Study Original Investigators, the Audit Team was able to recalculate most (although not all) of the summary measures of air pollutants from primary measurements. A similar audit of the ACS Study air quality data was not possible because no raw data were available at the time of the reanalysis. The original monitoring data had come from sources that were, by the time of the Reanalysis Project, either technologically difficult to access or had little or no documentation of methods, traceability of data collection procedures, or underlying coding conventions. Further, the monitoring locations had been selected and managed by the EPA to support its own regulatory objectives and had not been designed for the purposes of the ACS Study. For example, a sampling site might have been located by the EPA near a specific combustion pollution source, such as a highway, that might not represent regional pollutant concentrations.

RESULTS

Selected findings from the Reanalysis Project are summarized in Commentary Table 1 (fine particles), Table 2 (sulfate), and Table 3 (sulfur dioxide) and discussed in the next sections.

Key Findings

- An extensive audit of the study population data for both the Six Cities and ACS Studies and of the air quality data in the Six Cities Study revealed the data to be of generally high quality with a few exceptions. In both

Table 3. Relative Risks of Mortality from Various Causes Associated with an Increase in Sulfur Dioxide: A Comparison of Results from the Original Six Cities Study, the ACS Study, and the Particle Epidemiology Reanalysis Project[a]

	Six Cities Study			ACS Study			
	All Causes	Cardiopulmonary Disease	Lung Cancer	All Causes	Cardiopulmonary Disease	Lung Cancer	Source
Part II: Alternative Analytic Approaches							
Standard Cox Model							
SO_2	1.26 (1.08, 1.47)	1.25 (1.01, 1.54)	1.13 (0.66, 1.95)				Table 16
Seasonal Effects							
April-September				1.35 (1.25, 1.45)	1.48 (1.33, 1.64)	1.40 (1.10, 1.79)	Table 32
October-March				1.23 (1.17, 1.29)	1.29 (1.20, 1.38)	1.00 (0.85, 1.18)	
Ecologic Covariate							
SO_2 alone				1.30 (1.23, 1.38)			Summary Table 5
Spatial Analyses[b]							
Independent Cities Model							
SO_2 alone				1.33 (1.22, 1.45)			page 214
SO_4^{2-}				1.39 (1.24, 1.55)	1.42 (1.25, 1.61)	0.90 (0.67, 1.21)	Tables 41, 43, 45
$PM_{2.5}$				1.44 (1.23, 1.69)	1.40 (1.13, 1.73)		Tables 47, 49
Regional Adjustment Model							
SO_2 alone				1.26 (1.15, 1.39)			page 214
SO_4^{2-}				1.28 (1.12, 1.46)	1.30 (1.11, 1.52)		Tables 41, 43
$PM_{2.5}$				1.19 (0.99, 1.44)	1.21 (0.89, 1.65)		Tables 47, 49
Spatial Filtering Model[c]							
SO_2 alone[d]				1.35 (1.16, 1.57)			page 214
SO_4^{2-}				1.19 (1.09, 1.29)	1.33 (1.17, 1.51)		Tables 41, 43

[a] Relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. In the Six Cities study, this difference for SO_2 was 22.4 ppb (see Dockery et al 1993). In the ACS study, this difference for SO_2 was 22.57 ppb (see Appendix G to Part II, which is available on request from HEI).

[b] The models used to report the impact of adjustment for sulfate and fine particles on sulfur dioxide also include adjustment for gaseous copollutants: carbon monoxide and nitrogen dioxide with or without ozone. See source tables for details.

[c] Filtered Both Sides Model.

[d] Simultaneous Autoregressive Model.

studies, a few errors were found in the coding and inclusion of certain subjects; when those subjects were included in the analyses, they did not materially change the results as originally reported. Because the air quality data used in the ACS Study could not be audited, a separate air quality database was constructed for the sensitivity analyses described in Part II.

- The Reanalysis Team was able to replicate the original results in both studies using the same data and statistical methods as used by the Original Investigators. The Reanalysis Team confirmed the original point estimates: For the Six Cities Study, they reported the relative risk of mortality from all causes associated with an increase in fine particles of 18.6 $\mu g/m^3$ as 1.28, close to the 1.26 reported by the Original Investigators. For the ACS Study, the relative risk of mortality from all causes associated with an increase in fine particles of 24.5 $\mu g/m^3$ was 1.18 in the reanalysis, close to the 1.17 reported by the Original Investigators.

Questionnaire and Mortality Data Audit

For the Six Cities Study, a computer coding error in the database resulted in early termination of follow up of some individuals (referred to as *early censorship* of time on study), which resulted in a loss of 1% of person-years of follow up. This early censorship was unequal among the six cities: the greatest incidence was in Portage and Topeka, cities with relatively low levels of air pollutants. When the Reanalysis Team included the missing years of follow up, the relative risk of mortality generally increased.

For the ACS Study, two computer coding errors mistakenly excluded 7,706 female smokers and 5,421 female deaths. When the Reanalysis Team included these individuals and deaths, the relative risk of cardiopulmonary mortality associated with fine particles increased slightly from 1.27 (95% CI: 0.92–1.74) to 1.32 (95% CI: 1.01–1.72) among female ever-smokers (see Tables 27a and 27c, Part I); the same relative risk associated with sulfate increased more dramatically from 1.30 (95% CI: 1.01–1.66) to 1.44 (95% CI: 1.17–1.78) (see Tables 26a and 26c, Part I).

Audit of Six Cities Study Air Quality Data

The audit of the Six Cities Study data identified four changes in the sampling methods and in the criteria applied to the air quality data over the duration of the study (not shown in Commentary Tables 1 and 2). These changes reflected the natural evolution and improvement of the measurement technology over time; in some cases, these improvements had been developed by the Original Investigators themselves. The reasons for making the changes and improving the accuracy of the methods were generally logical.

First, the measurements of inhalable and fine ambient particles obtained from filters during 1979 to 1988 were analyzed by two different groups (EPA and the Six Cities Study investigators). One laboratory used a β-absorption gauge and the other used gravimetric analysis. The filters within the sampling devices were in two different modes (dry and oiled). Use of oiled filters was one of the major improvements the Original Investigators made to sampler efficiency. The Reanalysis Team did not assess the potential impact that different laboratories using different methods of filter analysis may have had on the computed mean particle levels. Such an assessment might not have changed the rank ordering of the six cities, but it might have changed the concentrations used in the original analyses and, hence, the Original Investigators' conclusion that an increase of 18.6 $\mu g/m^3$ of fine particles was associated with a 26% increase in all-cause mortality.

Second, the dichotomous sampler was relatively new and untested at the time the Six Cities Study began. One of the advantages in its design was that filters used in this sampler, unlike the old high-volume samplers, were not subject to artifactual sulfate. This is discussed in the section Artifactual Sulfate. (Sulfate data from dichotomous samplers were not used in the epidemiologic analyses by either the Original Investigators or the Reanalysis Team.)

Third, in accordance with early EPA guidance, the Six Cities Study data gathered during 1979–1981 (epoch 1 as defined in Part I) were systematically excluded whenever the coarse/fine mass ratio was less than 0.3 or greater than 1.3. Restricting the data in this manner eliminated valid measurements that were unusually high or low during the 1979–1981 period. Data from later years (1982–1985) were included regardless of the coarse/fine mass ratio on the recommendation from the Original Investigators' own research team (Briggs et al 1982). When the reconstructed data were compared with the original data with this exclusion criterion, the calculations of fine particle mass were generally similar for all cities except Topeka, where more than half of the data had been excluded because of the coarse/fine mass ratio criterion.

Fourth, another criterion excluded concentrations of pollutants measured using more than one set of filters per day. The need for more filters occurred on high-pollution days when filters became heavily loaded and the sampler automatically switching to new filters. This criterion eliminated many high-concentration measurements, especially in Steubenville during the early years of the Six Cities Study.

The only problem identified with measures of gaseous pollutants was a discrepancy of 4.9 ppb in the mean con-

centration of sulfur dioxide at St Louis (Original Investigators' annual mean sulfur dioxide [SO_2] = 14.1 ppb; Audit Team's annual mean sulfur dioxide = 9.2 ppb). Although this discrepancy modified slightly the place of St Louis in the rank order of cities by sulfur dioxide levels, it did not change the least-polluted or most-polluted cities and therefore did not change the risk of mortality from all causes expressed in terms of the range of sulfur dioxide concentrations. As reported in Part II, the relative risks of mortality associated with sulfur dioxide calculated by the Original Investigators and by the Reanalysis Team were identical to the third significant digit (relative risk [RR] = 1.26, 95% confidence interval [CI]: 1.08–1.47; and RR = 1.26, 95% CI: 1.08–1.48, respectively).

PART II: SENSITIVITY ANALYSES

TECHNICAL EVALUATION OF METHODS

In Part II, the Reanalysis Team performed a wide-ranging set of sensitivity analyses in order to test the strength of the original results. The analytic methods used are summarized in the sidebar, and details of the methods are discussed below.

Standard Cox and Random Effects Cox Models

The cities included in the Six Cities and ACS Studies may be regarded in two different ways: as a fixed collection of locations with fixed variance between the cities (standard Cox model), or as a random sample of cities with random variance in relationships between cities counted into the total variation (random effects model).

The standard Cox model assumes that all observations are statistically independent and, therefore, that the vital status of each study participant is a statistically independent outcome. Because the death of each individual depends on many complex health determinants, including characteristics of the city within which the study subject resided, potential intracity correlation (ie, correlation within a city) should be addressed via a random effects model. These different views lead to mathematical models that generate different estimates of association with different standard errors.

The reanalysis included a random effects component for a small number of associations in each study. This work required some extensions of the underlying statistical theory (described in Appendix I, Part II).

TERMS USED IN TECHNICAL EVALUATION OF METHODS

STATISTICAL ANALYTIC METHODS

standard Cox model: the Cox proportional-hazards regression model of survival

random effects model: the Cox random effects model

Poisson regression model: used to analyze time dependence in the variables

ALTERNATIVE RISK MODELS

These four models were used to assess the influence of each individual-level variable by incorporating or excluding different variables in the risk model.

Base Model: only the air pollutant of interest (adjusted for age, race (ACS only), and gender)

Original Model: the set of variables used by each group of Original Investigators

Full Model: the largest number of covariates for which data were available

Extended Model: excluded those covariates from the Full model that, when removed from the model, did not significantly change the goodness of fit of the data to the model ($P > 0.05$).

ALTERNATIVE ANALYTIC APPROACHES

Three alternative analytic approaches were designed to test whether the original results would remain robust to different analytic assumptions.

alternative air quality dataset: second dataset constructed by the Reanalysis Team for the ACS Study

ecologic covariates: city-wide variables that the Reanalysis Team used in combination with other analyses (both the alternative risk models and the spatial analyses)

spatial analyses (three components)

- maps that show the distribution of mortality rates, the pollutants themselves (fine particles, sulfate, or sulfur dioxide), or the pollutant levels overlaid with high, medium, and low relative risks of mortality
- Moran *I* and *G* statistics, which are designed to determine whether spatial correlation exists; and
- spatial analytic methods (a series of two-stage random effects regressions; see section Two-Stage Approach) to control for spatial correlation in the data

  REGIONAL ADJUSTMENT MODEL

  SPATIAL FILTERING MODELS (in two forms):

  FILTERED MORTALITY ONLY MODEL

  FILTERED BOTH SIDES MODEL

  SIMULTANEOUS AUTOREGRESSIVE MODEL

These models and their strengths and limitations are discussed in the Commentary text.

Alternative Risk Models

Critics of the original studies focused on how variables were selected and analyzed by the Original Investigators. Consequently, the Reanalysis Team expanded considerably the type and number of variables analyzed. Starting with the Base Model, they added all the variables each set of Original Investigators had used in their analyses to generate the Original Model; then they added all other variables for which data were available to create the Full Model. The Extended Model omitted every variable that had not significantly improved the goodness of fit of the data in the Full Model. The Extended Model was used as the basis of most of the analyses (eg, ecologic and spatial analyses). The variables included in each of the alternative risk models are summarized in Part II (see Table 2 for the Six Cities Study and Table 19 for the ACS Study).

For some variables, data had been collected during the original studies and for other variables, data were available from public records (ACS Study only): physical activity (ACS Study only), lung function measurements (forced expiratory volume in one second and forced vital capacity; Six Cities Study only); population mobility (Six Cities Study only), time-dependent covariates (smoking and body mass index; Six Cities Study only), marital status, and gaseous pollutants (carbon monoxide [CO], nitrogen dioxide [NO_2; ACS Study only], ozone [O_3], and sulfur dioxide).

The Reanalysis Team considered several important variables in more detail than had the Original Investigators: smoking, occupation, education, and age. Smoking was evaluated using smoking status, duration and intensity of smoking, age started smoking, pipe/cigar smoking (ACS Study only), and passive smoking (ACS Study only). In the original studies, educational attainment had been classified as having less than or more than a high school education; the Reanalysis Team considered three levels: less than high school, high school, and more than high school. The reanalysis used two methods for analyzing the effects of time (calendar year and age).

Occupational exposures to dusts, gases, and fumes may have confounded the original estimates of the association between particles and mortality by including self-reported occupational exposure to dust or fumes (both studies) and toxic air pollutants (ACS Study only). To reduce possible confounding due to occupation, the Reanalysis Team developed two new indicators of occupational exposure: a six-level dirtiness index to estimate the degree of occupational exposure to dusts, gases, and fumes; and a binary indicator denoting whether a subject's occupation was likely to be associated with exposure to a known lung carcinogen.

Alternative Analytic Approaches

Alternative Air Quality Dataset The Reanalysis Team constructed an air quality data set for the ACS Study (years 1980 and 1981) using databases of the EPA Aerometric Information Retrieval System (AIRS) and the Inhalable Particle Monitoring Network (IPMN). This new data set included sulfate data for 144 cities (AIRS and IPMN), fine particle data for 63 cities (IPMN), and gaseous copollutant data. Operation of the monitoring equipment, collection and review of data, and assembly of the air quality database were the responsibility of state and local environmental personnel in concert with the EPA. The air quality data were collected using standard reference methods established by the EPA. An independent audit of these data was beyond the scope of this project.

Artifactual Sulfate The glass-fiber filters used on high-volume samplers during the 1970s and early 1980s yielded artificially high measurements of fine particle mass and sulfate due to a reaction between ambient sulfur dioxide and the alkaline filter material. The product of this reaction was incorrectly measured as additional particulate sulfate. The impact of this artifact on measured sulfate concentrations varied due to differences in ambient levels of sulfur dioxide, ambient temperature, and relative humidity. For the reanalysis, the extent of artifactual sulfate data was important with respect to the Six Cities Study sulfate measurements and to the 80% of the ACS Study sulfate measurements which had come from EPA's databases. The Reanalysis Team chose to construct city-specific calibration equations to adjust the reported sulfate levels.

Ecologic (City-Level) Covariates In both of the original studies, the main risk factor of interest was city-level air quality, which is a group or ecologic variable. Using city-level air quality data may not present a serious difficulty if the measurements closely represent the exposure of each individual in a city (ie, no misclassification of exposure). However, misclassification of exposure is an inherent concern in epidemiologic studies that do not measure air quality exposure for individuals. In both studies, individual data from questionnaires or physical examinations were used to derive adjusted mortality rates for each city and to estimate air pollution–mortality relationships according to personal characteristics (eg, smokers vs nonsmokers, amount of education).

Other ecologic variables correlated with pollutant levels and mortality may confound these relationships. The primary purpose of the ecologic covariate analyses was to determine whether intercity variation in health risks might be a result of city characteristics other than air quality. The

Six Cities Study, with only six city-level (ecologic) data points, was not large enough for an informative analysis. Therefore, using the ACS Study data, the Reanalysis Team identified 30 separate ecologic covariates that represented demographic, socioeconomic, climatic, and environmental factors and health care services that could confound the calculated associations between air pollution and mortality. Of these, 20 had data of adequate quality to allow the Reanalysis Team to test their potential for confounding.

Gaseous Copollutants As with fine particles and sulfate, gases are ecologic variables measured at the city level. The ACS Study data were used in the reanalysis to assess the influence of gaseous copollutants on estimated relations between fine particles or sulfate and mortality. For four gaseous copollutants (carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide), city-specific annual means of daily one-hour maximum concentrations from the year 1980 were obtained from AIRS and used in the reanalysis (see Appendix E, Part II). In addition, the Reanalysis Team examined whether seasonal variations in gaseous pollutants affected their associations with mortality from all causes, cardiopulmonary disease, and lung cancer. They analyzed each gas in two seasons: a warm-weather period of April through September and a cool-weather period of October through March.

