SPECIAL REPORT

HEALTH EFFECTS INSTITUTE

July 2000

# 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

HEALTH
EFFECTS
INSTITUTE

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.

HEALTH
EFFECTS
INSTITUTE

# 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.

HEALTH
EFFECTS
INSTITUTE

# CONTENTS

## Particle Epidemiology Reanalysis Project




Release History: This document was posted as a preprint on *www.healtheffects.org* on 7/26/00 and finalized for print on 9/15/00.

Citation for whole report:

Health Effects Institute. 2000. 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. Health Effects Institute, Cambridge MA.

When specifying a section of this report, cite it as a chapter of this document.

Library of Congress Catalog Number for the HEI Report Series: WA 754 R432.
This publication is printed on acid-free coated paper.

HEALTH
EFFECTS
INSTITUTE

# 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 $\leq 10$ 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.

## REFERENCES

Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Beeson LW, Yang JX. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159(2):373–382.

Brunekreef B. 1997. Air pollution and life expectancy: Is there a relation? Occup Environ Med 54:781–784.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Gamble JF. 1998. $PM_{2.5}$ and mortality in long-term prospective cohort studies: Cause-effect or statistical associations? Environ Health Perspect 106:535–549.

Health Effects Institute. 1995. Particulate Air Pollution and Daily Mortality: Validation and Replication of Selected Studies. The Phase I Report of the Particle Epidemiology Evaluation Project. Health Effects Institute, Cambridge MA.

Health Effects Institute. 1997. Particulate Air Pollution and Daily Mortality: Analyses of the Effects of Weather and Multiple Air Pollutants. The Phase I.B Report of the Particle Epidemiology Evaluation Project. Health Effects Institute, Cambridge MA.

Künzli N, Kaiser R, Medina S, Studnika M, Oberfeld G, Horak F. 1999. Air Pollution Attributable Cases: Technical Report on Epidemiology and Health Costs Due to Road Traffic-Related Air Pollution (An Impact Assessment Project of Austria, France, and Switzerland). Prepared for the Third Ministerial Conference on Environment and Health, London. GVF-Report No. 326. Federal Department for Environment, Transport, and Energy and the Communications Bureau for Transport Studies, Bern, Switzerland.

Lipfert FW. 1993. Community Air Pollution Mortality: Analysis of 1980 Data from US Metropolitan Areas: I. Particulate Air Pollution. BNL 48446-R. US Department of Energy, Brookhaven National Laboratory, Upton NY.

Moolgavkar SH. 1994. Air pollution and mortality [letter]. N Eng J Med 330(17):1237–1238.

Moolgavkar SH, Luebeck EG. 1996. A critical review of the evidence on particulate air pollution and mortality. Epidemiology 7:420–428.

Natural Resources Defense Council. 1996. Breath-Taking: Premature Mortality Due to Particulate Air Pollution in 239 American Cities. Natural Resources Defense Council, New York NY.

Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151:669–674.

US Environmental Protection Agency, Office of Air Quality Planning and Standards. 1996a. Review of the National Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information. OAQPS Staff Paper. EPA-452\R-96-013. US Government Printing Office, Washington DC.

US Environmental Protection Agency, Office of Research and Development. 1996b. Air Quality Criteria for Particulate Matter. EPA/600/P-95/001cF. US Government Printing Office, Washington DC.

Vedal S. 1997. Ambient particles and health: Lines that divide. J Air Waste Manage Assoc 47:551–581.

HEALTH
EFFECTS
INSTITUTE

# 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*

Terésa Fasulo, *Senior Administrative Assistant*

Howard E Garsh, *Director of Finance and Administration*

Daniel S Greenbaum, *President*

L Virgi Hepner, *Senior Scientific Editor*, ***Publication Project Manager***

Robert O'Keefe, *Vice President*

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

Jane Warren, *Director of Science*

**Publication Assistance**

John B Abbott, *Desktop Publishing Specialist*

Sybil Carey, *Editorial Assistant*

John DeRosa, *Desktop Publishing Specialist*

Frederic R Howe, *Proofreader*

Genevieve MacLellan, *Scientific Editor*

Carol Moyer, *Scientific Copy Editor*

Susan L Shepherd, *Scientific Editor*

Quentin Sullivan, *Proofreader*

Gabe Weiss, *Desktop Publishing Specialist*

HEALTH
EFFECTS
INSTITUTE

# 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.

Although this document was produced with partial funding by the United States Environmental Protection 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.

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.

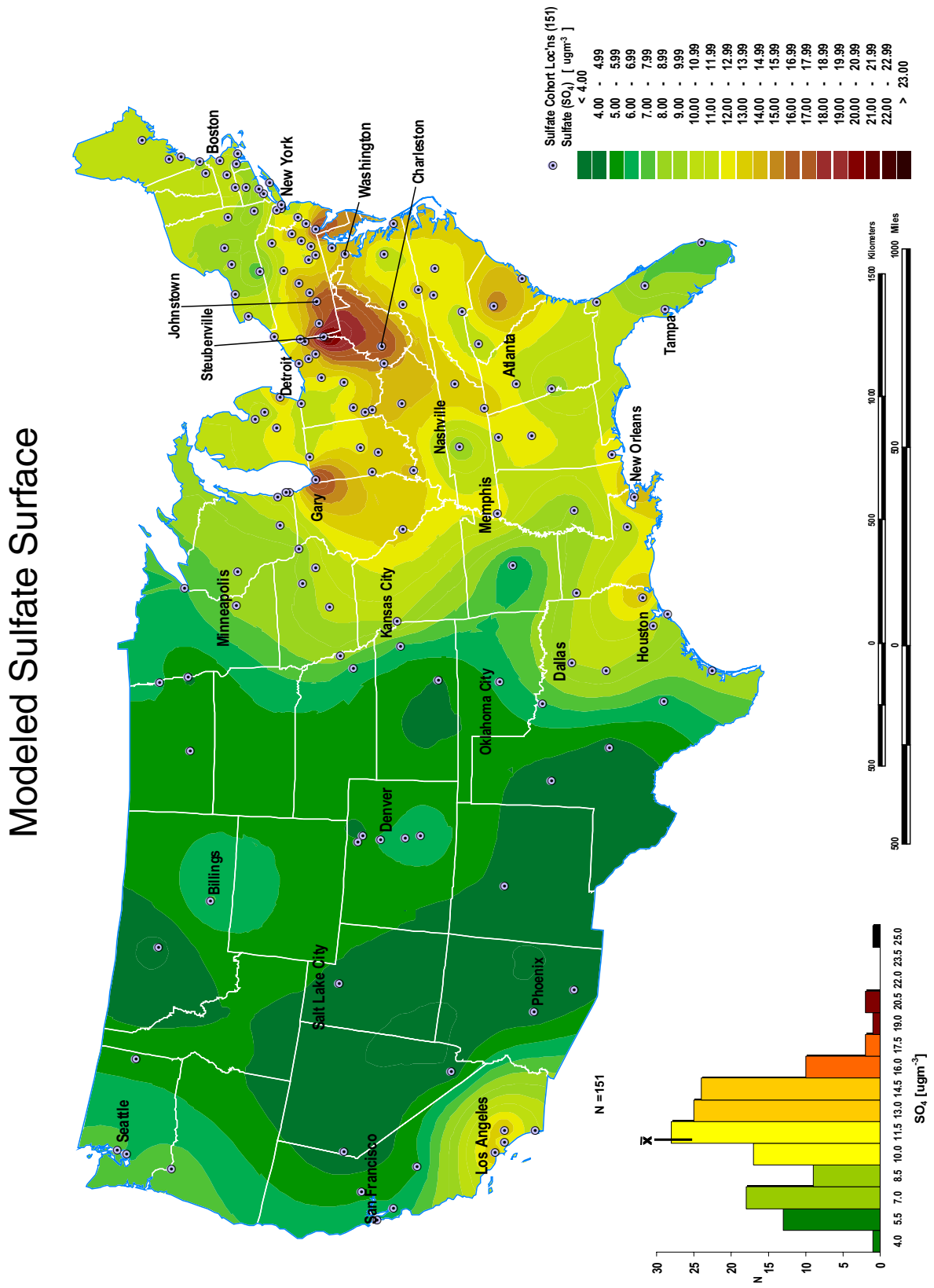
In the Six Cities Study, analysis of changes in BMI and smoking, determined from supplementary questionnaires administered during the follow-up period did not appreciably alter the relative risk of all-cause mortality for fine particles. However, allowing for the general decline in fine particles and 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.

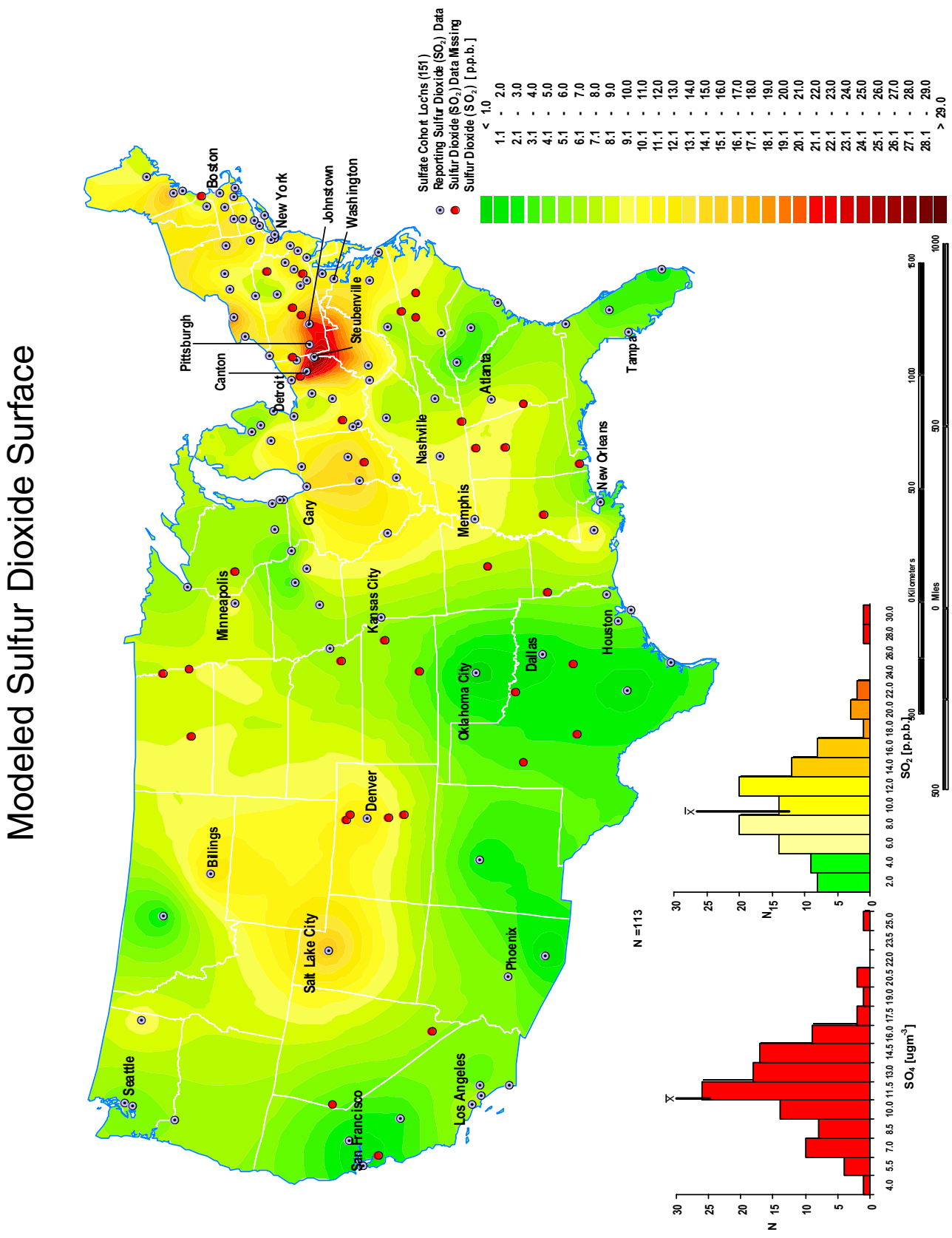
The Reanalysis Team considered a number of alternative indicators of fine particle and sulfate air pollution in the ACS Study. Our measures of fine particles and sulfate were highly correlated with those used by the Original Investigators, and led to comparable mortality risk ratios for all-cause, cardiopulmonary, 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.