Two-Stage Approach Both the Six Cities and ACS Studies provided multilevel data: some variables were measured at the level of the individual subject while others were measured at the level of the city in which the individuals resided. Correct statistical analysis of such data requires that computations allow for random influences (or errors) at both levels. The Six Cities Study data set was not large enough to allow this; the ACS Study data set did permit a two-stage analysis.

In general, exact maximum likelihood methods for such analyses are computationally intensive, and the need to derive an explicit likelihood function imposes considerable constraints on the models that can be fitted. The Reanalysis Team applied an approximate method, which relied on there being sufficient deaths within each city so that the likelihood distribution for each city-specific effect could be treated as approximately Gaussian (normal, bell-shaped).

In stage 1, the Reanalysis Team fitted the standard Cox model to assess the influence of covariates measured at the individual level. This model included a separate indicator term for each city, which may be viewed as a city-specific relative risk that has been standardized for all individual-level variables included in the model. These relative risks can be treated as floating absolute risks (see Easton et al 1991), and to a close approximation, the correlations between these estimates can be ignored. Just like any other standardized risks, however, their precision depends on the number of deaths on which they are based and this varies from city to city.

Stage 2 of the analyses then followed exactly the same course as an ecologic regression analysis of routinely collected data. The standardized city-specific risks were related to covariates, such as air quality and climatic measures, that had been measured at the city level. However, such analyses require appropriate assumptions about the errors of city-specific standardized rates. In particular, due to the limited number of deaths, it is not appropriate to assume that estimation error from the first stage of analysis is the only source of error. Additional random variation about the model must be included to allow for all the unmeasured factors operating at the city level.

The Independent Observations Model presented in this report inappropriately ignored such city-level variation. Conversely, the Independent Cities Model allowed for random differences among cities and assumed the influences on different cities to be uncorrelated. Even this assumption may not be correct, however, when spatial correlation is present in the data (discussed in detail in the following Spatial Analyses section). The most important difference between these two models is that the former, because it ignores a source of variation, produces incorrect estimates of the precision of the effects of city-level covariates.

An important aspect of any model such as the Independent Cities Model is the inclusion of an additional random term (denoted by τ^2 in this report) to represent residual unexplained variation of risks among cities. The Independent Cities Model assumed that these random influences that perturb city-specific rates from the value predicted by the ecologic regression were unrelated to observed pollutant concentrations; that is, they were not confounders. This assumption may not be true, however. If a large component of the variance is unexplained in the data, a model including sufficient variables to identify this residual variance might produce different regression coefficients for the variables of interest.

Spatial Analyses Findings for both the Six Cities Study and ACS Study are based on regression analyses in which the units of data are cities, not people, and standardized relative risks of mortality are modeled as functions of pollutant levels and other variables measured at the city level. Spatial correlations among cities could arise for a number of reasons. For example, nearby cities tend to have similar demographic characteristics and are subject to similar economic and environmental conditions. If spatial correlations exist but are ignored, they could bias both the

estimates and confidence intervals for the primary outcomes of interest. This aspect is difficult to assess for only six cities, but it could have a significant influence on analyses of the ACS study.

The spatial analyses conducted by the Reanalysis Team had three components: producing maps to illustrate spatial variations in both pollutants and mortality across the United States, testing for spatial correlation, and applying analytic methods that would correct regression analyses for spatial correlation.

For the first component, the maps present the relation between geography and several variables (air pollutants and mortality rates) both alone and in combination. For the second component, the Reanalysis Team applied statistical hypothesis tests for spatial correlation using the Moran *I* statistic, a global measure of spatial correlation, and the Moran *G* statistic, a local correlations measure within a specified distance of a given point. An iterative process led the Reanalysis Team to fix the distance at 600 km.

The third and most critical component was to correct for spatial correlation in the estimated associations between air pollutants and mortality. These corrections took place within the context of a two-stage regression analysis. Stage 2 was carried out three times using three different approaches to spatial correction. The first and simplest approach was to include an indicator variable to adjust for region (the Regional Adjustment Model). The second approach (Spatial Filtering Models) relied on spatially filtering either the city-specific relative risks (Filtered Mortality Only) or both relative risks and covariates (Filtered Both Sides) in order to create spatially independent variables for which the usual regression analyses could be performed without further adjustment. The robustness of the result was then examined using a third approach, the Simultaneous Autoregressive Model. (The second and third approaches were applied only to the 151 cities in the sulfate cohort because the authors viewed the 50 cities in the fine particle cohort as too few to support these sophisticated methods.)

Each of the three approaches to spatial adjustment had strengths and limitations. The Regional Adjustment Model depended on an arbitrary specification of regions and the assumption that spatial correlation within each region was negligible. The Spatial Filtering Model was sensitive to which precise form of spatial filter was applied; the definition of the form itself depended on unknown parameters and whatever uncertainty was involved in defining the spatial filter was not reflected in the final estimates and confidence intervals for the relative risks. The Simultaneous Autoregressive Model depended first on specifying a lattice with an associated neighborhood structure, which in turn depended on a specific network of cities; if some cities were added to or deleted from the network, the form of the spatial model would change. Furthermore, even within this structure, the spatial dependence of the entire lattice was expressed in terms of a single parameter (ρ) and no attempt was made to verify that the spatial correlation structure assumed by the model was consistent with the real data.

In summary, the three methods of spatial adjustment were reasonable approaches given the constraints of time and available software. Ideally, all three should be subjected to further research.

RESULTS

A selected subset of the findings of the reanalysis are reported in Commentary Tables 1–3. A similar analytic strategy was followed for fine particles and sulfate, as described in the methods section and indicated by the analyses presented in the tables. The sulfur dioxide findings reported in Commentary Table 3 are somewhat more limited since this pollutant was not the main focus of the original studies and therefore of the reanalysis.

Key Findings

- First, the Reanalysis Team used the standard Cox model used by the Original Investigators and included variables in the model for which data were available from both original studies but had not been used in the published analyses (eg, physical activity, lung function, marital status). The Reanalysis Team also designed models to include interactions between variables. None of these alternative models produced results that materially altered the original findings.
- Next, for both the Six Cities and ACS Studies, the Reanalysis Team sought to test the possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of the population. Although different subgroups did show some variation in their estimated effects, the results were not statistically significant with one exception. The estimated effects of fine particles did appear to vary with educational level; the association between an increase in fine particles and mortality tended to be higher for individuals without a high school education than for those who had completed high school or those with more than a high school education.
- In the ACS study, the Reanalysis Team tested whether the relationship between ambient concentrations and mortality was linear. They found some indications of both linear and nonlinear relationships, depending

upon the analytic technique used, suggesting that the issue of concentration-response relationships deserves additional analysis.

- In the Six Cities Study where data were available, the Reanalysis Team tested whether effect estimates changed when certain key risk factors (smoking, body mass index [BMI], and air pollution) were allowed to vary over time. One of the criticisms of both original studies has been that neither analyzed the effects of change in pollutant levels over time. In general, the reanalysis results did not change when smoking and body mass index were allowed to vary over time. The Reanalysis Team did find for the Six Cities Study, however, that when the general decline in fine particle levels over the monitoring period was included as a time-dependent variable, the association between fine particles and all-cause mortality dropped substantially, but the effect continued to be positive and statistically significant.
- Using its own air quality data set constructed from historical data to test the validity of the original ACS air quality data, the Reanalysis Team found essentially the same results.
- Any future analyses using the sulfate data should take into account the impact of artifactual sulfate. Sulfate levels with and without adjustment differed by about 10% for the Six Cities Study. Both the original ACS Study air quality data and the newly constructed data set contained sulfate levels inflated by approximately 50% due to artifactual sulfate. For the Six Cities Study, the relative risks of mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS Study, adjusting for artifactual sulfate resulted in slightly higher relative risks of mortality from all causes and cardiopulmonary disease compared with unadjusted data.
- Because of the limited statistical power to conduct most sensitivity analyses for the Six Cities Study, the Reanalysis Team conducted the majority of its sensitivity analyses using only the ACS Study data set with 154 cities. In that data set, when a range of city-level (ecologic) variables (eg, population change, measures of income, maximum temperature, number of hospital beds, water hardness) were included in the analyses, the results generally did not change. Two exceptions were that associations for both fine particles and sulfate were reduced when city-level measures of population change or sulfur dioxide were included in the model.
- A major contribution of the Reanalysis Project is the recognition that both pollutant variables and mortality appear to be spatially correlated in the ACS data set. If not identified and modeled correctly, spatial correlation could cause substantial errors in both the regression coefficients and their standard errors. The Reanalysis Team identified several methods for dealing with this, all of which resulted in some reduction in the estimated regression coefficients. The full implications and interpretations of spatial correlations in these analyses have not been resolved and appear to be an important subject for future research.
- When the Reanalysis Team sought to take into account both the underlying variation from city to city (random effects) and the spatial correlation between cities, only sulfur dioxide as a city-level variable continued to decrease the originally reported associations between mortality and fine particles or sulfate. This effect was more pronounced for sulfate.
- When the Reanalysis Team conducted spatial analyses of sulfur dioxide, the association between sulfur dioxide and mortality persisted after adjusting for sulfate, fine particles, and other variables.
- As a result of these extensive analyses, the Reanalysis Team was able to explain much of the variation between cities, but some unexplained city-to-city variation remained.

Base, Original, Full, and Extended Models

The Base Model produced the highest relative risks. Relative to the Base Model and using either calendar year or age as the time axis, the Original, Full and Extended Models produced lower relative risks for each cause of death. For data from both the Six Cities Study and the ACS Study, the Original, Full, and Extended Models produced similar relative risks, sometimes to the third significant digit.

Population Mobility

Individual mobility data were available for the Six Cities Study, allowing separation of the cohort into a mover and a nonmover group. The relative risk of fine particles for all-cause mortality in the nonmover group was 1.30 (95% CI: 1.10–1.54). Reanalysis of the mover group ignoring follow-up data before the time the subjects first moved from the city of enrollment resulted in a relative risk for mortality of 1.25 (95% CI: 0.75–2.10). This finding was lower than that of the nonmover group and similar to the point estimate reported by the Original Investigators (RR = 1.26; 95% CI: 1.08–1.47).

Occupation

With some exceptions, the associations between air pollution and mortality remained similar to original results after being adjusted by the dirtiness index and the index for known lung carcinogens. For the Six Cities Study, when entered as a covariate in the Extended Model, neither the dirtiness index nor the lung carcinogen index had much impact on the estimates for all-cause mortality or cardiopulmonary mortality. For lung cancer, however, the originally reported point estimate (RR = 1.37, 95% CI: 0.81–2.31) was sensitive to different model specifications and inclusion of additional covariates (eg, RR = 1.05, 95% CI: 0.59–1.89) when the binary lung carcinogen variable and continuous dirtiness variable were included in the Extended Model). In the ACS Study data, neither index had a noticeable impact on relative risks. However, audit of the occupational data for the ACS Study used in Part II found coding errors up to 15%.

Educational Attainment

The Reanalysis Team found that educational attainment significantly modified the air pollutant-mortality associations in both the Six Cities Study and the ACS Study. For all-cause mortality and fine particles, relative risks decreased as educational attainment increased; although similar, this pattern was less consistent for mortality from cardiopulmonary disease and lung cancer. No statistically significant elevation in relative risk was estimated for the subgroup with more than high school education except for mortality from cardiovascular disease in the ACS Study (RR = 1.24, 95% CI: 1.05–1.47; see Summary Table 3).

Time-Dependent Covariates

Certain key variables (BMI, smoking, and air pollution) varied over the time of the study, and some critics questioned whether considering time patterns in that variation could change the results. The Reanalysis Team tested how inclusion of BMI, smoking, and time-specific (rather than averaged) pollution levels would affect the associated relative risks for all-cause mortality. To do so, they used the Poisson regression model, which is designed to analyze time-dependent data.

The results of this analysis (Part II, Table 14) show that, first, when they fitted the Poisson regression model without taking the time dependence of the covariates into account, the results were similar to the Original Investigators' results using the standard Cox model. Second, when the Poisson regression model included either BMI or smoking, the relative risks of all-cause mortality for fine particles were hardly changed from those calculated with the Poisson model with no time dependence. Third, when the model included time-dependent data for fine particles, the estimated relative risk dropped substantially from 1.31 to 1.16, with a similar reduction in the upper and lower confidence limits (see Commentary Table 1).

Alternative Air Quality Dataset

The air pollution data sets used by the Reanalysis Team and the Original Investigators of the ACS Study were highly correlated. They resulted in similar findings for fine particles and sulfate even after sulfate concentrations were adjusted for artifactual sulfate. On the basis of the limited coincident measurements from high-volume samplers and dichotomous samplers (not subject to artifactual sulfate), the Reanalysis Team estimated the average difference between the two types of sulfate data to be no more than 10% for the Six Cities Study. Sulfate levels for both the original ACS data and the alternative data set were inflated by approximately 50% due to artifactual sulfate. The range in adjusted sulfate values (see Table 30, Part II) decreased slightly but remained comparable to the range for the unadjusted sulfate (19.9 $\mu g/m^3$). Using adjusted sulfate values slightly increased the relative risks for all-cause and cardiopulmonary disease mortality. For 144 cities, adjusting for artifactual sulfate (RR = 1.18; 95% CI: 0.96–1.47) or using unadjusted sulfate (RR = 1.18; 95% CI: 0.97–1.44) produced the same decreased relative risks for lung cancer.

The Reanalysis Team used unadjusted sulfate concentrations for the sensitivity analyses to facilitate comparisons with the original findings. Thus, the analyses reported in the original studies, and most analyses reported in the current report, did not use data adjusted for artifactual sulfate.

Seasonal Variation in Gaseous Copollutants

The Reanalysis Team showed that sulfur dioxide levels measured in different seasons produced different relative risks: higher when based on warm-weather concentrations than when based on cool-weather concentrations (see Table 32, Part II). Relative risks and confidence intervals for the other three gases (ozone, nitrogen dioxide, and carbon monoxide) varied around 1.0 regardless of season, but warm-weather ozone was significantly associated with mortality from cardiopulmonary disease (RR = 1.08, 95% CI: 1.01–1.16). The Reanalysis Team did not develop models in which seasonal gaseous pollutant concentrations were considered as confounders.

Ecologic Covariates and Spatial Analyses in the ACS Cohort

Ecologic covariates associated with mortality included population change, high school completion, various measures of income, maximum temperature, hospital beds per

unit of population, water hardness, sulfur dioxide, and nitrogen dioxide. Because many of these ecologic covariates were correlated with each other (and varied, for example, by region of the country), associations determined with ecologic covariates in the model require careful interpretation.

Only two ecologic covariates, population change between 1980 and 1986 and mean sulfur dioxide concentration, caused marked reductions in the associations between all-cause mortality and fine particles or sulfate (see Commentary Tables 1 and 2). Associations for mortality from cardiovascular disease showed similar patterns, whereas the association between sulfate and lung cancer mortality was not altered after adjusting for sulfur dioxide. In a model without other air pollutants, sulfur dioxide was a significant predictor of an increased risk of mortality (RR = 1.30, 95% CI: 1.23–1.38; see Commentary Table 3). No effect was found for other gaseous copollutants (ozone, nitrogen dioxide, carbon monoxide).

When spatial correlation was taken into account, the estimated relative risks due to fine particles or sulfate were reduced for all cause and cardiopulmonary disease mortality. For sulfate, the reduction was greater using the Spatial Adjustment Model than using the Regional Adjustment Model.

In two-pollutant models, inclusion of sulfur dioxide consistently diminished the associations of both fine particles and sulfate with mortality; this was true when analyzing both ecologic covariates and spatial correlation. In several cases, the accompanying confidence intervals showed that adjusting for spatial correlation changed the associations between fine particles or sulfate and mortality so that they were no longer statistically significant. By comparison, spatial models of the sulfur dioxide-mortality relationship showed the estimated effect on mortality was robust to adjustment for other ecologic variables such as fine particles and sulfate (see Commentary Table 3).

Residual Variation

Because the standard Cox model was not designed to analyze city-level variables, the Reanalysis Team used a two-stage regression to take into account random influences at the city level in the ACS Study data. Both standard Cox and random effects models produced similar point estimates (see Table 50, Part II), but the more important finding was the extent of unexplained residual variation, measured by τ^2. Unexplained variance for fine particles was roughly equivalent for the random effects ($\tau^2 = 0.0056$) and two stage models ($\tau^2 = 0.0067$), although it was reduced when sulfur dioxide was included in the analysis ($\tau^2 = 0.0034$ and 0.0036, respectively). Analysis in more cities and including both sulfate and sulfur dioxide in the model resulted in smaller variation, although city-to-city variation remained ($\tau^2 = 0.0023$ and 0.0029, respectively).