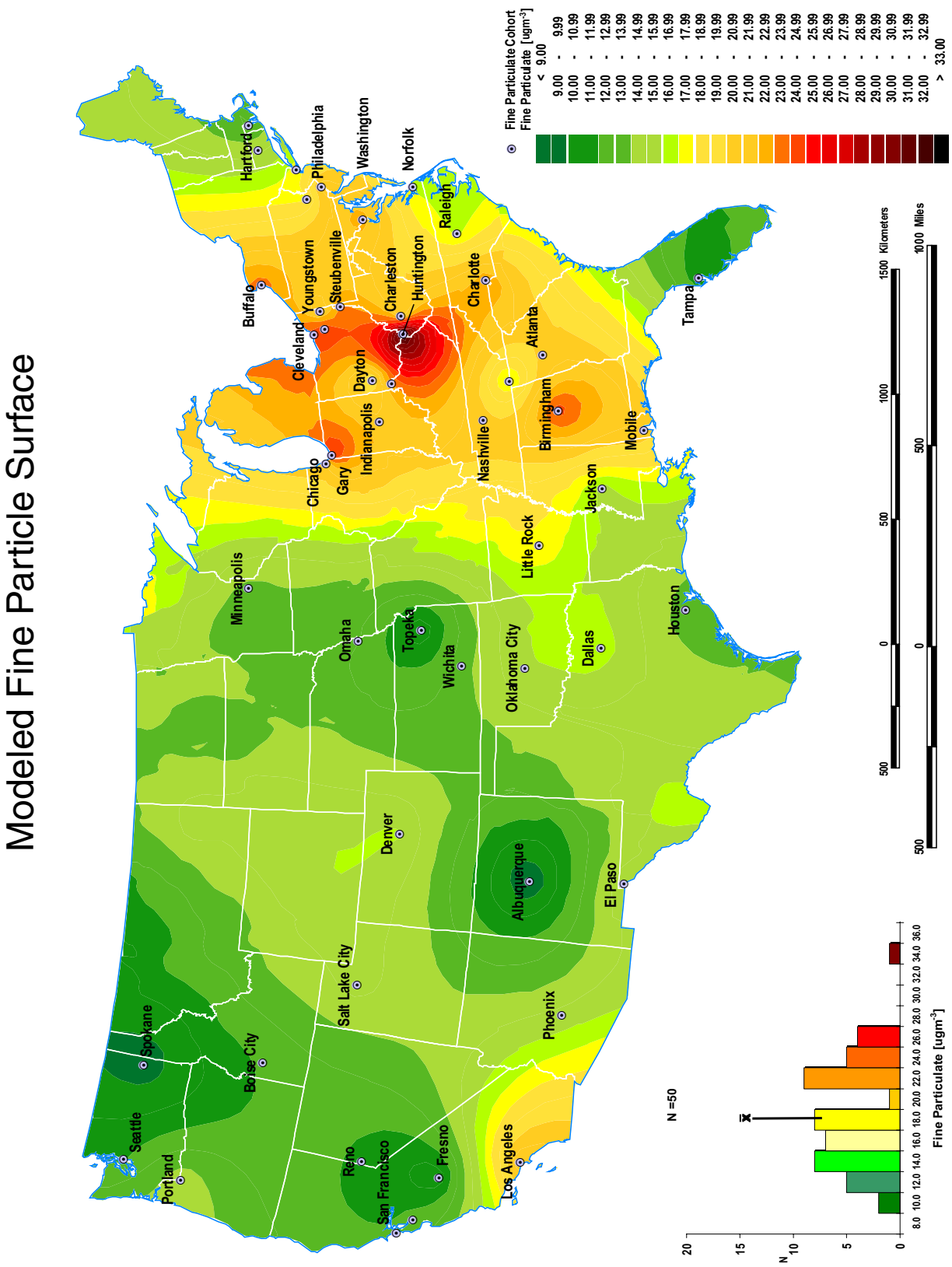
- With two exceptions, our audit demonstrated that the data used in both the original analyses and reanalyses were of high quality. Although we were unable to audit the air pollution data in the ACS Study, as noted above, our reconstruction of the air pollution data from the AIRS and IPMN databases confirmed 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.

## REFERENCES

Boffetta P, Kogevinas M, Simonato L, Wilbourn J, Saracci R. 1995. Current perspectives on occupational cancer risks. Int J Occup Environ Health 1:315–325.

Cox DR. 1972. Regression Models and life tables (with discussion). J R Stat Soc B34:187–200.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Lipfert FW, Malone RG, Daum ML, Mendell NR, Yang CC. 1988. A Statistical Study of the Macroepidemiology of Air Pollution and Total Mortality. BNL 52122 US-404. US Department of Energy, Brookhaven National Laboratory, Upton NY.

Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151:669–674.

Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW, Schwartz J, Zanobetti A. 2000. The National Morbidity, Mortality, and Air Pollution Study, Part II. Morbidity, Mortality, and Air Pollution in the United States. Research Report 94. Health Effects Institute, Cambridge MA.

Schwartz J, Dockery DW, Neas LM. 1996. Is daily mortality associated specifically with fine particles? J Air Waste Manage Assoc 45:927–939.

# 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.

Although this document was produced with partial funding by the United States Environmental Protection 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 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.

## REFERENCES


Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Beeson LW, Yang JX. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159:373–382.

Bates D, Hayes CG, Knowles M. 1985. Geographic variation in declining ischemic heart disease mortality in the United States, 1968–1978. Am J Epidemiol 122:657–672.

Burnett RT, Dales R, Krewski D, Vincent R, Dann R, Brook JR. 1995. Associations between ambient particulate sulfate and admission to Ontario hospitals for cardiac and respiratory diseases. Am J Epidemiol 142:15–22.

Burnett RT, Jessiman B, Stieb D, Krewski D. 1997. Health effects of ambient particulate matter: A Canadian perspective. In: Health Effects of Particulate Matter in Ambient Air (Vostal EJ, ed). Prague, Czech Republic.

Burnett RT, Krewski D. 1994. Air pollution effects on hospital admission rates: A random effects modeling approach. Can J Stat 22:441–458.

Ciocco A, Thompson DJ. 1961. A follow-up on Donora ten years after: Methodology and findings. Am J Public Health 51:155–164.

Delfino RJ, Murphy-Moulton AM, Burnett RT, Brook JR, Becklake MR. 1997. Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. Am J Respir Crit Care Med 155:568–576.

Dockery DW. 1993. Percentile curves for evaluations of repeated measures of lung function. Occup Med 8:323–338.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Dockery DW, Schwartz J, Spengler J. 1992. Air pollution and daily mortality: Associations with particulates and acid aerosols. Environ Res 59:362–373.

Firket J. 1936. Fog along the Meuse Valley. Trans Faraday Soc 32:1191–1194.

Hoek G, Brunekreef B. 1993. Acute effects of a winter air pollution episode on pulmonary function and respiratory symptoms of children. Arch Environ Health 48:328–335.

Hoek G, Brunekreef B. 1994. Effects of low-level winter air pollution concentrations on respiratory health of Dutch children. Environ Res 64:136–150.

Koenig JQ, Larson TV, Hanley QS, Rebolledo V, Dumler K. 1993. Pulmonary function changes in children associated with fine particulate matter. Environ Res 63:26–38.

Koenig JQ, Larson TV, Norris G, Claiborn C, Finn D, Zweidinger R, Lewtas J, Schwartz J. 1998. A fine particulate composition variability and exacerbation of asthma [Particulate Matter Research Activities Web site]. January 24, 2000. Available at: http://www.pmra.org/pmra/PM.nsf. Accessed March 22, 2000.

Lave LB, Seskin EP. 1970. Air pollution and human health. Science 169:723–733.

Lipfert FW, Malone RG, Daum ML, Mendell NR, Yang CC. 1988. A Statistical Study of the Macroepidemiology of Air Pollution and Total Mortality. BNL 52122. US Department of Energy, Brookhaven National Laboratory, Upton NY.

Logan WPD. 1953. Mortality in the London fog incident. Lancet 1:336–338.

Özkaynak H, Thurston G. 1987. Associations between 1980 US mortality rates and alternative measures of airborne particle concentration. Risk Anal 7:449–460.

Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151:669–674.

Ransom MR, Pope CA III. 1992. Elementary school absences and $PM_{10}$ pollution in Utah Valley. Environ Res 58:204–219.

Roemer W, Hoek G, Brunekreef B. 1993. Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. Am Rev Respir Dis 147:118–124.

Schwartz J. 1991. Particulate air pollution and daily mortality: A synthesis. Public Health Rev 19:39–60.

Schwartz J. 1994. What are people dying of on high air pollution days? Environ Res 64:26–35.

US Environmental Protection Agency. 1995. National Air Pollution Emissions Trends, 1990–1994. EPA-454/R-95-011. Office of Air Quality Planning and Standards, Research Triangle Park NC.

World Health Organization. 1975. *International Classification of Diseases, Ninth Revision*, Vol 1. World Health Organization, Geneva, Switzerland.

HEALTH EFFECTS INSTITUTE

# Part 1: Replication and Validation

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

# ∞ *Errata* ∞

Created 11/01/01

---

## 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

Final version, July 2000
Posted to the HEI Website 10/27/00

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."

# Part I: Replication and Validation

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

## THE HARVARD SIX CITIES STUDY

The Harvard Six Cities Study (hereafter referred to as the Six Cities Study) is a unique, long-term, prospective cohort study designed to evaluate the health effects of exposure to various airborne pollutants. The present reanalysis focused only on that portion of the entire Six Cities Study in which the Original Investigators analyzed an epidemiologic association between mortality and air pollution levels measured from 1977 through 1985, the results of which were reported in the *New England Journal of Medicine* (NEJM)* by Dockery and associates (1993)†. For that epidemiologic analysis, the study population consisted of a random sample of 8,111 white men and women who were between the ages of 25 and 74 years and who resided in one of six US cities at the time of enrollment: Steubenville OH, St Louis MO, Portage WI, Topeka KS, Watertown MA, and Kingston-Harriman TN (hereafter referred to as Harriman).

The data used in the Six Cities Study were derived from questionnaires completed by participants at their time of entry into the study, starting in 1974. Data were also obtained from follow-up questionnaires completed 3, 6, and 12 years after the time of enrollment. The questionnaires were used to elicit information about age, sex, weight, height, education level, smoking history, occupational exposure, and medical history (examples of original and follow-up questionnaires and the coding guidelines are included as Appendix C).

Mortality was assessed during 14 to 16 years of follow-up (totaling 111,076 person-years of follow-up) and 1,430 deaths among the 8,111 subjects were ascertained. Mortality status was determined using information collected from mailings to subjects and by searching the National Death Index (NDI) for the period 1979 through 1989. Underlying causes of death were coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) (World Health Organization 1975). Deaths from respiratory diseases (ICD-9 codes 485–495), cardiovascular diseases (ICD-9 codes 400–440), lung cancer (ICD-9 code 162), and deaths from all other causes were analyzed separately. These causes of death were coded by an external, certified nosologist not affiliated with the research team. The development of an air pollution database formed an integral component of the original study. Within each of the six communities, ambient concentrations of fine particles ($PM_{2.5}$), total suspended particles (TSP), sulfur dioxide ($SO_2$), ozone ($O_3$), nitrogen dioxide ($NO_2$), and sulfate ($SO_4^{2-}$) were measured at a centrally located air monitoring station established specifically for the Six Cities Study. Long-term mean concentrations for each pollutant were calculated for periods that were consistent among the six cities. Concentrations of fine particles were collected from 1979 through 1985.

Survival analysis was used to evaluate the association between air pollution and mortality. Life-table survival probabilities for each year of follow-up were estimated for each city, and differences between city-specific mortality rates were assessed using the log-rank test. Cox proportional-hazards models were used to estimate mortality rate ratios for airborne pollutants while simultaneously adjusting for potentially confounding variables. These variables included cigarette smoking, level of education, body mass index (BMI), and occupational exposures to gas, fumes, or dust. In these models, the subjects were stratified according to sex and 5-year age groups, thereby

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

† The original article appears in its 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 (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 from the Original Investigators. Correspondence concerning *Part I: Replication and Validation* 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.

Although this document was produced with partial funding by the United States Environmental Protection 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.

permitting the specification of a baseline hazard within each stratum of sex and age.

## AUDIT OF STUDY POPULATION DATA

### Data Provided and Source Documents Accessible for the Data Audit

Many of the personnel who were key to the Six Cities Study were still available at Harvard School of Public Health (HSPH) at the time of this reanalysis. Dr Douglas Dockery and Ms Martha Fay (among others) were available to answer questions and to locate relevant data and records. In planning for the data audit and throughout the site visits, the Audit Team (see Appendix A) had the full and generous cooperation and assistance of the HSPH staff.

The original Six Cities Study protocol was not found in the archives and could not be supplied by the Original Investigators. Nevertheless, the Original Investigators provided the Audit Team with a Statistical Application Software (SAS) electronic data file (referred to herein as "Mort6C.file"), which was a copy of the Six Cities database (referred to herein as "Mort6C/HSPH.file") that had been used for the mortality and air pollution analyses. The Original Investigators also supplied a copy of the code book describing each of these variables. (At least three different formal code books had been used during the Six Cities Study.) The Mort6C.file did not contain any information that could be used to identify the individual study participants.

Records were provided during site visits that contained individual identifier information. These included completed questionnaires, subject tracking sheets (known as "pink sheets" for their color), follow-up postcards, death certificates, spirometry sheets, and printouts of computer programs. These records included names, addresses, Social Security Numbers (SSNs), lifestyle habits, and medical history with spirometry printouts, cause of death, names and addresses of relatives, and place of burial. The Audit Team was able to link these records while on site to the Mort6C.file, which did not contain individual identifier information. The Original Investigators provided study participants with several written assurances that confidentiality of these records would be maintained throughout the study. Therefore, the Audit Team agreed to be bound by these same confidentiality requirements. No original records, copies, or notes pertaining to individual identifiers were removed from the site of the audit. Even subject identification numbers (SIDs) were considered confidential and no reference was made to these records in any audit reports.

Existing quality assurance (QA) audits that had been carried out during the course of the study also were made available to the Audit Team.

### Sampling the Dataset and Assessing Error Rates in the Original Data

Subjects had been selected in each of the six cities at random using household voting lists, private census lists, partial blocks from street lists, or alphabetized name lists. The Audit Team did not audit the methods for the selection of subjects in the study because none of the source documents could be located, and because the methods have been described in great detail by Ferris and colleagues (1979), including the methods used for minimizing biases in selecting subjects in each city (see Table 1 in Ferris et al 1979).

The Audit Team conducted data audits using two subsets of 250 subjects, each randomly selected. Some subjects happened to be randomly assigned to both audit samples: the subset of the study population and the subset of deceased subjects. This provided some overlap between the two subsets, which functioned as a check on the auditing system.

We chose this sample size for three reasons:

- it would ensure virtual certainty of finding some errors even if the true error rate was as small as 1%;
- it would be sufficiently large to distinguish between error rates of 1% and 5% with reasonable confidence; and
- it would produce quite accurate estimates of error rates, usually within two to four percentage points of the true value.

### Original Investigators' Internal Procedures

Questionnaires and mortality records had been thoroughly audited by Ms Fay and internal reports dated February 11, 1981, and March 2, 1981, were made available to the Audit Team. These reports described the scope of the internal audits and the problems found in the study on a variable-by-variable basis. At the time of the first internal audit, error rates by variable ranged from 0% to 23.6%, largely due to inconsistent coding. After corrective actions were taken, the second internal audit showed that the error rates generally fell in the range of 0% to 1% for the majority of variables. These audit reports described the nature of the errors and the decisions made about corrective actions. Some errors noted were so minor in nature that they would not be expected to affect the integrity of the study or the results. In some cases, the documentation showed that decisions were made not to correct variables

for which the error rates were low in frequency. It is clear from these internal audits that most errors were functions of the evolution of the forms used in the study. For example, Ms Fay had found that the education variable on Form 1-71 had an error rate of 18.6% due to a reformatting problem in the fine gradations of some educational levels. There was an inconsistency between the forms as to whether sixth grade constituted the end of grade school or the beginning of high school. The Original Investigators considered the possibility of reformatting the original database, but decided not to because these fine gradations were not relevant to the statistical analyses to be conducted in the future.