The random effects model assumed that unmeasured risk factors for mortality were independent of covariates; that is, they did not confound the effect of the pollutant of interest. Some residual variation often occurs from a variety of unmeasured influences in a model. The assumption of independence may be less appropriate, however, if the relative risks associated with the unmeasured influences are large compared to the relative risks of interest and if the unmeasured influences are highly associated with the risk factor of interest. If one assumed that one variable explained all this variation (which is unlikely to be the case), the relative risks associated with that variable would, based on the τ^2 values above, range from approximately 1.27 to 1.47 (depending on the analysis), levels that are of the same order of magnitude as the relative risks of interest. More likely, there are several or even many unexplained variances, with a variety of relative risks, about which we know little concerning their association with the risk factor of air pollution.

By incorporating a number of individual-level variables and two polluants in the model, the Reanalysis Team was able to reduce but not eliminate this variation. Because the reason for this residual city-to-city variation is not understood, the possibility that the reported associations between air pollution and mortality could be decreased or increased by other, unmeasured, variables cannot be excluded.

DISCUSSION

The main objective of Part II of the Reanalysis was to evaluate how results of the Six Cities Study and the ACS Study might change if the statistical models were changed in various reasonable ways. By nature, sensitivity studies can never be complete: further possibilities can always be explored given sufficient time and resources. The question, therefore, is whether all of the most important considerations were evaluated. The Reanalysis Team addressed many of the criticisms of the original studies and explored numerous potential avenues of explanation for the originally reported results. The following sections discuss the findings of the Reanalysis, the limitations, and some overall conclusions from this study.

OCCUPATIONAL CONFOUNDING

Despite considerable effort on the part of the Reanalysis Team, their assessment of confounding by occupational exposure may be compromised by poor specificity and accuracy in coding. The possibility that occupational exposure confounds the Reanalysis Team's results cannot be completely dismissed. First, as found in the data audit, the occupational data had the highest error rates (15.8% for current occupation in the ACS Study). Second, the two new indices of occupational exposure may not predict deaths due to cardiovascular disease, which make up most of the deaths in the Six Cities and ACS Studies. No data are provided to validate the ability of these indices to predict nonmalignant respiratory mortality or cardiovascular mortality better than the occupational variables originally employed in the two cohort studies. In the Six Cities Study data, however, the relative risks of mortality from lung cancer associated with fine particles were sensitive to the binary lung carcinogen index being included in the analyses. The Reanalysis Team acknowledged that attempts to more fully control for occupational confounding through the use of these two occupational exposure indices were constrained by limitations in the quality of the data and that, despite all their effort, the possibility of residual confounding by occupation remains.

EDUCATIONAL ATTAINMENT

The Reanalysis Team reported that educational attainment modified the effects of air pollution on mortality: higher relative risks of mortality occurred in the group with lower educational levels (less than high school attainment). This trend was observed for all-cause mortality in both studies and other mortality endpoints in the ACS study, although elevated effect estimates were observed for cardiovascular mortality in both studies and across all educational levels, including the most highly educated.

One explanation they suggest for lower relative risks and the near-absence of statistically significant associations among the more highly educated is that these individuals somehow experience lower concentrations of ambient particles. No current evidence supports this explanation with the exception of a possible (although not documented) relation between educational status, socioeconomic status, and availability of air conditioning. Environmental justice studies, which test increased risk for lower income populations, have generally focused on a population's proximity to industrial sources of air pollutants or on potentially higher exposures to ambient concentrations of pollutants in urban areas, some of which exhibit greater spatial variability than particles. Explanations also could be formulated on the basis of other factors associated with educational level—socioeconomic status, health status, access to high quality health care, nutrition, exposure to environmental tobacco smoke, cardiovascular risk factors (National Center for Health Statistics 1998). These factors are likely to have much greater impact on mortality than would partially-reduced exposure to ambient particulate air pollution, but these other risk factors could also increase the susceptibility of those with lower education levels to the risks of exposure to air pollution.

ANNUAL OR SEASONAL AVERAGING FOR GASEOUS POLLUTANTS

Ambient concentrations of gaseous pollutants can exhibit pronounced spatial and temporal gradients. For example, sulfur dioxide and carbon monoxide are likely to exhibit pronounced spatial and temporal variability because they are associated with primary emissions from local sources. On the other hand, ozone is a byproduct of atmospheric reactions among primary emissions and typically shows little spatial variation within a region but pronounced seasonal and daily variations. To the extent that these gradients are not adequately considered, misclassification may be introduced into estimated gaseous pollutant exposure levels.

Among the associations between mortality and gaseous copollutant metrics based on warmer weather and colder weather, only the relative risks associated with sulfur dioxide levels were markedly different (higher in the warm season). To a much lesser extent, this pattern was true for ozone but not for carbon monoxide or nitrogen dioxide. These differences in relative risk across season should be interpreted with caution, however, because the reported effect estimates are based on different ranges of pollutants, which were not provided (see Table 32 Part II).

SPATIAL ANALYSES

An important theme throughout the Reanalysis Project is that of individual-level versus group-level information. Tables 1, 2, and 3 of the Commentary present the models in the order of models that consider individual-level data to be statistically independent followed by models that include city-level data and consider cities located near one another as sharing similar characteristics due to spatial effects.

Important contributions of the Reanalysis Project have been, first, to establish that spatial correlations are indeed present in the ACS Study data and, second, to develop and implement methods that correct the regression analyses to account for the spatial correlation. The spatial analyses are technically intricate and useful in beginning to illustrate

the extent and importance of spatial correlation. Further research using more sophisticated spatial analytic methods could improve our understanding of the impact that spatial correlation of data has on the estimated associations between air pollution and mortality. Specifically, the Reanalysis Team relied on standard but rather simple models for spatial covariances that do not adequately account for the possibility that spatial covariances between the eastern and western US are not homogeneous. In addition, the Reanalysis Team was not able to test fully the assumptions behind the spatial analyses.

The maps (Figures 16–21, Part II) are useful in describing visually how both pollution and mortality are spatially correlated; particularly interesting are the high levels of mortality and pollutants (sulfate, sulfur dioxide, and fine particles) in the lower Great Lakes region. Although they are visually stimulating, however, any direct scientific interpretation of these maps should be done with caution. They are all produced by the technique of kriging, which consists of fitting parametric models to the spatial correlations in the data and then using the same parametric models to interpolate values optimally between the cities for which data are available (Cressie 1993). Unfortunately, little detail is provided about the spatial analytic methods themselves, how they were estimated, and whether certain key assumptions such as spatial stationarity are satisfied in the data. The uncertainty estimates described in Appendix H (Part II) address prediction errors due to interpolation but not the more fundamental model-specification issues.

The ideal approach to spatial modeling would begin with more directly examining the form of spatial correlations in the actual data set and then would select a model that reflected those correlations. Such a model probably would be nonstationary, and a number of models now exist to identify spatial correlations among data in nonstationary settings (Sampson and Guttorp 1992; Brown et al 1994; Guttorp et al 1994; Nychka and Saltzman 1998; Holland et al 1999). The reanalyses performed in this project are more complicated than those considered in most of the cited papers because of the two-stage regression analyses that use estimated relative rates (with standard errors) from the first stage as the raw data for the second stage. However, hierarchical models to incorporate two-phase analyses are also being developed (Holland et al 2000, Dominici et al 2000). Ultimately, a more comprehensive analysis that takes into account hierarchical models with two-step analyses would be useful.

REGIONAL HETEROGENEITY

Descriptive maps of the United States show clear spatial patterns for air pollutants. Sulfate and, to a somewhat lesser extent, sulfur dioxide concentrations tend to be higher in the east than in the west. Sulfate is a secondary pollutant formed during long-range transport of a pollutant, whereas sulfur dioxide is a primary pollutant. Thus, concentrations of sulfate tend to be more uniform over broad regions and reflect regional effects. Measurements of sulfur dioxide may be more sensitive to the location of individual monitoring sites and tend to reflect local or city effects. Therefore, spatial patterns that are adjusted uniformly may result in overadjustment of the estimated effects of regional pollutants such as sulfate and underadjustment of the estimated effects of city-level pollutants such as sulfur dioxide. Possibly a city marker of air quality (sulfur dioxide) is a more important determinant of individual risk than is a regional marker (sulfate). This possibility is highly speculative, however, and requires further research to evaluate its likelihood properly. The spatial analyses the Reanalysis Team applied could not resolve the extent to which the estimated effects of sulfate were overadjusted; this limitation needs to be acknowledged when interpreting the findings of these reanalyses.

CONCENTRATION–RESPONSE FUNCTIONS AND POLLUTANT LEVELS OVER TIME

Apparent Nonlinear Effects of Fine Particles and Sulfate (ACS Study Only)

Most models assumed a linear relation between the logarithm of relative risk for each city and the level of fine particles or sulfate. The possibility of a nonlinear relation should be considered, however, because the difference between a linear and a nonlinear relation might influence the appropriateness of a standard being set by the EPA.

Tests for linearity of the relation between mortality rates and air pollutant concentrations in the ACS Study data are graphically presented in Figure 5 in Part II. For all-cause and cardiopulmonary mortality, the results show an increasing effect across the entire range of fine particles or sulfate but no clear evidence either for or against overall linearity. For lung cancer mortality, the whole effect is weaker and, again, the plots do not show strong evidence of a linear or nonlinear effect. In all cases, the results could be influenced by a small number of cities with pollution levels much higher than most other cities, a possibility that was not explored by the Reanalysis Team. Overall, these plots provide a useful perspective even though (as might have been anticipated) they do not resolve whether the observed effects are linear.

Interpretation of Figures 10 and 11 in Part II is less clear. These plots were produced as part of the flexible modeling strategy, in which both the baseline hazard function and the concentration-response curve were modeled nonlinearly using quadratic spline functions. The switch from LOESS methods to quadratic splines does not explain such a drastic change in the estimated shapes of these curves, or their confidence limits, compared with Figure 5 in Part II.

Acute Versus Chronic Effects

Scientists and regulators understand that the relative risks from the many time-series studies of daily mortality may reflect small reductions in survival (days or weeks) among already frail individuals. One reason that the Six Cities and ACS Studies have played an important role in recent discussions is that their results have been interpreted as indicating an effect of long-term exposure to particulate air pollution on chronic disease mortality with projected impact on survival on the order of years. Some reviewers, however, and the Original Investigators, have noted the difficulty in distinguishing between acute effects and chronic effects in these studies (Dockery et al 1993, Vedal 1997). As Dockery commented concerning the Six Cities Study (1993, *New England Journal of Medicine*, page 1759), "it is not possible to differentiate the influences of historical exposure from those of recent exposure." Not surprisingly, given the limitations of these data sets, the sensitivity analyses conducted by the Reanalysis Team provide interesting questions but no definitive answers on this issue.

Some findings from reanalysis of the Six Cities Study seem consistent with at least some of the effect being relatively acute (that is, related to recent air pollution levels). First, the estimated excess relative risk did not increase with duration of residence in a highly polluted city. Second, flexible modeling of fine particles and sulfate (Figures 2 and 3, Part II, respectively) showed a pattern of higher relative risk later in the study (12+ years). Third, fine particle levels in Steubenville went up at the beginning of the study; consequently, the air pollution gradient among the cities became more extreme, and the differences in their respective mortality rates increased. Measurement error (for example, due to the inability to account for exposure prior to the beginning of the cohort) makes interpretation of these results difficult. Nonetheless, we might expect to see some evidence of effects at shorter time scales based on recent results from time-series studies of daily mortality (Samet et al 2000).

Other results from reanalysis of the Six Cities study suggest effects of exposure in the more distant past. In analyses that considered recent exposure (time-dependent analysis), the relative risk for fine particles in the Six Cites Study decreased from 1.31 to 1.16. As shown in the original study, levels of fine particles decreased slightly over the study duration (see Figure 1, Dockery et al 1993), indicating the decrease in relative risk was not due to an overall decline in air pollution. Although this result seems to suggest that past exposure is more strongly associated with mortality than is recent exposure, the measurement error for the long-term average may be higher, complicating the interpretation. Early studies of lung cancer in migrant populations (Speizer and Samet 1994) and, more recently, in long-term urban residents (Nyberg et al 2000) provide some support for a persisting effect on mortality of air pollution exposure in past decades, as do some studies of long-term exposure to air pollution and lung function and chronic respiratory symptoms in children (eg, Raizenne et al 1996) and adults (eg, Van De Lende 1981).

Clearer insight into these biologically interesting and policy-relevant questions must await additional studies in which the temporal (as opposed to spatial) patterns of exposure can be better characterized.

SENSITIVITY OF RESULTS TO DISEASE GROUP

In both the Six Cities Study and the ACS Study, the relative risks for mortality from certain diseases associated with fine particles were higher for subjects with preexisting heart or lung disease. This finding is not surprising given that relative risks of cardiovascular mortality were somewhat larger in these analyses than were risks for all-cause mortality.

The relative risks for mortality from lung cancer were sensitive to the specific air quality data used. Fine particles were not associated with lung cancer in the ACS Study data, but in the Six Cities Study data they were (except after the new indices of occupational exposure had been applied and after subjects had been stratified by educational attainment). In the ACS Study data, sulfate was associated with lung cancer regardless of adjustment for occupation, ecologic covariates, or spatial analyses (RRs $\cong$ 1.35) although they were reduced after adjustment for artifactual sulfate and with a change in the number of cities from 151 to 144 (RR = 1.18, 95% CI: 0.96–1.47) (see Commentary Table 2).

In addition to lung cancer, relative risks for other cancers were associated with air pollution, although not as strongly as either cardiovascular or cardiopulmonary disease despite the fact that a large portion of deaths were from cancers other than lung cancer (27%; Table 20, Part II). This finding suggests that some residual confounding may be present in the ACS cohort.

SEVENTH-DAY ADVENTIST HEALTH STUDY ON SMOG

Results were recently published for a third cohort study (Abbey et al 1999; AHSMOG) that followed 6,338 nonsmoking, non-Hispanic white Seventh-day Adventists living in one of three air basins in California. A random sample of participants ages 27 through 95 years was recruited in 1976 and followed though 1992. Monthly estimates of ambient concentrations of certain pollutants (nitrogen dioxide, ozone, coarse particles, and sulfur dioxide) were obtained from 348 fixed-site monitoring stations. Because Abbey and colleagues had not finished analyzing their data when the Reanalysis Project began, the study was not included in this project (see Preface). However, the investigators' findings are relevant to the current discussion of the evidence from prospective cohort studies on long-term exposure to air pollution.

Neither the ACS Study nor Six Cities Study found an association between air pollution and mortality due to respiratory disease. By contrast, Abbey and associates found a significant association between coarse particles and adjusted relative risk of mortality when both underlying and contributory causes of respiratory deaths were combined in the category reported as any mention of respiratory disease. In the Six Cities and ACS Studies, only underlying causes of death were available, and respiratory disease accounted for only 7% of deaths. Small sample sizes and under-reporting of deaths due to respiratory disease may account for the inconsistency in findings across the three cohort studies. Respiratory diseases are often not diagnosed in life, and even when they are, they may not be mentioned on the death certificate. Further, cardiovascular and respiratory conditions have some symptoms in common and may occur together (Higgins and Thom 1989; National Heart, Lung and Blood Institute 1998). Cardiovascular conditions are the leading causes of death in the US and deaths are more likely to be attributed to them especially for older people when several diseases are present.

LIMITATIONS

GENERALIZATION OF ORIGINAL STUDIES TO THE UNITED STATES POPULATION

Six Cities Study

In the Six Cities Study, fine particles and sulfate were measured at the city level; therefore, for most analyses, this study had six city-wide data points. The number of individual subjects is relevant only in that it determines how accurately the city-specific relative risks were measured. (This limitation is also true for the ACS Study but has less impact because the number of cities is larger). Multiple regression analyses and the estimation of regression coefficients and standard errors cannot be justified with only six data points. Rather than estimate a regression coefficient for particulate effects together with standard errors based on the standard Cox model, the more appropriate approach would have been to calculate standardized mortality rate ratios for each city and to simply list them together with the other characteristics of the six cities. The Original Investigators of the Six Cities Study understood the limitations in their data set, which is why they called for and helped develop other studies such as the ACS Study.

ACS Study

The results of the ACS Study have been more central to the regulatory policy debates (eg, these findings have been used to estimate the number of premature deaths that would be avoided if further pollution controls were put into place). Because of the limitations inherent in the design of the Six Cities Study, the Reanalysis Team focused their alternative analytic approaches on the ACS Study data. The ACS Study data are also limited, however, because the subjects were friends, relatives, and neighbors of ACS Study volunteers and were not necessarily representative of the population in any given city. Figures 23a and 23b in Part II, which compare the ACS Study cohort to 1980 US Census data, show clearly that the ACS Study cohort was more highly educated and racially homogeneous (white) than the US population as a whole. Whether this sampling bias confounds or limits the ability to generalize the findings of these studies to the greater US population is not known.

ALTERNATIVE AIR QUALITY DATASET FOR SENSITIVITY ANALYSES

The Reanalysis Team constructed an alternative air quality data set to test the validity of the original air quality data in the ACS Study and to conduct analyses similar to those in the original study. Two points are important to consider in differentiating whether exposure biases existed from how the alternative fine particle and sulfate data were used. First, for the fine particle and sulfate cohorts, annual mortality data were obtained from 1982 through 1989; however, annual air quality data were obtained for only 1980 and 1981. In essence, air quality data collected during the two years before subjects were enrolled were used to represent subject exposures over the seven years of follow up. Both the Original Investigators and the Reanalysis Team were restricted in the sulfate data

they could include because sulfate monitoring was severely curtailed after 1981. The implications of this analytic limitation are not clear.

Second, the fine particle and sulfate measurements available from the IPMN and AIRS networks typically were taken every sixth day. At best, this system yields approximately 60 24-hour concentrations for a one-year period from each air sampling site. In the sensitivity analyses, the Reanalysis Team used data from any site that had yielded 20 or more observations in a year. Because fine particles and sulfate exhibit seasonal trends, those trends can only be captured by ensuring that an adequate number of samples are obtained for each season and that various seasons are evenly weighted in contributing to the annual averages. The Reanalysis Team did not evaluate the IPMN and AIRS data collected for each city to ensure that sufficient observations had been captured and adequately weighted to account for the seasonal variations in fine particle and sulfate mass.

Finally, establishing a scientifically sound correction for artifactual sulfate is difficult, and a case could be made for using correction equations specific to the city, site, or season. The Reanalysis Team considered these and other calibration equations. Any future use of either the original or reconstructed data sets should take into account both that the data sets contain artifactual sulfate and the difficulty in adjusting for this artifact.

MEASUREMENT ERROR

Typically, epidemiologic studies of the health effects of air pollutants rely on air quality data gathered by a monitor positioned in a fixed central site; the monitor may even be located near a known source of combustion air pollution (eg, a highway or factory). Thus, using data from a fixed-site monitor to evaluate the exposure level of a mobile human population can result in measurement error from assigning to each individual an exposure based on instruments some distance away.

This issue could not be addressed by the Reanalysis Team because the required information had not been collected; doing so would require personal exposure measurements, more numerous ambient monitors, or spatially interpolated ambient concentrations. In general, however, most exposure measurement errors produce estimates that are biased toward the null (ie, toward a relative risk of 1.0, or no increased risk)(Samet et al 2000). Thus measurement error alone would not be likely to produce a spurious association.

The Reanalysis Team investigated the possible impact on the findings of choosing the data from one monitor over those from another. (The Original Investigators of the ACS Study had chosen values from a single monitor when data from several montiors had been available). The Reanalysis Team did not find a large impact on the results by using the mean value of several available monitors. They also investigated the potential impact of using data from monitors that had been originally established to register the contributions of air pollutants from specific stationary or mobile sources. For the ACS Study sulfate data, the Reanalysis Team used only those monitors designated as residential or urban and excluded sites designated as industrial, agricultural, or mobile. Again, this analysis showed only slight alteration in the results.

CONCLUSIONS

The Reanalysis Team designed and implemented an extensive and sophisticated series of analyses that included a set of new variables, all the gaseous copollutants, and the first attempts to apply spatial analytic methods to test the validity of the data and the results from the Six Cities Study and the ACS Study. Overall, the reanalyses assured the quality of the original data, replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality.

At the same time, the reanalyses did extend and challenge our understanding of the original results in several important ways.

- The Reanalysis Team identified a possible modifying effect of education on the relation between air quality and mortality in that estimated mortality effects increased in the subgroup with less than high school education.
- The use of spatial analytic methods suggested that, when the analyses controlled for correlations among cities located near one another, the associations between mortality and fine particles or sulfate remained but were diminished.
- An association between sulfur dioxide and mortality was observed and persisted when other possible confounding variables were included; furthermore, when sulfur dioxide was included in models with fine particles or sulfate, the associations between these pollutants (fine particles and sulfate) and mortality diminished.

In reviewing these results, the Special Panel of the HEI Health Review Committee identified the following factors to consider when interpreting the results from the Reanalysis Team.

- The inherent limitations of using only six cities, understood by the Original Investigators, should be taken into account when interpreting results of the Six Cities Study.
- The Reanalysis Team did not use data adjusted for artifactual sulfate for most alternative analyses. When they did use adjusted sulfate data, relative risks of mortality from all causes and cardiopulmonary disease increased. This result suggests that more analyses with adjusted sulfate might result in somewhat higher relative risks associated with sulfate.
- Findings from spatial analyses applied to the ACS Study data need to be interpreted with caution; the spatial adjustment may have overadjusted the estimated effect for regional pollutants such as fine particles and sulfate compared with the effect estimates for more local pollutants such as sulfur dioxide.
- After the Reanalysis Team completed its spatial analyses, residual spatial variation was still noticeable; this finding suggests that additional studies might further refine our understanding of the spatial patterns in both air pollution and mortality.
- No single epidemiologic study can be the basis for determining a causal relation between air pollution and mortality.

In conclusion, the Reanalysis Team interpreted their findings to suggest that increased relative risk of "mortality may be attributed to more than one component of the complex mix of ambient air pollutants in urban areas in the United States". The Review Panel concurs. In the alternative analyses of the ACS Study cohort data, the Reanalysis Team identified relatively robust associations of mortality with fine particles, sulfate, and sulfur dioxide, and they tested these associations in nearly every possible manner within the limitations of the data sets. Future investigations of these issues will enhance our understanding of the effect of combustion-source air pollutants (eg, fine particles, sulfate, and sulfur dioxide) on public health.

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HEALTH
EFFECTS
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COMMENTS AND ORIGINAL ARTICLES

Original Investigators

Douglas W Dockery, C Arden Pope III, Frank E Speizer, and Michael J Thun

Harvard School of Public Health, Brigham Young University,
Harvard Medical School and Channing Laboratories, American Cancer Society

COMMENTS ON THE REANALYSIS PROJECT

Original Investigators: Douglas W Dockery, C Arden Pope III, Frank E Speizer, and Michael J Thun

As Original Investigators of the Harvard Six Cities Study and the American Cancer Society (ACS)* Study, we entered into the HEI Reanalysis Project with considerable trepidation. This project was a direct response to letters we received from the US Environmental Protection Agency (EPA) stating that the "EPA would encourage reasonable accommodations within the scientific and governmental community that would permit interested scientists and agencies to understand fully the basis for your work" (letters from Mary Nichols to Douglas Dockery and Arden Pope, January 31, 1997). We agreed to the HEI project as a way to provide this understanding in a credible fashion while assuring the confidentiality of the information provided by the study participants and the rights of the Original Investigators. We hoped that this project would provide a model for objective, structured, open, and sound evaluation of our studies that addressed both the scientific and public policy questions being raised. We entered into this project knowing neither who the analysts would be nor the composition of the Advisory Board, Expert Panel, or Special Panel of the HEI Health Review Committee. We also did not know the range or scope of the validation and reanalysis. Certainly we hoped that the process would be conducted with integrity, sound scientific judgement, and a constructive approach to reanalysis, but we had no guarantee that this would be so.

The result, reported here, was decidedly a thoughtful and constructive effort by skilled researchers, with guidance and oversight by the Expert Panel and Advisory Board, and with feedback from the Review Panel. The reanalysis was extensive. The researchers not only explored the reproducibility of the originally reported results but also fine-tuned the data, improving the analytic rigor and sophistication and adding interpretive insights. As Original Investigators, we have not fully agreed with all of the analyses that were conducted, nor do we fully agree with all of the Reanalysis Team's interpretations. Nevertheless, we consider this reanalysis to be a substantial contribution and are pleased to have been able to facilitate this effort by providing data, background information, and cooperation when needed.

CONTRIBUTIONS OF THE REANALYSIS

From our perspective, there are several important contributions of the reanalysis. It demonstrated that the original data were "generally of high quality" and that the basic numerical results presented in the original publications were reproducible. The careful data audit and validation efforts revealed some data and analytic problems that required additional fine tuning. However, the resulting corrections produced no substantial changes from the original risk estimates.

The reanalysis further demonstrated the robustness of the risk estimates to alternative model specifications. This point is illustrated in Figures 1 and 2. Relative risks of mortality are presented for many different model specifications in the reanalysis compared with the original published values (dashed line) for the Six Cities Study (Figure 1) and the ACS Study (Figures 2 through 4). The relative risks of mortality associated with exposure to air pollution were not sensitive to alternative modeling of tobacco consumption, education, body mass index, and other individually measured risk factors (Original versus Full and Extended models). The associations between exposure to fine particles and mortality in both studies were not affected by modeling age versus calender year or by alternative modeling for time-varying exposures or covariates. The Reanalysis Team developed new indicators of occupational exposure, but their extensive expert recoding and remodeling to control for occupational exposures did not significantly change the air pollution risk estimates. Similar risk estimates were obtained with random effects modeling.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

This is one section of an HEI Special Report that includes an HEI Statement about the research project, a Preface to the Particle Epidemiology Reanalysis Project, the Investigators' Report (Introduction, Summary, Part I, and Part II), a Commentary by the Institute's Health Review Committee, and the Original Articles and Comments on the Reanalysis Project by the Original Investigators. Correspondence concerning the Original Investigators' Comments on the Reanalysis Project may be addressed to Dr C Arden Pope III, Brigham Young University, 142 FOB, Provo UT 84602.

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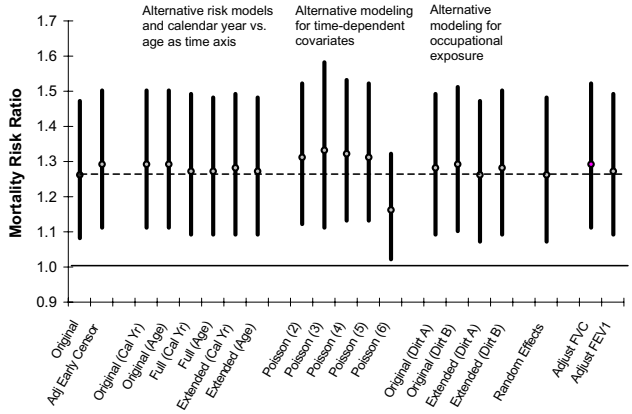

Figure 1. Estimated risk ratios for mortality from all causes calculated for each increase of 18.6 μg/m^3 in $PM_{2.5}$ in the Six Cities Study. Values reported in the original publication are represented by the dashed line; values (and 95% CIs) are shown for alternative models considered in the reanalyses. Labels on the x-axis refer to discriptions of models in the tabulated values from Part II of the Investigators' Report.

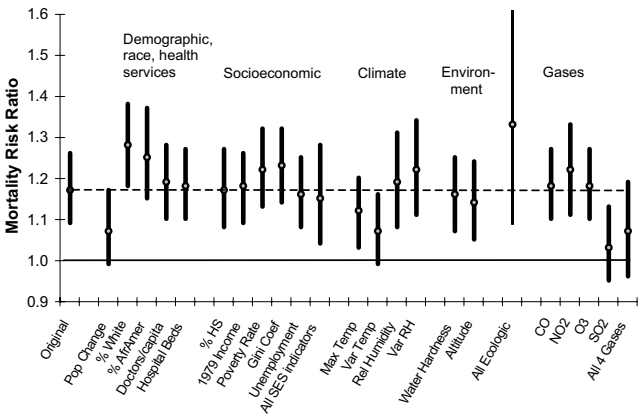

Figure 3. Estimated risk ratios for mortality from all causes in the ACS Study after inclusion of possible confounders in the reanalyses. Values reported in the original publication are represented by the dashed line; values (and 95% CIs) are shown for the Extended Model used in the reanalyses. Labels on the x-axis refer to specific ecologic covariates from Part II of the Investigators' Report.

Risk estimates were similarly robust to alternative modeling in both the Six Cities Study and the ACS Study. Because the ACS Study included a larger number of cities and represented a larger geographic area, however, its data were subjected to further analysis that incorporated a series of additional ecologic covariates and a set of models that allowed for alternative spatial analysis. As can be seen in Figure 3, the risk estimates were more sensitive to inclusion of ecologic covariates (especially copollutants such as sulfur dioxide, which is spatially correlated with fine particles and sulfate) and modeling of spatial variability. But even with these additional sensitivity challenges, we were impressed that the basic associations between measures of fine particles and mortality risk generally remained.

The apparent effect modifications of education (in both the Six Cities Study and the ACS Study) and stable residency (in the Six Cities Study) are interesting and important observations that had not been detected originally. Persons with higher educational attainment had a lower relative risk of mortality associated with exposure to fine particle air pollution, although the interpretation of this finding remains unclear. Nevertheless, the implication is that the ACS cohort, which over-represents relatively well-educated individuals, potentially underestimates the

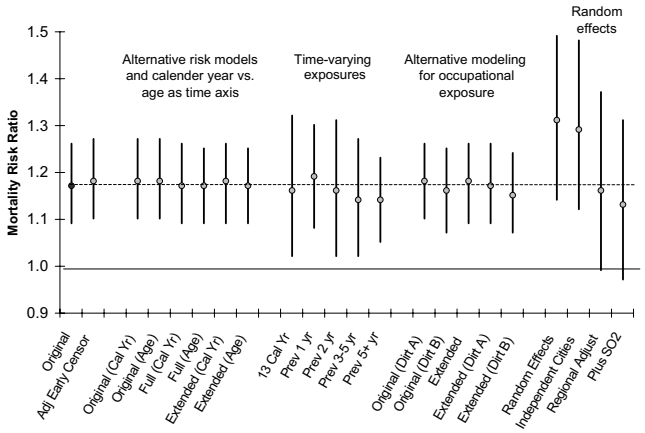

Figure 2. Estimated risk ratios for mortality from all causes calculated for each increase of 24.5 μg/m^3 in $PM_{2.5}$ in the ACS Study. Values reported in the original publication are represented by the dashed line; values (and 95% CIs) are shown for alternative models considered in the reanalyses. Labels on the x-axis refer to discriptions of models in the tabulated values from Part II of the Investigators' Report.

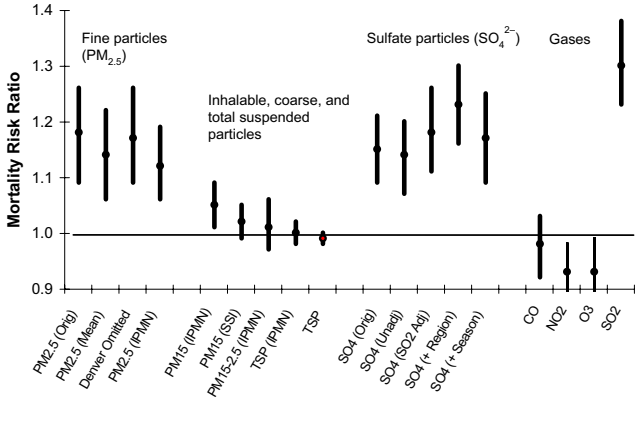

Figure 4. Estimated risk ratios for mortality from all causes calculated for the original fine particle and sulfate data used in the ACS Study and for the alternative fine particle, sulfate, particulate matter, and gaseous pollutant data used in the reanalyses.

overall risk of mortality associated with air pollution, compared with the Six Cities Study, which was by design a random sample of the population.

Some of the most impressive contributions of the reanalysis are the advances in statistical modeling—especially the random effects Cox proportional-hazards model. The different two-stage models, notably the spatial filtering models, are also innovative and reasonable applications. In the original analysis of the Six Cities Study, the Cox model was estimated with indicator variables for each city, but with only six cities we did not consider additional spatial analysis. In the original analysis of the ACS Study data, we wanted to estimate indicator variables for each city, which would have allowed for additional spatial analysis, but we could not do so because of computing constraints. We disagree with the interpretation of some of the results that accompany regional adjustments or spatial smoothing, but we cannot help but be impressed with the skillful development and application of these techniques.