These audits demonstrated to the Audit Team that during the conduct of the study, the investigators were concerned with issues of data quality and that they took the steps necessary to eliminate or reduce the impact of these problems.

### Original Investigators' Data Collection and Computer Processing

The Audit Team evaluated the documentation of data collection procedures while auditing the questionnaires (administered at baseline) and death certificates, and verified for each subject in the two audit subsets the recorded value of each variable.

For the questionnaires and mortality data, coding conventions and rules were generally quite clear and well documented. As the forms in the study changed, the methods for interpreting the data using established coding conventions and rules were also clear. The resolutions of any discrepancies in coding were well documented. "Missing" data points were handled consistently. In the beginning of the Six Cities Study (late 1970s and early 1980s), data were recorded via handwritten records, typed documents, and computer punch cards; in later years, many versions of computer software were used to record information and data. For the questionnaires and mortality records, the Audit Team was able to start with questionnaires or death certificates and follow the data trail to the Mort6C.file.

### Subset of Study Population: Questionnaires

Different versions of the questionnaires were used in different years and different locations in the study. For Watertown, Harriman, and St Louis, the earliest questionnaire was Form 1-71. For Steubenville and some subjects in Topeka, the earliest version was Form 77 (1-76). For the remaining subjects in Topeka and all of Portage, Form 77 (1-76) or Form 78 (1/77) was used. [Form 78 (1/77) and follow-up Form 82 (8/81) are included in Appendix C.] Revisions appeared to have been made to facilitate the accurate recording and coding of responses. Early forms allowed for ambiguous responses, particularly in the occupational exposure sections.

**Table 1.** List of Questionnaire Variables for Reanalysis Team to Audit and the Criteria for Declaring Errors in the Six Cities Study

| Original Questionnaire Variable | Subvariable | Criteria[a] |
|---|---|---|
| Subject identification number | Match with city and questionnaire (also match with other records) | Any difference |
| Sex | | Any difference |
| Exposure to dusts | Total years of occupational exposure to dust | Any difference |
| Exposure to fumes | Total years of occupational exposure to fumes or gases | Any difference |
| Education | Category assignment (more or less than high school) | Any difference |
| Diabetes | | Any difference |
| High blood pressure | | Any difference |
| Smoking status | Current-, former-, or never-smoker | Any difference |
| Current-smoker pack-years | | Any difference |
| Former-smoker pack-years | | Any difference |
| Height | | Any difference |
| Weight | | Any difference |
| Body mass index | Calculated variable that was not audited directly | Same to whole number |
| Initiation date of subject on study | | Any difference |
| Time-on-study | | Any difference |

[a] Any difference between the Mort6C.file and the questionnaires.

The Audit Team coordinator met with the Reanalysis Team to determine which variables in the Mort6C.file would be audited against the Six Cities questionnaires. Table 1 presents the list of 15 variables selected for the audit. We also tried to determine criteria for what would constitute "an error" in the original data, but found that an a priori definition was of limited value. We therefore decided to record any difference found between the Mort6C.file and the questionnaires.

For each of the 15 variables chosen for the data audit, we compared the data in the Mort6C.file with the data on the initial questionnaires to verify that the information recorded on the questionnaires had been correctly entered into the database.

***Questionnaire Variables*** The Audit Team reviewed only the data derived from the questionnaires that were administered at enrollment. We could not audit variables for 1 (0.4%) of the 250 study participants because the initial questionnaire for that individual was missing from the file. A check of files directly before and after this folder failed to locate the missing questionnaire. We did find subsequent questionnaires and other documentation for this subject.

Depending on the variable under examination, more than one auditor evaluated each of the remaining 249 questionnaires in the study population subset. In cases of apparent discrepancies between the Mort6C.file and the questionnaire for any variable, we followed a number of steps to verify that a difference actually existed. If the discrepancy could not be resolved in this way, we gave a detailed written description of the discrepancy to study personnel, who consulted computer programs, other documents, or individuals and then provided a response to the Audit Team.

Table 2 summarizes the percentage of errors the Audit Team found in the variables we examined for the questionnaires.

*Subject Identification Number* We matched each SID from the Mort6C.file with the SID on each questionnaire. Furthermore, we matched SIDs and personal identification on questionnaires to any other records filed for the same subject: other records included postcards, pink cover tracking sheets, and death certificates. The SID contained a code for the city so the SID checking process also confirmed that the individual was assigned to the correct city. We noted no errors in SIDs in any part of the study.

*Race* We did not formally audit the race of the subjects because "white" was noted in the inclusion criteria and demographic distribution for the study. However, as we reviewed the questionnaires, we noted no instances that did not meet the established criteria.

**Table 2.** Audit Results for a Subset of the Six Cities Study Population

| Variable | Number of Records | Number of Inconsistencies | Percentage |
|---|---|---|---|
| Date of birth | 250 | 0 | 0.0 |
| Sex | 250 | 0 | 0.0 |
| Occupational exposure | | | |
| Job exposure to dust | 249 | 14 | 5.6 |
| Total years of exposure to dust | 249 | 0 | 0.0 |
| Job exposure to fumes or gases | 249 | 15 | 6.0 |
| Total years of exposure to fumes or gases | 249 | 0 | 0.0 |
| Education level | 250 | 0 | 0.0 |
| Diabetes | 250 | 0 | 0.0 |
| High blood pressure | 250 | 0 | 0.0 |
| Smoking status | 250 | 0 | 0.0 |
| Current cigarette smoker (pack-years) | 250 | 0 | 0.0 |
| Former cigarette smoker (pack-years) | 250 | 0 | 0.0 |
| Height (meters) | 250 | 8 | 3.2 |
| Weight (pounds) | 250 | 2 | 0.8 |
| Body mass index | 250 | 0 | 0.0 |
| First year of follow-up | 250 | 0 | 0.0 |
| Last year of follow-up | 250 | 0 | 0.0 |
| Time-on-study (years) | 250 | 0 | 0.0 |

*Sex* The sex of the subject from the questionnaire was converted to a binary code in the Mort6C.file. We checked each code against the questionnaire. In addition, because we had access to personal identification information and subjects' medical histories, we were also able to informally verify that the coded information in the Mort6C.file was correct. For example, a subject reported to be female might have corresponding sex-specific medical information; also, many names are culturally considered to refer primarily to one gender. Although these were not absolutes (eg, some men have breast cancer, and some women are named "Billie"), they were flags to the auditors to check further into study data to confirm the questionnaire information. We found no errors in this variable in the audit subset.