The reanalysis provided interesting further investigation of other pollutants and measures of air quality. The Reanalysis Team found that the air quality data for the Six Cities Study were of high quality, and they obtained relative risk associations for the different pollutants that were nearly identical to those originally reported. Because they were unable to audit the air quality data from the ACS Study, the Reanalysis Team constructed their own alternative air quality dataset from basically the same original sources and collected data on various gaseous pollutants as well. The details are provided in the report; in Figure 4, we have summarized the associations between risks of mortality and exposure to various air pollutants using the ACS Study data. As can be seen, significant mortality associations existed for all of the measures of fine particles ($PM_{2.5}$) and sulfate. When PM_{15} was used as the measure of exposure, the mortality association was greatly attenuated. When the coarse particle fraction ($PM_{15-2.5}$) or total suspended particles (TSP) was used, there was no significant effect of air pollution on mortality. Exposure to the gaseous pollutants carbon monoxide, nitrogen oxide, and ozone was not associated with elevated mortality risk, but exposure to sulfur dioxide was strongly associated with mortality risk.

BASIC CONCERNS ABOUT THE REANALYSIS

Although we recognize many of the contributions, we also have concerns. From the very beginning of the reanalysis, we were opposed to the idea of taking a myriad of available ecologic variables and including them as covariates in the models. Much of this opposition was rooted in the basis of our original approach to dealing with the different strengths and limitations of the two studies. For example, the strengths of the Six Cities Study were related to its direct and relatively balanced study design, the planned prospective collection of study-specific air quality data, the specific hypotheses formulated a priori, and its ability to present some of the basic analytic results in an easy-to-understand graphical format. In contrast, the major strength of the ACS Study was the relatively large number of participants and cities. The ACS Study simply linked independently collected datasets and allowed us to further directly test the hypothesis generated in the Six Cities Study—that mortality is associated with exposure to combustion-source particulate air pollution. We considered the original work to be a straightforward, clean, elegant way to generate and test a specific well-defined hypothesis.

Much of the elegance has been lost in the reanalysis, which at times seemed not to be hypothesis-driven at all, but to be an attempt to bludgeon the data until they succumbed. In fairness, this was done very systematically and skillfully. Because of its small size, the Six Cities Study was spared the worst of the bludgeoning with ecologic covariates and spatial smoothing. Also in fairness, the reanalysis, by being somewhat selective with regard to the ecologic covariates used, showed reasonable restraint with the ACS Study data and was cautious in its interpretation of the regional controls and spatial smoothing results. We understand the motivation for the approach that was taken in the reanalysis; nonetheless, we think it went too far.

We understand the inappropriateness of estimating many alternative statistical models that use many combinations of often correlated variables while searching for a preferred result or a statistical explanation for a disavowed result. We know that the Reanalysis Team, Expert Panel, Advisory Board, and Review Panel also understand the inappropriateness of such an approach. But, of course, it is hard to know when to stop. A systematic and skillful estimation of dozens (maybe even hundreds) of alternative statistical models with different variables and combinations of variables, even when it is done in the name of sensitivity analyses, will ultimately produce spurious associations. For example, what statistical inferences can be drawn when twenty additional ecologic covariates, sometimes in combination, are sequentially added to the models? How do you interpret the finding that all but two covariates had little effect on the relative risks of mortality associated with fine particles and sulfate, and that one of those (sulfur dioxide) was a chemically related and highly correlated copollutant? On the basis of these results, can we conclude that the risk associated with exposure to fine particles or

sulfate was not due to confounding by water hardness, but was due to sulfur dioxide? What inferences can be drawn when a study is designed to take advantage of spatial variability and then we find that the results are sensitive to various ways to control for or smooth out spatial variability? What amazes us is not that the results began to become somewhat sensitive, but how robust they ultimately were.

We leave to society to judge whether this reanalysis was worth the approximately one million dollars it cost. Certainly, this process, as intended, has gone beyond traditional scientific peer review. We would argue that, because of the substantial costs and potentially fundamental changes in the way science is conducted and reviewed, this process should not be the norm. It should be undertaken only for unique situations in which very serious concerns are at issue and then only after careful consideration of added value.

CONCLUSION

On the basis of a wide variety of daily time-series studies conducted by ourselves and others, and our previously reported results of the Six Cities Study and the ACS Study, we had concluded that combustion-source air pollutants were important probable risk factors contributing to cardiopulmonary disease and mortality. In the Six Cities Study, we concluded "Although the effects of other, unmeasured risk factors cannot be excluded with certainty, these results suggest that fine-particulate pollution, or a more complex pollution mixture associated with fine particulate matter, contributes to excess mortality in certain US cities." Similarly, in the ACS Study, we concluded: "Increased mortality is associated with sulfate and fine particulate air pollution at levels commonly found in US cities. The increase in risk is not attributable to tobacco smoking, although other unmeasured correlates of pollution cannot be excluded with certainty."

The results of this extensive reanalysis not only support our original conclusions but strengthen them by adding confidence that the associations between excess mortality and exposure to fine particles and other combustion-related pollutants did not result from individual differences in age, sex, occupational exposure, body mass index, alcohol consumption, or smoking of tobacco—all potential confounders that we also considered, in alternative ways, in the original analyses.

The results of this reanalysis do not provide definitive answers regarding the confounding potential of various ecologic covariates. They add to the debate on the role of sulfur oxides (especially sulfur dioxide versus sulfate and other particles) and the role of education, and possibly other socioeconomic factors, as risk modifiers. However, given the size and richness of the datasets, the analytic complexity of the statistical model-building and estimation, and the enormous frequency with which investigators' judgments are required, we find remarkable concordance between our original results and those of the reanalysis.

ABOUT THE ORIGINAL INVESTIGATORS

Douglas W Dockery is professor of environmental epidemiology at Harvard School of Public Health and professor of epidemiology at Harvard Medical School. He earned his MS in meteorology from the Massachusetts Institute of Technology and his ScD in environmental health sciences from Harvard School of Public Health. His research interests focus on the health effects of air pollution, asthma, lead toxicity, and water quality.

C Arden Pope III is professor of economics at Brigham Young University. He received his PhD from Iowa State University where he studied economics and statistics. He has appointments at Iowa State and Texas A & M Universities and has been an IPH fellow in environmental health and public policy at Harvard School of Public Health. Dr Pope has conducted research dealing with a wide range of natural resource and environmental issues; his most recent research has focused on the health effects of air pollution.

Frank E Speizer is Edward H Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, and Department of Medicine, Brigham and Women's Hospital. He earned his medical degree at Stanford University Medical School in 1960. He also completed his undergraduate studies at Stanford University and in 1989 received an honorary master's degree from Harvard University. His major research interests include environmentally and occupationally related acute and chronic diseases, the natural history of chronic obstructive lung disease, and epidemiologic studies of risk factors for cancer, heart disease, and diabetes.

Michael J Thun is director of analytic epidemiology and vice president of epidemiology and surveillance research at the American Cancer Society. He earned his MD at the University of Pennsylvania School of Medicine and his MS in epidemiology at Harvard School of Public Health. His major research interests include cancer surveillance and the causes and prevention of cancer. He has written over 100 peer-reviewed publications and numerous books and has extensive teaching experience.

AN ASSOCIATION BETWEEN AIR POLLUTION AND MORTALITY IN SIX U.S. CITIES

DOUGLAS W. DOCKERY, SC.D., C. ARDEN POPE III, PH.D., XIPING XU, M.D., PH.D., JOHN D. SPENGLER, PH.D., JAMES H. WARE, PH.D., MARTHA E. FAY, M.P.H., BENJAMIN G. FERRIS, JR., M.D., AND FRANK E. SPEIZER, M.D.

Abstract *Background.* Recent studies have reported associations between particulate air pollution and daily mortality rates. Population-based, cross-sectional studies of metropolitan areas in the United States have also found associations between particulate air pollution and annual mortality rates, but these studies have been criticized, in part because they did not directly control for cigarette smoking and other health risks.

Methods. In this prospective cohort study, we estimated the effects of air pollution on mortality, while controlling for individual risk factors. Survival analysis, including Cox proportional-hazards regression modeling, was conducted with data from a 14-to-16-year mortality follow-up of 8111 adults in six U.S. cities.

Results. Mortality rates were most strongly associated with cigarette smoking. After adjusting for smoking and other risk factors, we observed statistically significant and robust associations between air pollution and mortality. The adjusted mortality-rate ratio for the most polluted of the cities as compared with the least polluted was 1.26 (95 percent confidence interval, 1.08 to 1.47). Air pollution was positively associated with death from lung cancer and cardiopulmonary disease but not with death from other causes considered together. Mortality was most strongly associated with air pollution with fine particulates, including sulfates.

Conclusions. Although the effects of other, unmeasured risk factors cannot be excluded with certainty, these results suggest that fine-particulate air pollution, or a more complex pollution mixture associated with fine particulate matter, contributes to excess mortality in certain U.S. cities. (N Engl J Med 1993;329:1753-9.)

SEVERAL cross-sectional investigations have found associations between mortality rates and particulate air pollution in U.S. metropolitan areas.[1-3] A recent study reported associations between infant mortality and particulate air pollution in the Czech Republic.[4] These studies have often been criticized because they did not control directly for cigarette smoking or other covariates. Recent daily time-series studies, which are likely to be free of confounding by individual characteristics, have reported associations between daily mortality rates and changes in air pollution, specifically particulate pollution, in London[5] and in several cities in the United States.[6-12]

Particulate air pollution is a mixture of solid particles and liquid droplets that vary in size, composition, and origin. Because only very small particles can be inhaled into the lungs, U.S. national health standards for the quality of ambient air are based on the mass concentration of "inhalable particles," defined to include particles with an aerodynamic diameter of less than 10 μm.[13] Fine-particulate air pollution includes particles with an aerodynamic diameter equal to or below 2.5 μm. Whereas larger particles are derived chiefly from soil and other crustal materials, fine particles are derived primarily from the combustion of fossil fuels in transportation, manufacturing, and power generation. Fine-particulate pollution typically contains a mixture of particles including soot, acid condensates, and sulfate and nitrate particles. Fine particles are thought to pose a particularly great risk to health because they are more likely to be toxic than larger particles and can be breathed more deeply into the lungs.[14]

In this study, a well-characterized cohort of adults participating in the Harvard Six Cities Study of the health effects of air pollution was followed prospectively, beginning in 1974.[15] The objective of this study

From the Environmental Epidemiology Program (D.W.D., C.A.P., X.X., M.E.F., B.G.F., F.E.S.), the Exposure Assessment and Engineering Program (J.D.S.), and the Interdisciplinary Program in Health (C.A.P.), Department of Environmental Health, and the Department of Biostatistics (J.H.W.), Harvard School of Public Health, Boston; the Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston (D.W.D., F.E.S.); and the Economics Department, Brigham Young University, Provo, Utah (C.A.P.). Address reprint requests to Dr. Dockery at the Environmental Epidemiology Program, Department of Environmental Health, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115.

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was to estimate the effects of air pollution on mortality, with control for individual smoking status, sex, age, and other risk factors.

Methods

Study Population

We selected random samples of adults from six communities[15]: Watertown, Massachusetts (where study enrollment was conducted in 1974); Harriman, Tennessee, including Kingston (1975); specific census tracts of St. Louis (1975); Steubenville, Ohio (1976); Portage, Wisconsin, including Wyocena and Pardeeville (1976); and Topeka, Kansas (1977). The sample was restricted to the 8111 white subjects who were 25 through 74 years of age at enrollment, had undergone spirometric testing, and had completed a standardized questionnaire. The questionnaire included questions about age, sex, weight, height, education level, complete smoking history, occupational exposures, and medical history.

Informational letters and postage-paid return postcards including a question on vital status were mailed to the subjects annually. The vital status of the subjects who did not respond was determined by questioning family members, friends, or neighbors. In addition, we searched the National Death Index[16] for the years 1979 through 1989. Death certificates were obtained for 1401 of the 1430 subjects who had died (98 percent); the causes of death were coded according to the *International Classification of Diseases, 9th Revision* (ICD-9) by an independent certified nosologist who was blinded both to pollution levels and to the study design and objectives. The ending date of the study for each city was March or June of 1991, depending on the date of the last follow-up contact; the total duration of follow-up was 14 to 16 years (111,076 person-years).

For subjects who died, survival times were calculated by subtracting the date of enrollment from the exact date of death. For surviving participants who were not lost to follow-up, censored survival times were defined as the date of the end of the study minus the enrollment date. For those who were lost to follow-up before the period covered by our National Death Index search (i.e., before 1979), censored survival times were estimated by subtracting the enrollment date either from the date of the last follow-up contact plus six months or from the first day of the National Death Index search period (January 1, 1979), whichever came first. For those who were lost to follow-up after the National Death Index search period (i.e., after 1989), censored survival times were estimated by subtracting the enrollment date either from the date of the last follow-up contact plus six months or from the last day of the study period, whichever came first. For those who were lost to follow-up during the period covered by the National Death Index search, the censored survival times were estimated by subtracting the date of enrollment from the last date in the search period (December 31, 1989).

Air-Pollution Data

As part of the original study design, ambient (outdoor) concentrations of total suspended particulate matter, sulfur dioxide, ozone, and suspended sulfates were measured in each community at a centrally located air-monitoring station.[15] Size-selective aerosol samplers were placed at these sites in the late 1970s; data were collected for two classes of particle: fine particles (aerodynamic diameter <2.5 μm) and inhalable particles (aerodynamic diameter, <15 μm before 1984 and <10 μm starting in 1984). In the mid-1980s, supplemental 24-hour integrated sampling of aerosol acidity by the measurement of hydrogen ion concentrations[17] was conducted for approximately one year in each city. Mean pollution levels for each pollutant were calculated for periods that were consistent and comparable among the six cities.

Statistical Analysis

Life-table survival probabilities for each year of follow-up were estimated for each city, and differences between city-specific mortality rates were assessed with a log-rank test.[18] We estimated adjusted mortality-rate ratios for air pollution by simultaneously adjusting for other risk factors in Cox proportional-hazards regression models.[18-22] In these models the subjects were stratified according to sex and five-year age groups, and each sex–age group had its own baseline hazard. Each model also included indicator variables for current or former smokers, the number of pack-years of smoking (evaluated separately for current and former smokers), an indicator variable for less than a high-school education, and body-mass index (defined as the weight in kilograms divided by the square of the height in meters).

Two approaches were used to evaluate the effects of air pollution in the Cox proportional-hazards models. First, indicator variables for the city of residence were included, with Portage, Wisconsin, the city with the lowest levels of particulate air pollution, as the reference category. Adjusted mortality-rate ratios for each of the six cities were then compared graphically with the mean pollution levels in those cities. Next, adjusted mortality-rate ratios were estimated by including city-specific pollution levels directly in the Cox proportional-hazards models. Adjusted rate ratios were calculated and reported for a difference in air pollution equal to that between the city with the highest levels of air pollution and the city with the lowest levels — that is, the adjusted rate ratios across the range of exposure for each pollutant among the six cities.

Analyses were conducted to evaluate the robustness of the models and the possibility of residual confounding. Models were estimated after the data were separated according to the subjects' smoking status, sex, and occupational exposure to dust, gases, or fumes. The effect of the inclusion of different covariates on the estimated effect of pollution was evaluated. Models were also estimated after the exclusion of subjects who had been treated for high blood pressure within 10 years of enrollment in the study and subjects who had ever been told by a doctor that they had diabetes, had glucose in their urine, or had too much glucose in their blood. We also used a variety of approaches to estimate censored survival times.

Mortality-rate ratios from the Cox proportional-hazards models (with adjustment for cigarette smoking, education, and body-mass index) were estimated separately for the following cause-of-death categories: cardiopulmonary (ICD-9 codes 400 through 440 and 485 through 496), lung cancer (162), and all others. For each cause-of-death category, data on subjects whose deaths were not in that specific category were censored at the time of death.

Results

Characteristics of the Cohort and Air-Pollution Data

The characteristics of the cohort and the values for air-pollution measures are summarized in Table 1. For all measures of air pollution except the ozone level and aerosol acidity, ambient concentrations were highest in Steubenville and lowest in Portage or Topeka. The mean acidity of the aerosol was highest in Harriman, but second-highest in Steubenville. The mean ozone concentrations were highest in Portage and Topeka. The concentrations of total particles declined during the study period, especially in Steubenville and St. Louis; the annual average concentrations of fine and sulfate particles varied relatively little during the study period (Fig. 1). Crude mortality rates (Table 1) and survival curves (Fig. 2) both show that mortality was highest in Steubenville and St. Louis and lowest in Portage and Topeka. Differences in the probability of survival among the cities were statistically significant ($P<0.001$).