*Exposure to Dust, Fumes, and Gases* Information regarding lifetime occupational exposures to dust, fumes, and gases was requested in the section on residential and occupational history, page 2 of Form 1-71 (used for Watertown, Harriman, and St Louis). Industry, job, and materials handled were requested with approximate dates. Information was coded by years of exposure to dust and years of exposure to fumes, and a dichotomous variable was created. During an earlier internal audit of 89 Form 1-71 questionnaires, the investigators had found inconsistencies in the coding of these exposure data (a 15.7% coding error rate for occupational exposure to dust, and a 12.4% error rate for occupational exposure to fumes and gases. The dichotomous variable was not subjected to an internal audit).

We audited the data for occupational exposure variables against information listed on the initial questionnaire. We found the highest percentage of inconsistencies in the coding of occupational exposure to dust, fumes, and gases. Most of the coding errors in these variables were from the earliest form of the questionnaire, used in Watertown, Harriman, and St Louis. The section for occupational history on Form 1-71 allowed for variability in the way the interviewer recorded information. We found start and stop dates for exposure difficult to determine because no space had been provided on the form for the interviewer to summarize years of exposure. Of the 14 coding errors for the dust category, 12 involved the early questionnaire. Of the two errors in the later version, one was a rounding error. For the exposure to fumes category, 13 of 15 coding errors involved the first questionnaire. The two errors we noted in the later version were both due to rounding errors.

On the revised questionnaire used for Steubenville and for some respondents in Topeka [Form 77 (1-76)], a "years of exposure" column was added for dust and fumes and this information had been directly coded. The Audit Team found some inconsistencies in rounding of data. The only frank error we identified was that on one questionnaire, 26 years of exposure to coal dust had not been noted in the summary column and was not captured electronically.

We found exposures to dust in offices, schools, and libraries to have been coded inconsistently. For example, two long-time teachers had been coded as "0" exposure to dust, whereas another had been assigned a dust code representing "40" years, and dust in a library had been coded for another subject. No criteria used to classify exposures were mentioned in the code books.

Other potential inconsistencies included a bookkeeper in a service station with a code for "7" years of exposure to fumes (carbon monoxide). Another subject's 5 years of employment as a service station attendant had not been coded (this subject had other exposures to fumes for 8 years). In most cases, the subject's description of "materials handled" guided the coding, even if the information was not consistent with the job title. For example, a long-time carpenter did not mention dust exposure and had been coded as "0". A construction worker did not mention exposures and had also been coded as "0" for dust. The Audit Team did not note these as errors because the code book guidelines were to code information in the "materials handled" column. Nevertheless, we noted that the "0" codes for occupational exposures were not necessarily accurate descriptors.

The Original Investigators collapsed the fumes and gases exposure data into a binary variable of yes-no occupational exposure. Therefore, the rounding errors and questions about duration of exposure would not have affected this binary variable. However, recording a "0" for occupational exposure in cases such as the carpenter and construction worker would have influenced the binary categorization. The Audit Team questioned the assignment of "0" for dust exposure in 7 cases and for fumes and gases in 9 cases.

In summary, the Audit Team found (1) 14/249 (5.6%) inconsistencies for occupational exposure to dust: 1 rounding error, 2 overestimates of exposure, and 11 underestimates of exposure; and (2) 15/249 (6.0%) inconsistencies for occupational exposure to fumes: 2 rounding errors, 2 overestimates of exposure, and 11 underestimates of exposure. Underestimates typically had been coded "0" years.

*Education* As previously discussed, contemporary internal audits showed errors in recording levels of education because of the forms used and the fine distinctions present on the questionnaires. Form 77 (1-76) (used for all of Steubenville and some subjects in Topeka) contained a misprint so that code "1" meant "grade school not completed". The older Form 1-71 (for Watertown, Harriman, and St Louis) used code "1" to mean "grade school completed". Some interviewers using Form 77 (1-76) had crossed out the word "not" and coded this as "1" for "grade school completed" to make it consistent with the previous form. The Audit Team found several instances of this.

*Diabetes* Subjects were asked if their doctor had ever said they had diabetes or if they had been told they had sugar in their urine. No errors were found in the 249 questionnaires examined.

*High Blood Pressure* Subjects were queried as to whether they had been told their blood pressure was high and if

they had been treated for it in the last 10 years. In one case, the auditors concluded that notes written on the margin of the questionnaire suggested that a woman who had been coded as not having high blood pressure was likely treated for hypertension. This was not considered a coding error.

*Smoking Status* Subjects in this study were classified as current-smokers, former-smokers, or those who never smoked. This variable referred only to cigarettes because the coding protocol allowed cigar and pipe smokers to be classified as nonsmokers. We checked the Mort6C.file for each of the 249 subjects to determine that subjects classified as "nonsmokers" had no history of cigarette smoking, that "former-smokers" had matching data for former-smokers, and that "current-smokers" were matched with current smoking data. We found no differences in this variable.

*Pack-Years for Current-Smokers and Former-Smokers* An internal audit from 1981 showed that the calculation of pack-years of smoking cigarettes had been somewhat inconsistent in this study. The rules for calculating this variable had not been followed closely, especially for data from the earliest Form 1-71 with regard to "total amount of cigarettes currently smoked" and to "periods of smoking abstinence". Early calculations appear to have introduced a six-month correction factor to address the idea that people probably did not begin smoking on January 1 of a given year and did not stop smoking on December 31. Smoking data for respondents who initially completed Forms 77 (1-76) and 78 (1/77) were different from those for subjects who were interviewed using Form 1-71 because the six-month correction factor was dropped from later calculations. Furthermore, this study included a number of subjects who smoked their own hand-rolled cigarettes, and the use of hand-rolled cigarettes was factored into the total consumption. The 1981 internal audit clearly described limitations in how these problems in smoking data could be addressed. It concluded that the change from Form 1-71 to Forms 77 (1-76) and 78 (1/77) resulted in an underestimate of smoking pack-years by about 3% in the three cities where Form 1-71 was used (Watertown, Harriman, and St Louis).

The Audit Team spent a considerable amount of time resolving issues about smoking data. We discussed with Dr Dockery and Ms Fay the rules and formulas for recalculating pack-years, and then performed recalculations on the basis of these discussions and the documentation present in the code books. The Audit Team confirmed the findings of the 1981 internal audit; specifically, a slight underestimate of smoking for former-smokers versus current-smokers due to changes in the forms, and a slight underestimate (approximately 3%) of pack-years of smoking in the study.

*Height, Weight, and Body Mass Index* Height and weight were measured by the interviewers and recorded manually on the questionnaires. We audited height and weight against the Mort6C/HSPH.file because the printout of Mort6C.file provided to the Audit Team supplied only the aggregate calculation of BMI. After the audit, values for height and weight from the Mort6C/HSPH.file were validated against the Mort6C.file.

The audit of the height variable revealed six instances in which the Mort6C.file and the questionnaires differed. One was a simple rounding error; in the other five cases, the data file had been changed because subsequent spirometry measurements or questionnaires showed that the initial measurements of height had been inaccurate.

The audit of the weight variable revealed two differences, of which one was a simple rounding error. The other was for one of the subjects whose initial height measurement had been recorded incorrectly and changed later. Likewise, the subject's weight had been changed from 121 to 140 pounds. During the data editing phase, corrections were made to the data by the investigators whenever possible. It is possible that this change in weight was made during the editing process. Given the changes in data for this subject, we concluded that the original height and weight data had accidently been recorded in opposite fields for this individual.

These differences demonstrate the Original Investigators' attention to the consistency of data over time and have no negative impact on the study's results. Our recalculation of BMI revealed that differences were due only to the height and weight values as discussed. Our recalculation of the overall mean BMI for each city, as reported in Table 1 of the NEJM publication (see Table 17a), showed very minor differences.

*Initiation Date of Subject on Study* We crosschecked the date of enrollment into the study against the date of the interview on the initial questionnaire, the Mort6C.file provided to the Reanalysis Team, and the precursor file at HSPH (Mort6C/HSPH.file). For one subject, the month reported on the questionnaire was poorly legible; it appeared to us that the handwritten date of the interview could be November instead of December. The December date appeared in the Mort6C.file and in the Mort6C/HSPH.file. All other enrollment dates matched in their entirety (mm/dd/yr) for the audit subset.

*Time-on-Study (Initiation Date and Last Date)* We could not audit "time-on-study" directly because it was a calculated variable. The calculation depended upon what cutoff date had been used for each city. Another factor in verifying these calculations was that some records had been updated after the ending date for the study analyses.

If the Audit Team found that the subject had died between the dates of completing the initial questionnaire and the last date of follow-up for that city, we verified the date of death against the death certificate (or, in cases where no death certificate was available, against information supplied by the subject's family) and calculated the time-on-study accordingly. To audit this vital status variable for subjects who had not died during follow-up, we used information on dates from the last completed questionnaire, the pink cover tracking sheet, work cards, some summary computer printouts, and postcards that were sent periodically to study participants and returned by them. We compared all of this information against interim printouts from the Mort6C/HSPH.file.

After we completed the audit for time-on-study in Watertown, several discrepancies were noted in the data for each of the other five cities. When we discussed this with Ms Fay and Dr Dockery, a search of their records showed that an error in a computer program had resulted in some data for some subjects not being updated in each of the other five cities. This led to a loss in the total number of years of follow-up. (In epidemiologic studies, this is referred to as "early censorship of person-years of follow-up".) For the Audit Team's subset of 249 subjects, Dr Dockery and Ms Fay re-created the time-on-study and found a loss of approximately 1% in the reported person-years for the entire study. The Original Investigators also provided a summary of the entire study showing the number of subjects in each city for which early censorship of data had occurred (Table 3). Early censorship was greater in Portage and Topeka than in other cities.

**Table 3.** Early Censorship of Person-Years of Follow-Up in the Six Cities Study

| City | Number of Subjects | Number of Subjects with Early Censorship | Percentage |
|---|---|---|---|
| Harriman | 1,258 | 35 | 2.8 |
| Portage | 1,631 | 185 | 11.3 |
| Steubenville | 1,351 | 51 | 3.8 |
| St Louis | 1,296 | 36 | 2.8 |
| Topeka | 1,239 | 152 | 12.3 |
| Watertown | 1,336 | 0 | 0 |
| Total | 8,111 | 459 | 5.7 |

**Subset of Deceased Subjects: Death Certificates**

The Audit Team randomly selected another independent subset of 250 SID numbers that had been coded as deceased in the Mort6C.file. We examined the 248 (92.2%) of the matching death certificates that were found. We compared the following information in the Mort6C.file and the source documents:

- date of death in Mort6C.file against the date of death on the retrieved death certificate;
- identifying information of subjects contained on the death certificate against the same information on the subject's initial questionnaire so as to determine that the correct death certificate had been obtained for the person who completed the study questionnaire;
- cause of death recorded in the Mort6C.file against the ICD-9 code the study nosologist wrote on the pink cover tracking sheet attached to the death certificate;
- cause-of-death code assigned by the study nosologist against the ICD-9 code interpreted by the Audit Team from the death certificate;
- cause-of-death groupings recorded in Mort6C.file against the criteria for assigning the cause of death to a group;
- date of subject's initiation on study and date of death on the death certificate against calculation of time-on-study.

***Date of Death*** When we matched the Mort6C.file with the death certificates, we found errors for two subjects. One error (year of death) had been detected by the Original Investigators after the epidemiologic analysis had been completed, and the current Mort6C/HSPH.file reflected the correct information. The second error (month of death) had not been corrected in the current Mort6C/HSPH.file.

***Correct Death Certificate*** Using information from the questionnaires, the Audit Team verified that the death certificate on file reflected the correct study participant by matching the full name, SSN, birth date, and gender. Social Security Numbers were not recorded on all death certificates, and the Audit Team noted other minor inconsistencies between the death certificates and the questionnaires, which usually involved one digit of the SSN or birth date. However, the 247 available death certificate and questionnaire pairs matched in enough fields to verify that all the death certificates pertained to the correct study participants.

**Table 4.** Discrepancies Between Cause-of-Death Codes by Study Nosologist and Audit Team for the Six Cities Study

| Code by Study Nosologist | Comments | Code by Audit Team's Nosologist | Change of Code Would Have Altered the Category in the Epidemiologic Analysis |
|---|---|---|---|
| Diabetes with ophthalmic manifestations (250.5) | | Diabetes with renal manifestations (250.4) | |
| Malignant neoplasm without specification of site (199.1) | The death certificate reads, "metastatic ADCA [adenocarcinoma] to liver, unknown primary". | Secondary neoplasm to liver (197.7) | |
| Congenital mitral stenosis (746.5) | The coding of this case appears to have been in question because one notation in red ink lists 394.0, but then a comment is added that the "patient's age affects the coding". The death certificate reads, "rheumatic heart disease (mitral stenosis)"; rheumatic heart disease is an acquired, not congenital, condition. Therefore, the nosologist's first code of 394.0 is consistent with the death certificate. | Mitral valve stenosis (394.0) | |
| Chronic obstructive pulmonary disease (COPD) (496.0) | The death certificate lists the following causes of death: line a, respiratory failure; line b, COPD; line c, metastatic malignant melanoma. | Malignant melanoma (172.9) | This death would have changed categories from "cardiopulmonary" to "lung cancer". |
| Chronic ischemic heart disease (414.9) | The death certificate lists the following causes of death: line a, hypotension; line b, massive stroke; line c, congestive heart failure (CHF). The order listed by the physician is questionable because the underlying (primary) cause of death most likely was the massive stroke, although the physician lists CHF on line c. | Cardiovascular aneurysm (CVA; stroke) (436.0) or CHF (428.0) | |
| Acute myocardial infarction (410.0) | The death certificate lists the following causes of death: line a, acute myocardial failure; line b, atherosclerotic heart disease; and line c, cancer of kidney. | Malignant neoplasm of kidney (189.0) | This death would have changed categories from "cardiopulmonary" to "other". |

***Cause-of-Death Codes*** First, the Audit Team compared the primary cause of death listed in the Mort6C.file as a four-digit ICD-9 code against the nosologist's code recorded on the pink cover tracking sheet attached to the death certificate and found that 100% of the codes matched. In three cases, the Mort6C.file included no ICD-9 code because the death certificate had not been coded.

Two areas on the death certificate record the causes of death: Cause of Death Part I and Part II. Part I has three lines. One, two, or three lines may be completed by the physician as follows: line a, immediate cause of death; line b, explanation of the immediate cause (immediate cause due to or a consequence of); and line c, explanation of line b (due to or a consequence of). The final entry in Part I is considered the underlying (or primary) cause of death. Part II is a one-line area for the physician to detail other significant conditions that are not directly related to the underlying cause of death.