Adjusted Mortality Rates

On the basis of the proportional-hazards model, mortality was most strongly associated with cigarette smoking (Table 2). Increased mortality was also associated with having less than a high-school educa-

Table 1. Characteristics of the Study Population and Mean Air-Pollution Levels in Six Cities.*

Characteristic	Portage, Wis.	Topeka, Kans.	Watertown, Mass.	Harriman, Tenn.	St. Louis	Steubenville, Ohio
No. of participants	1,631	1,239	1,336	1,258	1,296	1,351
Person-years of follow-up	21,618	16,111	19,882	17,836	17,715	17,914
No. of deaths	232	156	248	222	281	291
Deaths/1000 person-years	10.73	9.68	12.47	12.45	15.86	16.24
Female sex (%)	52	56	56	54	55	56
Smokers (%)	36	33	40	37	35	35
Former smokers (%)	24	25	25	21	24	23
Average pack-years of smoking						
Current smokers	24.0	25.6	25.2	24.5	30.9	28.0
Former smokers	18.0	19.7	21.8	21.1	22.0	25.0
Less than high-school education (%)	25	12	22	35	45	30
Average age (yr)	48.4	48.3	48.5	49.4	51.8	51.6
Average body-mass index	26.3	25.3	25.5	25.1	26.0	26.4
Job exposure to dust or fumes (%)	53	28	38	50	40	48
Total particles ($\mu g/m^3$)	34.1	56.6	49.2	49.4	72.5	89.9
Inhalable particles ($\mu g/m^3$)	18.2	26.4	24.2	32.5	31.4	46.5
Fine particles ($\mu g/m^3$)	11.0	12.5	14.9	20.8	19.0	29.6
Sulfate particles ($\mu g/m^3$)	5.3	4.8	6.5	8.1	8.1	12.8
Aerosol acidity ($nmol/m^3$)	10.5	11.6	20.3	36.1	10.3	25.2
Sulfur dioxide (ppb)	4.2	1.6	9.3	4.8	14.1	24.0
Nitrogen dioxide (ppb)	6.1	10.6	18.1	14.1	19.7	21.9
Ozone (ppb)	28.0	27.6	19.7	20.7	20.9	22.3

*Air-pollution values were measured in the following years: total particles, sulfur dioxide, nitrogen dioxide, and ozone, 1977 through 1985; inhalable and fine particles, 1979 through 1985; sulfate particles, 1979 through 1984; and aerosol acidity, 1985 through 1988.

tion and with increased body-mass index (the latter was especially true for women). After simultaneous adjustment for these other risk factors, the differences in mortality among the six cities remained significant.

City-specific mortality rates, adjusted for a variety of health risk factors, were associated with the average levels of air pollutants in the cities (Fig. 3). The small differences in ozone levels among the cities (Table 1) limited the power of the study to detect associations between mortality and ozone levels. Mortality was more strongly associated with the levels of inhalable, fine, and sulfate particles than with the levels of total suspended particles, the sulfur dioxide levels, the nitrogen dioxide levels, or the acidity of the aerosol.

When the mean concentrations of each pollutant were included individually in the proportional-hazards model, we found significant associations between mortality and inhalable, fine, or sulfate particles ($P<0.005$). For a difference in the air-pollution level equal to that between the most polluted city and the least polluted city and with inhalable particles (range, 18.2 to 46.5 μg per cubic meter), fine particles (range, 11.0 to 29.6 μg per cubic meter), and sulfate particles (range, 4.8 to 12.8 μg per cubic meter) used as indicators of air pollution, the adjusted rate ratios were nearly equal at 1.27 (95 percent confidence interval, 1.08 to 1.48), 1.26 (95 percent confidence interval, 1.08 to 1.47), and 1.26 (95 percent confidence interval, 1.08 to 1.47), respectively.

Sensitivity

Estimates of the association between mortality and fine-particle pollution among subjects with different smoking status and among men and women (Table 3) showed only small and nonsignificant differences between subgroups. Associations with air pollution were somewhat stronger among subjects with occupational exposure to dust, gases, or fumes (Table 3). However, positive associations between mortality and air-pollution levels were observed in all subgroups defined by occupational exposure and sex, and differences among the subgroups were not statistically significant.

Although cigarette smoking and other risk factors were associated with mortality, our estimates of pollution-related mortality were not significantly affected by the inclusion or exclusion of these variables in the models (Table 4). The estimated association of air pollution and mortality was unchanged when subjects who had been treated for high blood pressure or subjects with diabetes were excluded from the analysis (Table 4). When censored survival times were recalculated as the date of the last follow-up contact minus the enrollment date, or when the analysis was restricted to data on deaths in 1979 through 1989 (the years of the National Death Index searches), no appreciable differences in the estimated association between air pollution and mortality were observed.

Causes of Death

The estimated effects of air pollution on mortality varied among causes of death (Table 5). For comparison, rate ratios were estimated for current smokers and for former smokers with approximately the average number of pack-years of smoking at enrollment (Table 5). Smoking was most strongly associated with mortality due to lung cancer, significantly associated with mortality due to cardiopulmonary disease, but not associated with mortality from all other causes. Similarly, air pollution was positively associated with mortality due to lung cancer and cardiopulmonary disease but not with mortality from all other causes. Only 98 deaths were coded on the death certificates as due to nonmalignant respiratory disease (ICD-9 codes 485 through 496), as compared with 646 deaths due to cardiovascular disease (codes 400 through 440). An analysis restricted to deaths from nonmalignant respi-

ratory disease produced unstable and statistically nonsignificant estimates of the association with air pollution. When mortality from all causes was considered, or when deaths due to cardiovascular and respiratory diseases were grouped together, the effects of air pollution were consistent and the association was robust.

Discussion

In this prospective cohort study, the mortality rate, adjusted for other health risk factors, was associated with the level of air pollution. Mortality was more strongly associated with the levels of fine, inhalable,

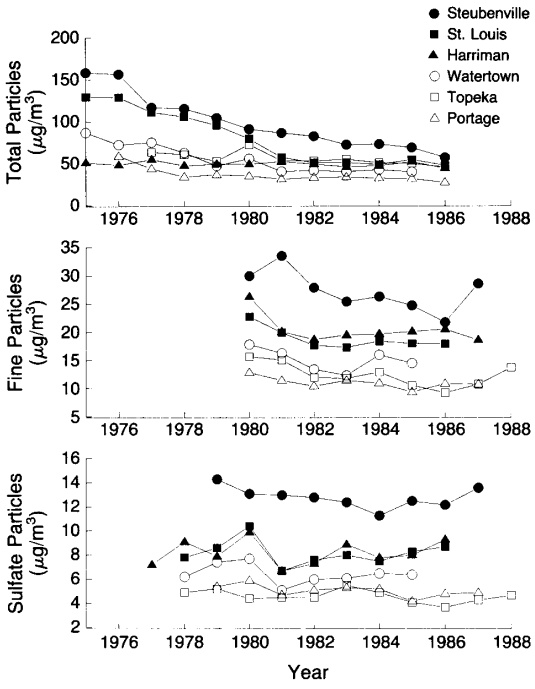

Figure 1. Annual Average Concentrations of Total Particles, Fine Particles, and Sulfate Particles in the Six Cities.

and sulfate particles than with the levels of total particulate pollution, aerosol acidity, sulfur dioxide, or nitrogen dioxide. As with all other epidemiologic studies, it is possible that the observed association was due to confounding — that is, that it resulted from a risk factor that was correlated with both exposure and mortality. Potential confounders of the effects of air pollution include cigarette smoking and occupational exposure to pollutants. In our study, however, the association of air pollution with mortality was observed even after we directly controlled for individual differences in other risk factors, including age, sex, cigarette smoking, education level, body-mass index, and occupational exposure.

The estimated effect of air pollution on mortality was not altered by the inclusion or exclusion of indica-

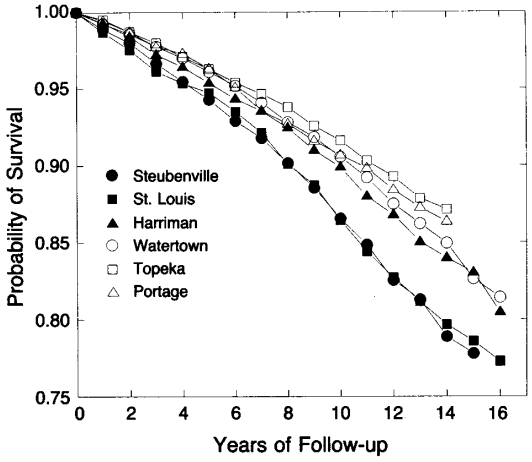

Figure 2. Crude Probability of Survival in the Six Cities, According to Years of Follow-up.

tor variables for other risk factors in our models. Analyses were conducted for subgroups defined according to sex, smoking status, and occupational exposure. Although the effects of pollution were somewhat stronger among subjects occupationally exposed to dust, gases, or fumes, positive associations between mortality and air pollution were observed among all the smoking-status, occupational-exposure, and sex groups, and the differences among these subgroups were not statistically significant. The estimated association of pollution and mortality remained essentially unchanged when subjects who had been treated for high blood pressure or who had diabetes were excluded from the analysis.

In our analysis, the mortality-rate ratios have been expressed in terms of the range of exposure to air pollutants in the six cities. When the range of expo-

Table 2. Adjusted Mortality-Rate Ratios Estimated from Cox Proportional-Hazards Models.*

Variable	All Subjects	Men	Women
	rate ratio (95% CI)		
Current smoker	1.59 (1.31–1.92)	1.75 (1.32–2.32)	1.54 (1.16–2.04)
25 Pack-years of smoking	1.26 (1.16–1.38)	1.25 (1.12–1.39)	1.18 (1.00–1.41)
Former smoker	1.20 (1.01–1.43)	1.17 (0.93–1.48)	1.34 (1.02–1.77)
10 Pack-years of smoking	1.15 (1.08–1.23)	1.16 (1.09–1.25)	1.15 (0.97–1.36)
Less than high-school education	1.19 (1.06–1.33)	1.22 (1.06–1.41)	1.13 (0.95–1.35)
Body-mass index	1.08 (1.02–1.14)	1.03 (0.95–1.12)	1.11 (1.03–1.20)
City			
Portage, Wis.†	1.00 (—)	1.00 (—)	1.00 (—)
Topeka, Kans.	1.01 (0.82–1.24)	1.04 (0.79–1.36)	0.97 (0.71–1.34)
Harriman, Tenn.	1.17 (0.97–1.41)	1.21 (0.96–1.54)	1.07 (0.79–1.45)
Watertown, Mass.	1.07 (0.89–1.28)	0.94 (0.73–1.20)	1.22 (0.93–1.61)
St. Louis	1.14 (0.96–1.36)	1.15 (0.91–1.44)	1.13 (0.86–1.50)
Steubenville, Ohio	1.26 (1.06–1.50)	1.29 (1.03–1.62)	1.23 (0.93–1.61)

*Rates have been adjusted for age, sex, and all other variables listed in the table. The rate ratios for body-mass index are for an increase of 4.52 (1 SD). CI denotes confidence interval.

†City-specific rate ratios are all expressed in relation to Portage.

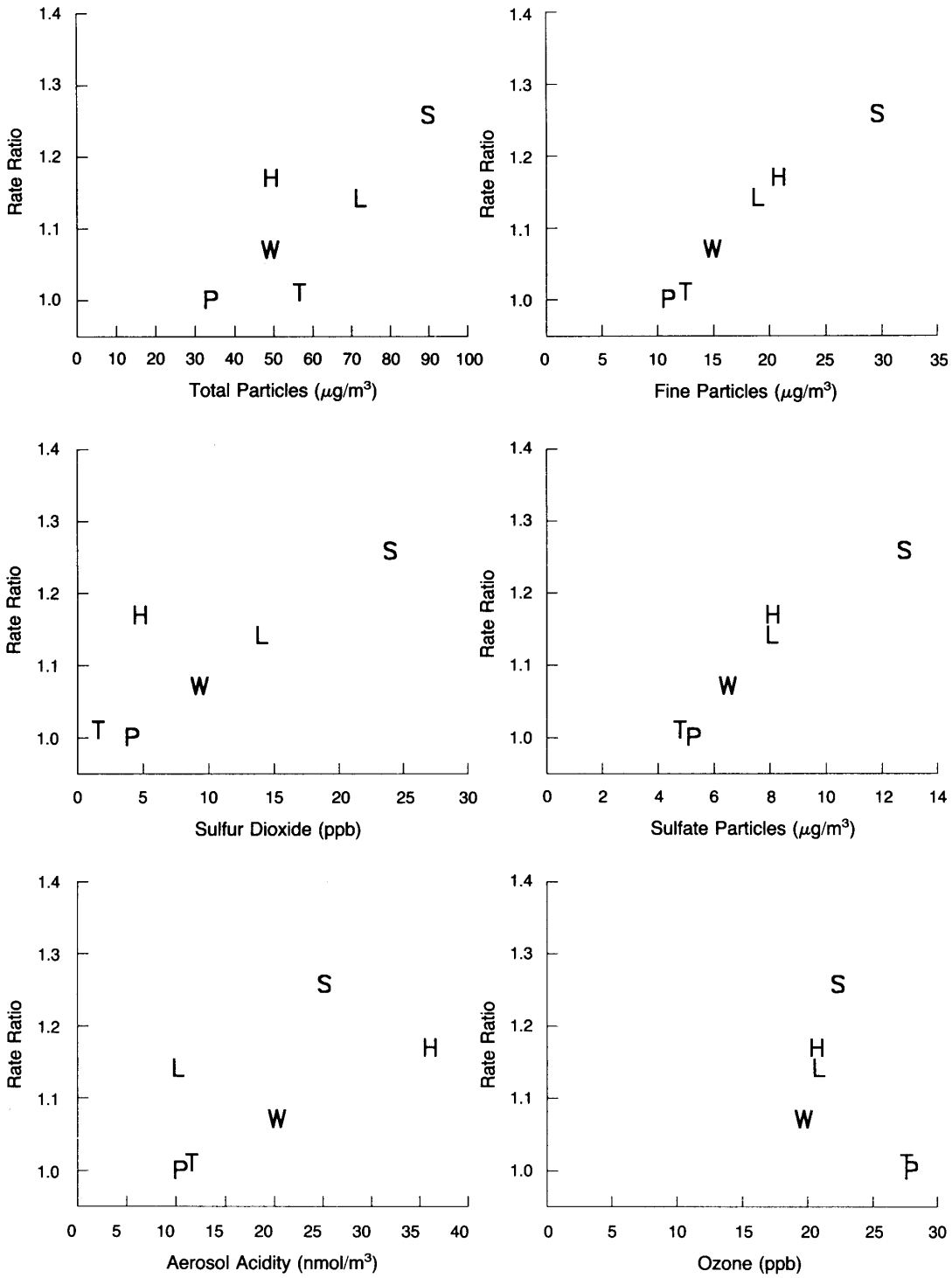

Figure 3. Estimated Adjusted Mortality-Rate Ratios and Pollution Levels in the Six Cities.
Mean values are shown for the measures of air pollution. P denotes Portage, Wisconsin; T Topeka, Kansas; W Watertown, Massachusetts; L St. Louis; H Harriman, Tennessee; and S Steubenville, Ohio.

Table 3. Adjusted Mortality-Rate Ratios for the Most Polluted and Least Polluted Cities Studied, According to Smoking Status, Sex, and Occupational Exposure, with Fine Particles Used as the Indicator of Air Pollution.*

Group of Subjects	No. of Subjects	No. of Deaths	Rate Ratio (95% CI)†
All	8096	1429	1.26 (1.08–1.47)
Nonsmokers	3266	431	1.19 (0.90–1.57)
Women	2280	292	1.15 (0.82–1.62)
Men	986	139	1.29 (0.80–2.09)
Former smokers	1934	432	1.35 (1.02–1.77)
Women	670	106	1.48 (0.82–2.66)
Men	1264	326	1.31 (0.96–1.80)
Current smokers	2896	566	1.32 (1.04–1.68)
Women	1478	201	1.23 (0.83–1.83)
Men	1418	365	1.42 (1.05–1.92)
No occupational exposure‡	4455	686	1.17 (0.93–1.47)
Women	3151	417	1.13 (0.85–1.50)
Men	1304	269	1.27 (0.85–1.92)
Occupational exposure‡	3641	743	1.35 (1.10–1.65)
Women	1277	182	1.32 (0.86–1.50)
Men	2364	561	1.35 (1.07–1.69)

*The city with the highest level of fine-particulate air pollution was Steubenville, Ohio, and that with the lowest was Portage, Wisconsin. Rates have been adjusted for age, sex, smoking, education, and body-mass index. Fifteen subjects were excluded because of missing data on weight.

†CI denotes confidence interval.

‡To gases, fumes, or dust.

Table 4. Estimated Mortality-Rate Ratios for the Most Polluted City as Compared with the Least Polluted City, with Fine Particles Used as the Indicator of Air Pollution, in Selected Models.*

Model No.	Variables Included†	Rate Ratio (95% CI)‡
1	Fine particles	1.31 (1.13–1.52)
2	Model 1 + all smoking variables	1.29 (1.11–1.49)
3	Model 2 + high-school education	1.26 (1.08–1.47)
4	Model 3 + body-mass index	1.26 (1.08–1.47)
5	Model 4 + occupational exposure	1.26 (1.08–1.46)
6	Model 5, excluding 1439 subjects with hypertension	1.25 (1.04–1.50)
7	Model 5, excluding 561 subjects with diabetes	1.29 (1.09–1.52)

*The city with the highest level of fine-particulate air pollution was Steubenville, Ohio, and that with the lowest was Portage, Wisconsin. In addition to the variables specified, rates have been adjusted for age and sex.

†Subjects with hypertension were those who had been treated for high blood pressure within 10 years before enrollment; subjects with diabetes were those who had ever been told by a doctor that they had diabetes, had glucose in their urine, or had too much glucose in their blood.

‡CI denotes confidence interval.

Table 5. Adjusted Mortality-Rate Ratios for Current and Former Cigarette Smokers and for the Most Polluted City as Compared with the Least Polluted, According to Cause of Death.*

Cause of Death	Percentage of Total	Current Smokers†	Former Smokers‡	Most vs. Least Polluted City
		rate ratio (95% CI)		
All	100	2.00 (1.51–2.65)	1.39 (1.10–1.75)	1.26 (1.08–1.47)
Lung cancer	8.4	8.00 (2.97–21.6)	2.54 (0.90–7.18)	1.37 (0.81–2.31)
Cardiopulmonary disease	53.1	2.30 (1.56–3.41)	1.52 (1.10–2.10)	1.37 (1.11–1.68)
All others	38.5	1.46 (0.89–2.39)	1.17 (0.80–1.73)	1.01 (0.79–1.30)

*The city with the highest level of air pollution (indicated by the level of fine particles) was Steubenville, Ohio, and that with the lowest was Portage, Wisconsin. CI denotes confidence interval. Rates have been adjusted for age, sex, smoking, education, and body-mass index.

†The risk of death for a current smoker with approximately the average number of pack-years of smoking at enrollment (25 pack-years), as compared with that for a nonsmoker.

‡The risk of death for a former smoker with approximately the average number of pack-years of smoking at enrollment (20 pack-years), as compared with that for a nonsmoker.

sure was used, the estimated relative rate ratios for inhalable, fine, and sulfate particles were nearly equal at 1.27 (95 percent confidence interval, 1.08 to 1.48), 1.26 (95 percent confidence interval, 1.08 to 1.47), and 1.26 (95 percent confidence interval, 1.08 to 1.47), respectively. Because the six cities were selected as representative of the range of particulate air pollution in the United States, these rate ratios roughly represent the relative risk associated with that range.

In this study, exposure to air pollution was estimated by monitoring outdoor air pollution at a central site in each of the six cities. Long-term transport and large-scale mixing of combustion products play a large part in establishing the levels of sulfate and fine-particulate air pollution. Therefore, concentrations of sulfates and fine particles are relatively uniform within each of these communities.[23] Furthermore, sulfate and fine-particulate air pollution penetrates indoors, resulting in strong correlations between indoor and outdoor concentrations.[24-26] Thus, measurements of the outdoor concentrations of sulfate and fine particles may be better indicators of individual exposure than the other pollutants we considered.

The associations observed in this study between air pollution and mortality are consistent with associations observed in recent time-series studies, including studies from three of these six cities.[5-12] Because the daily time-series studies evaluated only the effect of short-term changes in pollution levels, whereas our study evaluated associations with long-term exposure (including recurring episodes of relatively high pollution), quantitative comparisons with these investigations are difficult to make. Nevertheless, as was found in the time-series studies, particulate air pollution was associated with death due to cardiopulmonary causes. In our study, in which we evaluated the effects of long-term exposure, lung cancer was associated with particulate air pollution; such an association with lung cancer was not observed in the daily time-series studies. Little or no association with other causes of death was evident in our study or the time-series studies. The small number of reported deaths due to nonmalignant respiratory disease and the potential for misclassification of primary causes inherent in the use of death-certificate data limited our ability to evaluate cause-specific mortality in more detail.

The pollution concentrations used in our analysis represent only exposures monitored during the study period. Increased mortality, however, may reflect the cumulative burden of a lifetime of exposure. Concentrations of total particles clearly declined during the study period (especially in Steubenville and St. Louis), whereas concentrations of fine particles and sulfate particles were relatively stable. Given the lack of data on pollution levels before the study period and in view of the fact that the relative

ranking of the cities in terms of air-pollution levels did not change during the study period, it is not possible to differentiate the influences of historical exposure from those of recent exposure. The observed association between mortality and mean exposure to fine-particulate and sulfate air pollution during the study period may also partially reflect exposure to air pollution before the study period.

The strength of the observed association between air pollution and mortality is confirmed by previous observations of associations between particulate air pollution and other health end points. Elevated levels of particulate air pollution have been associated with declines in lung function or with increases in respiratory symptoms such as cough, shortness of breath, wheezing, and asthma attacks.[27-36] Other studies have found associations between particulate air pollution and rates of hospitalization,[37-41] chronic obstructive pulmonary disease,[42] and restricted activity due to illness.[43,44]

A large and growing body of literature documents the adverse health effects associated with particulate air pollution. Although the effects of unmeasured risk factors cannot be controlled for, in this prospective cohort study we observed significant effects of air pollution on mortality even when we controlled for sex, age, smoking status, education level, and occupational exposure to dust, gases, and fumes. The compatibility of the effects of air pollution on mortality in this study with those observed in population-based cross-sectional studies and daily time-series studies provides further evidence for the conclusion that exposure to air pollution contributes to excess mortality. This study, therefore, provides additional impetus to the development of strategies to reduce urban air pollution.

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Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults

C. ARDEN POPE, III, MICHAEL J. THUN, MOHAN M. NAMBOODIRI, DOUGLAS W. DOCKERY, JOHN S. EVANS, FRANK E. SPEIZER, and CLARK W. HEATH, JR.

Environmental Epidemiology Program and Interdisciplinary Program in Health, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts; Department of Epidemiology and Statistics, American Cancer Society, Atlanta, Georgia; and The Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Time-series, cross-sectional, and prospective cohort studies have observed associations between mortality and particulate air pollution but have been limited by ecologic design or small number of subjects or study areas. The present study evaluates effects of particulate air pollution on mortality using data from a large cohort drawn from many study areas. We linked ambient air pollution data from 151 U.S. metropolitan areas in 1980 with individual risk factor on 552,138 adults who resided in these areas when enrolled in a prospective study in 1982. Deaths were ascertained through December, 1989. Exposure to sulfate and fine particulate air pollution, which is primarily from fossil fuel combustion, was estimated from national data bases. The relationships of air pollution to all-cause, lung cancer, and cardiopulmonary mortality was examined using multivariate analysis which controlled for smoking, education, and other risk factors. Although small compared with cigarette smoking, an association between mortality and particulate air pollution was observed. Adjusted relative risk ratios (and 95% confidence intervals) of all-cause mortality for the most polluted areas compared with the least polluted equaled 1.15 (1.09 to 1.22) and 1.17 (1.09 to 1.26) when using sulfate and fine particulate measures respectively. Particulate air pollution was associated with cardiopulmonary and lung cancer mortality but not with mortality due to other causes. Increased mortality is associated with sulfate and fine particulate air pollution at levels commonly found in U.S. cities. The increase in risk is not attributable to tobacco smoking, although other unmeasured correlates of pollution cannot be excluded with certainty. **Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath Jr CW. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 1995;151:669–74.**

Many studies have observed associations between particulate air pollution and human health (1). Increases in sickness and death associated with severe air pollution episodes have been well documented. Recent daily time-series studies have observed associations between daily mortality and changes in particulate air pollution (2–6) at levels below U.S. air quality standards. Elevated particulate air pollution has been associated with declines in lung function (6–9), increases in respiratory symptoms (6, 8–11), increases in respiratory hospitalizations (6, 12–13), and restricted activity (14, 15).

Ecologic cross-sectional studies have reported associations between mortality rates and sulfate or fine particulate pollution levels across metropolitan areas (16–19). Mortality risks of air pollution have also been estimated using data from a 14 to 16 year prospective follow-up of over 8,000 adults living in six U.S. cities (20) which controlled for individual differences in age, sex, cigarette smoking, and other factors. In both the ecologic studies and the recent prospective cohort study, mortality was more strongly associated with sulfate or fine particulate air pollution than with other measures of air pollution.

Particulate air pollution is a mixture of particles that vary in size, composition, and origin. Fine particles (those with aerodynamic diameters equal to or less than 2.5 μm) are the largest health concern because they can be breathed most deeply into the lung. This size range includes most sulfate particles (which generally make up the largest fraction of fine particles by mass). Unlike larger particles which are derived primarily from soil and other crustal materials, fine particles (including sulfates) are derived chiefly from combustion of fossil fuels in processes such as transportation, manufacturing, and power generation. Sulfate particles are commonly generated by conversion from primary sulfur emissions and a varying portion of sulfate particles may be acidic.

Previous studies of particulate pollution and mortality have been limited by ecologic design or small number of subjects or study areas. In the present study, a large cohort of adults living in 151 U.S. metropolitan areas was followed prospectively between 1982 and 1989. Ambient concentrations of sulfates and fine particles were used as indices of exposure to combustion source ambient particulate air pollution. Exposure to ambient air pollution was estimated from national data bases. Associations between

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Correspondence and requests for reprints should be addressed to C. Arden Pope, III, Department of Economics, Brigham Young University, 130 FOB, Provo, UT 84602.

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mortality and particulate pollution were evaluated at pollution levels common to many U.S. metropolitan areas while directly adjusting for individual differences in smoking status, gender, age, education, and other risk factors.

METHODS

Study Population

This analysis relied on data for 552,138 men and women drawn from the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II), an ongoing prospective mortality study of approximately 1.2 million adults (21). Participants were enrolled by ACS volunteers in the fall of 1982. They resided in all 50 states, the District of Columbia, and Puerto Rico, and were usually friends, neighbors, or acquaintances of the ACS volunteers. Enrollment was restricted to persons who were at least 30 yr of age and who were members of households with at least one individual 45 yr of age or more. Participants completed a confidential questionnaire which included questions about age, sex, weight, height, demographic characteristics, smoking history, alcohol use, occupational exposures, and other characteristics.

Vital status of participants was assessed from September 1, 1982 to December 31, 1989 using two approaches. First, vital status was determined by personal inquiries by the volunteers in September of 1984, 1986, and 1988. Second, automated linkage using the National Death Index (22) was used to extend vital status follow-up through December 31, 1989 and to identify deaths among the approximately 2% of participants who were lost to follow-up between 1982 and 1988. Death certificates were obtained for approximately 96% of deaths. A nosologist coded cause-of-death according to the International Classification of Diseases, 9th revision (ICD-9) (23), without knowledge of pollution levels. The analytic cohort used in this analysis included all CPS-II participants who provided complete questionnaire data on other risk factors evaluated, whose death certificates were obtained, and who resided in U.S. metropolitan areas within the 48 contiguous states (including the District of Columbia) that had available pollution data. Cohort characteristics are summarized in Table 1.

TABLE 1

SUMMARY CHARACTERISTICS OF SUBJECTS IN BASELINE ANALYTIC COHORT DERIVED FROM THE ACS, CPS-II STUDY COHORT, 1982–1989

Characteristics	Analysis with Sulfate Particles	Analysis with Fine Particles
Number of metropolitan areas	151	50
Number of subjects	552,138	295,223
Number of deaths	38,963	20,765
Age at enrollment, mean	56.5	56.6
Sex, % Female	56.0	55.9
Race, % White	94.2	94.0
Black	4.1	4.1
Other	1.7	1.9
Current cigarette smoker, %	22.0	21.6
Cigarettes/day, mean	22.0	22.1
Years smoked, mean	33.5	33.5
Former cigarette smoker, %	29.1	29.4
Cigarettes/day, mean	22.0	22.0
Years smoked, mean	22.3	22.2
Pipe/cigar smoker only, %	4.1	3.9
Passive smoke, hours/day, mean	3.2	3.2
Occupational exposure, %	20.0	19.5
Less than high school education, %	12.3	11.3
BMI, mean	25.1	25.0
Alcohol, drinks/day, mean	1.0	1.0
Sulfate particles, $\mu g/m^3$, mean (Standard deviation)	11.0 (3.6)	–
Sulfate particles, $\mu g/m^3$, range	3.6–23.5	–
Fine particles, $\mu g/m^3$, mean (Standard deviation)	–	18.2 (5.1)
Fine particles, $\mu g/m^3$, range	–	9.0–33.5

Air Pollution Exposure Estimates

Based on participant addresses at time of entry into the study and 3-digit zip code areas (24), each participant was assigned a metropolitan area of residence. Smoking status and other individual risk factors were assessed at the time of entry into the cohort. Pollution exposure also was assessed for a time period just prior to entry into the cohort.

Two indices of exposures to combustion source particulate air pollution were used. The first was mean concentration of sulfate air pollution for 1980 in the participant's area of residence based on data from the U.S. Environmental Protection Agency's (EPA) National Aerometric Data Base. Means were calculated as the average of annual arithmetic mean 24-h sulfate values for all monitoring sites in the Standard Metropolitan Statistical Areas or, in New England, New England County Metropolitan Areas that corresponded with defined areas of residence. Across the 151 metropolitan areas with matching data, mean sulfate concentrations averaged 11 $\mu g/m^3$ and ranged from 3.6 to 23.5 $\mu g/m^3$.

The second index of exposure to combustion source particulate air pollution was median fine particulate concentration for 1979 to 1983 calculated from the EPA dichotomous sampler network by Lipfert and coworkers in a population-based cross-sectional analysis of mortality across U.S. cities (17). There were 50 metropolitan areas with matching data that could be analyzed using this pollution measure. Across these 50 areas, median fine particulate concentrations averaged 18.2 $\mu g/m^3$ and ranged from 9.0 to 33.5 $\mu g/m^3$.

Because both fine and sulfate particles are derived chiefly from the combustion of fossil fuels and because sulfates make up the largest fraction of fine particles by mass, both pollution measures serve as indexes of combustion source particulate pollution and are highly correlated. For the 47 metropolitan areas with both pollution measures, the Pearson correlation coefficient between sulfate and fine particulate pollution was 0.73 ($p < 0.001$).

Statistical Analysis

Adjusted mortality relative risk ratios were estimated using multiple regression analysis based on the Cox proportional hazards model (25) using SAS/STAT Software (26). The time variable used in the model was survival time from date of enrollment. Survival times of participants who did not die were censored at the end of the study period. Adjusted risk ratios were calculated and reported for differences in air pollution equal to the range of pollution observed across the areas (Table 1). All models were stratified by 5-yr age categories, gender, and race (white, black, and other) which allowed each sex-race-age category to have its own baseline hazard. Models were estimated including air pollution as an independent variable. To control for smoking at entry, the following variables were included in the models: an indicator variable for current smoker, an indicator variable for pipe and/or cigar smoker only, years smoked for current smoker, cigarettes per day for current smoker, years smoked for former smoker, number of cigarettes per day for former smoker, and number of hours per day exposed to passive cigarette smoke. To control for other individual risk factors, several other variables were included: body-mass index (BMI), drinks per day of alcohol, a variable indicating less than a high school education, and a variable indicating regular occupational exposure to any of the following: asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel engine exhaust, or formaldehyde.

Cox proportional hazards models were estimated separately for three cause-of-death categories: lung cancer (ICD-9 162), cardiopulmonary disease (ICD-9 401–440 and 460–519), and all others. Deaths not in that specific category were censored at time of death. To evaluate the robustness of the estimated effects, the models were reestimated after separating the data by smoking status, and gender. Additionally, to evaluate if the results were confounded by differences in climates across the metropolitan areas, weather variables that accounted for relatively hot or cold conditions were added to the models.

Ecologic Analysis

To compare these results with more commonly available population based mortality rates, U.S. metropolitan area mortality rates for 1980 were obtained from the National Center for Health Statistics (27). These population-based mortality rates were from metropolitan areas that correspond approximately

to areas used in this study. These mortality rates were adjusted based on age-sex-race specific population counts from the 1980 census (28) (with seven age categories and a white/nonwhite race designation). The adjusted mortality rates were then correlated with sulfate and fine particulate pollution levels.

RESULTS

Adjusted Mortality Risk

Although small relative to active smoking (Table 2), an association between mortality and air pollution was observed. The latter association persisted after adjusting for age, sex, race, cigarette smoking, pipe and cigar smoking, exposure to passive cigarette smoke, occupational exposure, education, BMI, and alcohol use. For all-cause, cardiopulmonary, and lung cancer mortality, the associations with sulfates were statistically significant ($p < 0.001$). For all-cause and cardiopulmonary mortality, significant associations were also found using fine particulate matter as the index of air pollution. Mortality due to other causes was not significantly associated with pollution levels (Table 2).

Lung cancer mortality was associated with combustion source air pollution when sulfates were used as the index but not when fine particles were used as the index. To evaluate whether this inconsistency was due to the use of different study areas or different pollution measures, sulfate pollution measures were included in models that were restricted to use data only from the 47 metropolitan areas that had both sulfate and fine particulate measures. The adjusted mortality risk ratios (and 95% CI) for lung cancer and cardiopulmonary disease mortality for all persons combined controlling for the other risk factors were 1.44 (1.11 to 1.86) and 1.20 (1.08 to 1.34), respectively. The results were similar to those from our initial analysis suggesting that the inconsistency was not due to differences in study areas, but lung cancer seems to be more strongly associated with sulfate particles than the more general index of fine particulate mass.

The association between air pollution and all-cause and cardiopulmonary mortality was consistent across both men and women, and among smokers and nonsmokers. Cox proportional hazard regression models showed no statistically significant differences in pollution-related mortality risk when the data were separated by smoking and gender strata (Table 3). Estimated pollution-related mortality risk was as high for never-smokers as it was for ever-smokers and as high for women as it was for men.

After adjusting for cigarette smoking, the association between air pollution and all-cause and cardiopulmonary mortality was not sensitive to the inclusion of BMI, alcohol consumption, education, and occupational exposure variables. There was also little evidence that the results were due to differences in climates across the metropolitan areas. Normal daily high, low, or mean temperature was not correlated with either sulfate or fine particulate pollution. Absolute Pearson correlation coefficients between mean temperature variables and sulfate and fine particulate pollution

TABLE 2

ADJUSTED MORTALITY RISK RATIOS (AND 95% CONFIDENCE INTERVALS) BY CAUSE OF DEATH FOR CIGARETTE SMOKING AND FOR A DIFFERENCE IN POLLUTION*

Cause of Death	Current Smoker†	Sulfates‡ (19.9 μg/m³)	Fine Particles‡ (24.5 μg/m³)
All	2.07 (1.75–2.43)	1.15 (1.09–1.22)	1.17 (1.09–1.26)
Lung cancer	9.73 (5.96–15.9)	1.36 (1.11–1.66)	1.03 (0.80–1.33)
Cardiopulmonary	2.28 (1.79–2.91)	1.26 (1.16–1.37)	1.31 (1.17–1.46)
All other	1.54 (1.19–1.99)	1.01 (0.92–1.11)	1.07 (0.92–1.24)

* Difference in pollution equal to the most polluted areas compared with the least polluted using sulfates and fine particles as measures of combustion source air pollution.

† Risk ratios for cigarette smoking are estimated from the model using sulfate data and correspond to the risk of death for a current smoker with 25 yr of smoking 20 cigarettes per day as compared with a never-smoker. Risk ratios have been adjusted for age, sex, race, exposure to passive cigarette smoke, body-mass index, drinks per day of alcohol, education, and occupational exposure.

‡ Risk ratios have been adjusted for age, sex, race, cigarette smoking, exposure to passive cigarette smoke, body-mass index, drinks per day of alcohol, education, and occupational exposure.

TABLE 3

ADJUSTED MORTALITY RISK RATIOS* (AND 95% CI) FOR THE MOST POLLUTED AREAS COMPARED WITH THE LEAST POLLUTED FOR ALL-CAUSE AND CARDIOPULMONARY DEATHS SEPARATED BY GENDER AND SMOKING STATUS

	Sulfates (19.9 μg/m³)			Fine Particles (24.5 μg/m³)		
	All Cause	Lung Cancer	Cardiopulmonary	All Cause	Lung Cancer	Cardiopulmonary
All combined	1.15 (1.09–1.22)	1.36 (1.11–1.66)	1.26 (1.16–1.37)	1.17 (1.09–1.26)	1.03 (0.80–1.33)	1.31 (1.17–1.46)
Women	1.18 (1.06–1.30)	1.17 (0.80–1.72)	1.39 (1.20–1.61)	1.16 (1.02–1.32)	0.90 (0.56–1.44)	1.45 (1.20–1.78)
Men	1.14 (1.06–1.23)	1.43 (1.13–1.81)	1.20 (1.08–1.33)	1.18 (1.07–1.30)	1.10 (0.81–1.47)	1.24 (1.08–1.41)
Never-smokers	1.18 (1.06–1.30)	1.51 (0.73–3.11)	1.36 (1.19–1.58)	1.22 (1.07–1.39)	0.59 (0.23–1.52)	1.43 (1.18–1.72)
Women	1.20 (1.06–1.36)	1.61 (0.66–3.92)	1.44 (1.20–1.74)	1.21 (1.02–1.43)	0.65 (0.21–2.06)	1.57 (1.23–2.01)
Men	1.14 (0.97–1.34)	1.36 (0.40–4.66)	1.28 (1.03–1.58)	1.24 (1.00–1.54)	0.49 (0.09–2.66)	1.24 (0.93–1.67)
Ever-smokers	1.14 (1.06–1.23)	1.35 (1.10–1.66)	1.20 (1.08–1.33)	1.15 (1.05–1.26)	1.07 (0.82–1.39)	1.24 (1.08–1.42)
Women	1.14 (0.97–1.33)	1.10 (0.72–1.68)	1.30 (1.01–1.66)	1.10 (0.90–1.33)	0.95 (0.57–1.58)	1.27 (0.92–1.74)
Men	1.14 (1.05–1.24)	1.44 (1.14–1.83)	1.17 (1.05–1.32)	1.16 (1.05–1.29)	1.12 (0.83–1.52)	1.23 (1.06–1.43)

* Risk ratios have been adjusted for age, sex, race, cigarette smoking, exposure to passive cigarette smoke, body-mass index, drinks per day of alcohol, education, and occupational exposure.

were all less than 0.1 and statistically insignificant ($p > 0.25$). However, on average sulfate particulate levels were slightly lower in both the relatively cold and relatively hot metropolitan areas. Therefore indicator variables were created for the relatively hot and cold cities (those with normal mean temperatures greater than 60° F and less than 50° F). The inclusion of these weather indicator variables in the Cox proportional hazard models had little impact on the estimated association between particulate air pollution and mortality. When these weather indicator variables were included in the models, adjusted relative risk ratios (and 95% confidence intervals) for lung cancer and cardiopulmonary mortality equaled 1.36 (1.11 to 1.66) and 1.23 (1.13 to 1.34) respectively when sulfate is used as the pollution measure and 1.05 (0.82 to 1.36) and 1.26 (1.13 to 1.40) respectively when fine particulate pollution is used as the pollution measure.

Ecologic Comparison

Age-, sex-, and race-adjusted population-based mortality rates for 1980 (using metropolitan areas also used in this prospective cohort study) are plotted against sulfates and fine particles in Figures 1 and 2, respectively. Sulfate and fine particle pollution were associated with higher mortality rates. Regression coefficients between mortality rates and air pollution equaled 10.5 (SE = 1.3) and 8.0 (SE = 1.4) deaths/year/100,000 persons in the population per $\mu g/m^3$ of sulfate and fine particulate pollution respectively. Although this ecologic analysis did not control for risk factors except age, sex, and race, these correlations were statistically significant ($p < 0.001$) and demonstrated an association similar to that observed in the prospective cohort study of participants from the same communities. Using the mean age-sex-race adjusted mortality rate as the baseline risk, estimated risk ratios for the most polluted city versus the least polluted city using sulfate and fine particulate measures of pollution equaled 1.25 and 1.24, respectively.

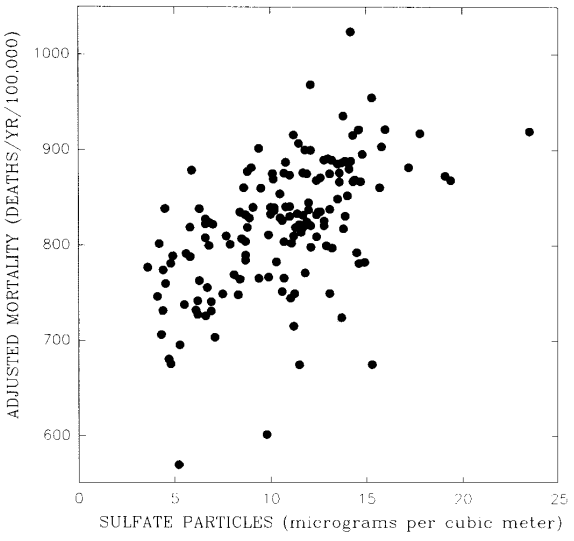

Figure 1. Age-, sex-, and race-adjusted population-based mortality rates for 1980 plotted against mean sulfate air pollution levels for 1980. Data from metropolitan areas that correspond approximately to areas used in prospective cohort analysis.

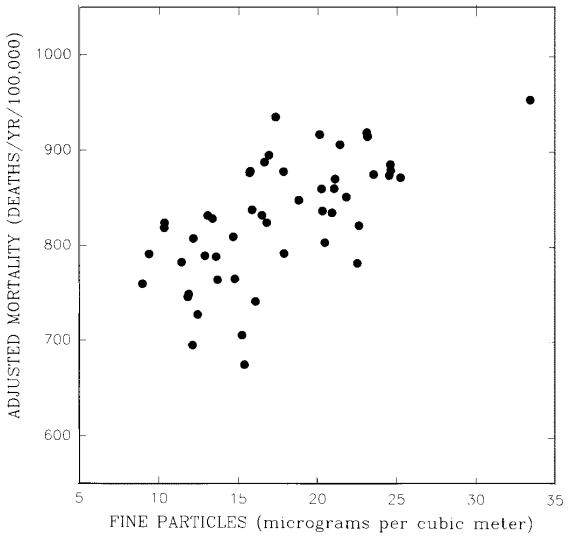

Figure 2. Age-, sex-, and race-adjusted population-based mortality rates for 1980 plotted against mean fine particulate air pollution levels for 1979 to 1983. Data from metropolitan areas that correspond approximately to areas used in prospective cohort analysis.

DISCUSSION

In this study, sulfate and fine particulate air pollution were associated with a difference of approximately 15 to 17% between mortality risks in the most polluted cities and those in the least polluted cites. Previous studies have observed similar results but have been limited by ecologic design or by small number of subjects or study areas. This study differs fundamentally from purely ecologic cross-sectional studies in using a prospective cohort design that allows for direct control of other individual risk factors, particularly cigarette smoking. Furthermore, because this study linked ambient air pollution data from national data bases with a large nationwide prospective cohort, this study is larger and represents a wider geographic area.

Although the increased risk associated with air pollution was small compared with that from cigarette smoking, results of this study suggest that the association between pollution and mortality was not likely due to inadequate control of smoking: (*1*) The associations between air pollution and mortality persisted after controlling for cigarette smoking status, pipe and/or cigar smoking, years smoked, and cigarettes smoked per day for both current and former smokers, and hours per day exposed to passive cigarette smoke. (*2*) Associations between particulate air pollution and mortality were as large and statistically significant for never-smokers as they were for ever-smokers.

Other potential sources of confounding are inadequate control of occupational, socioeconomic, or weather factors. Nevertheless, such residual confounding seems unlikely because: (*1*) The association between pollution and mortality was not very sensitive to the inclusion of variables reflecting occupational exposure, education, BMI, alcohol consumption, and relatively hot or cold weather conditions. (*2*) In the U.S., men are more likely to be employed in jobs with high industrial exposure to dust and fumes than women; yet the association between mortality and particulate air pollution was as high for women as for men. (*3*) Associations between particulate air pollution and mortality have also been

observed in daily time-series studies from various cities (2–6), yet community-specific occupational and socioeconomic conditions do not fluctuate daily with pollution levels.

In this study, individual data on smoking and other risk factors were obtained directly by questionnaire. Although accurate measures of lifetime personal exposure to air pollution would be ideal for many research purposes, such measures are unavailable and impractical for large cohorts. Furthermore public policy and pollution abatement strategies typically (and often necessarily) focus on ambient concentrations of air pollutants. Therefore, exposures to air pollution were estimated using ambient air pollution for metropolitan areas based on existing air pollution monitoring data.

The pollution data characterize differences in exposure between metropolitan areas for a specific period of time that corresponds roughly to the period of cohort enrollment and to the period when EPA dichotomous sampler network data were available. The biologically relevant exposure window for at least some of the mortality outcomes under study includes time periods for up to 15 or more years prior to death. The lack of long-term exposure data, therefore, results in some misclassification of exposure, the magnitude of which is largely dependent on the temporal constancy of the absolute and relative levels of pollution. Data from six cities in the East and Midwest U.S., indicate that annual average fine and sulfate particulate concentrations were relatively constant from the mid-1970s through the mid-1980s (20), suggesting that the pollution data used in this analysis also partially serve in proxy for longer-term exposures. While the lack of long-term exposure data constrains our ability to differentiate the time dependency of exposure and mortality, the air pollution measures used in this study partially reflect exposure to air pollution for periods preceding enrollment into the cohort. Furthermore, related exposure misclassification is unlikely to result in spurious associations between pollution and mortality. To the extent that the available exposure data do not adequately represent long-term exposure, the total chronic effects of air pollution may be underestimated.

Sulfate and fine particulate pollution data for a large number of communities are only available from central site ambient air pollution monitoring networks. These data can estimate variability in pollution exposure between communities, but within-community spatial variability of sulfate or fine particulate concentrations cannot be estimated for most of the areas included in this study. However, long-term transport and large-scale mixing of combustion products result in concentrations of sulfates and fine particles that are relatively uniform within communities (29). Variability of exposure within communities can also be due to differences in indoor versus outdoor concentrations and differences in time spent outdoors. Studies that conducted detailed monitoring within selected communities have concluded that measured indoor and personal exposures to sulfate and fine particles are strongly correlated with and similar to measured outdoor concentrations (30–32). Furthermore, these studies observed little within-community spatial variation in outdoor sulfate or fine particulate concentrations compared with between-community variations. For example, in Uniontown, Pennsylvania (31), nearly all of the variability in outdoor home site concentrations of sulfate particles was explained by concentrations at the central stationary ambient monitoring site (R^2 = 0.92); fine particle concentrations throughout Riverside, California (32) were similarly well estimated from the stationary central site monitor.

This study was limited by the use of death certificates to identify causes of death. Studies that used antemortem evidence or autopsy reports to verify cause of death have found that deaths due to respiratory disease are often recorded on the death certificate as cardiovascular (or circulatory) disease (33–35). Given this cross-coding between pulmonary and cardiovascular deaths and the potential that cross-coding may vary with age, survival analysis controlling for age and conducted separately for cardiovascular and pulmonary disease deaths may result in unstable and potentially biased estimates of pollution-related mortality risks. To avoid these problems, cardiovascular and pulmonary deaths were combined. All-cause mortality, or cardiovascular and pulmonary disease mortality grouped together, were consistently associated with air pollution.

This study and related epidemiologic studies provide little information on specific biologic mechanisms responsible for the observed effects. Additional research that will help provide a toxicologic framework for interpreting these findings is needed. Nevertheless, the biologic plausibility of these results is enhanced by several observations: (*1*) The increase in all-cause mortality associated with air pollution observed in this prospective cohort study is consistent with ecologic correlations presented here for the same metropolitan areas and with associations observed in several previous population-based cross-sectional mortality studies (16–19). (*2*) The results of this study are similar to those of the Harvard Six-Cities prospective cohort study (20) which estimated that the relative risk of mortality was 26% higher in the most, compared with the least polluted city. (*3*) Acute exposure studies have observed that particulate air pollution levels common to many of the metropolitan areas included in this study are associated with declines in lung function (6–9), increases in respiratory symptoms (6, 8, 9), increases in respiratory hospitalizations (6, 12, 13), restricted activity due to respiratory illness (14, 15), and increased mortality, especially respiratory and cardiovascular mortality (2–6). (*4*) While this and related epidemiologic studies suggest that combustion source air pollution is associated with a coherent cascade of cardiopulmonary health effects, this pollution is not typically associated with noncardiopulmonary health endpoints.

Findings of this study suggest that the associations observed between particulate air pollution and mortality in U.S. communities are not due to confounding by other risk factors, especially cigarette smoking. In combination with daily time-series mortality and morbidity studies, they suggest that combustion source air pollutants may be important contributing factors causing respiratory illness and early mortality due to cardiopulmonary diseases.

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955 Massachusetts Avenue
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