Using the ICD-9, Dr Donna Foliart of the Audit Team coded the underlying (primary) cause of death listed on each of the death certificates and the Audit Team compared them with the study nosologist's ICD-9 code (which had been recorded on the pink cover tracking sheet attached to the death certificate). In six cases, Dr Foliart's code did not match the full four digits of the study nosologist's code. In

**Table 5.** Audit Results for the Subset of Deceased Subjects in the Six Cities Study[a]

| Variable Used in Epidemiologic Analysis | Number of Records | Number of Inconsistencies | Percentage |
|---|---|---|---|
| Date of death | 248 | 2 | 0.8 |
| Death certificate and study participant identifiers | 247 | 0 | 0 |
| Nosology code | 248 | 6 | 2 |
| ICD-9 code in Mort6C.file | 248 | 0 | 0 |
| Cause-of-death group based on nosologist's code | 248 | 0 | 0 |
| Total | 1,239 | 8 | 0.6 |

[a] All source documents were death certificates.

the epidemiologic analysis, the investigators had grouped deaths into four cause-of-death categories: cardiopulmonary, lung cancer, other, and missing. Of the six discrepancies in ICD-9 codes, two would have altered the category used in the original analyses.

Details of the six discrepancies are described in Table 4, which gives Dr Foliart's code, the study nosologist's code, and comments from the Audit Team. The findings from the audit of the subset of deceased subjects are summarized in Table 5.

## AUDIT OF AIR QUALITY DATA

### Description of Original Air Quality Dataset

The original epidemiologic analysis characterized ambient air quality as long-term mean concentrations of various air pollutants. The following variables were reported for each of the six cities from measurements taken during the indicated years: concentrations of total particles (1977–1985), inhalable and fine particles (1979–1985), sulfate particles (1979–1984), aerosol acidity ($H^+$)(1985–1988), sulfur dioxide (1977–1985), nitrogen dioxide (1977–1985), and ozone (1977–1985). Measurements of air pollutants were taken using well established methods augmented with newly developed techniques as necessary. The methods used to calculate mean concentrations (eg, as the average of seasonal means, annual means, or individual observations) were not specified.

Further description of the Audit Team's decisions about which air quality data to audit and how to proceed is presented below for different groups of pollutants.

***Gases*** The gases ($SO_2$, $NO_2$, and $O_3$) had been monitored hourly by standard continuous instrumentation and recorded in parts per billion. The measurements had been checked by contemporary external audits (eg, Eaton et al 1982). Selective inspections by our Audit Team of the original data records, operator logs, and field audits for these measurements did not indicate any unusual problems. As a result, we decided not to audit these data or the findings associated with them.

***Acidity*** Aerosol acidity had been measured for about one year in each city. The hydrogen ion concentrations were determined using research-quality methods to analyze 24-hour fine particle samples collected with Harvard impactors (Koutrakis et al 1988). However, measurements were conducted in only two cities at a time, starting with Harriman and St Louis from December 1985 through August 1986 (9 months) and finishing with Topeka and Watertown in August 1988 (10 and 14 months, respectively). Thus, it was impossible to compare acidity for a common time period.

Furthermore, the acidity data were not necessarily linked with particle data in the same city; for example, dichotomous particle sampling at Watertown ended 18 months before the initiation of measurements of acidity. Because intercity comparisons were confounded by uncontrolled interannual variability, and the acidity measurements were disconnected from other particle measurements, we decided not to audit them.

***Particles*** The Original Investigators reported mean concentrations for four classifications of particles in each of the six cities: TSP (particles with aerodynamic diameters as large as 50 μm), inhalable particles, fine particles, and sulfate particles. In the sections that follow, we describe different samplers and methods of arriving at these four groups. All particle measurements were recorded as mass concentrations ($\mu g/m^3$).

Values of mass for TSP (for the years 1977–1985) and sulfate particles (for the years 1979–1984) were determined from 24-hour samples collected by General Metal Works (regulatory standard) high-volume samplers having unrestricted inlets. The sample was first weighed to determine the concentration and then subjected to chemical analysis to determine the concentration of sulfate ions. The methods used were Federal Reference Methods and they had been subjected to contemporary external audits (eg, Eaton et al 1982) of both the sample collection procedures and the laboratory analyses.

Inhalable particle mass was calculated from coarse and fine particle mass, which had been determined from 24-

hour sample pairs collected by Beckman dichotomous samplers. At the time of its introduction, the dichotomous sampler was relatively new and untested and was still undergoing a number of operational difficulties. Furthermore, most researchers had much less experience with it than they had with the older high-volume sampling technology.

Compared with the dichotomous sampler, the high-volume sampler is a "simple" tube with a single filter mounted in the middle; one end of the tube is open to the atmosphere and the other is attached to a powerful vacuum pump, thus allowing the filter to collect particles of all sizes. In contrast, the dichotomous sampler is designed on the complex principle of virtual impaction. In still air, and under the influence of gravity, large particles settle out more rapidly than small particles. In curving or decelerating airflows, and under the influence of centrifugal forces, large particles are correspondingly quicker than small particles to migrate to the outer boundaries and impact on outer surfaces. The inlets of particle samplers are designed to impose contortions on entering airflows sufficient to make nearly all particles above a selected size impact on the surfaces of the inlet. (This is the principle of the size-selective inlets [SSIs] routinely used to remove from the sample air particles greater than 10 or 15 μm in aerodynamic diameter.) The remaining smaller particles are captured on a fine particle filter.

The dichotomous sampler exploits this same aerodynamic separation phenomenon to separate from the same airstream particles both above and below 2.5 μm in diameter. The filter in the primary flow of intake air (the fine particle channel) collects only particles smaller than 2.5 μm. Most of the intake air (typically 90%) is forced to undergo a sharp deceleration (secondary flow) and is focused into a receptacle of dead air (the coarse particle channel). At the bottom of the receptacle is a coarse filter that collects coarse particles, any directly impacted particles, and any fine particles carried by the secondary air flow. The calculation of coarse particle mass concentration includes a correction factor for the fine particles collected in the coarse particle channel.

In the dichotomous samplers used in the Six Cities Study, the fine particle channel collected particles smaller than about 2.5 μm and the measurement was recorded directly as fine particle (FP) mass. The coarse particle channel collected particles between 2.5 μm and 10 or 15 μm in aerodynamic diameter (the upper bound measurement depended on the inlet size used at the time, which is discussed later). These samples were corrected for the inclusion of some fine particles, and the correction resulted in the coarse particle (CP) mass. Then both FP and CP values were added to yield the inhalable particle (IP = FP+CP) mass, which included all particles smaller than 10 or 15 μm in aerodynamic diameter.

In different years, measurements of mass from dichotomous samples were carried out by different organizations in different laboratories (described in detail in the next section) by two fundamentally different methods. The dichotomous sampler analyses also had not been verified by blinded audits of samples, as had the high-volume sample analyses. In addition, the Audit Team found the existing records of dichotomous samples to be more fragmented than those for the high-volume sampler measurements. For these reasons, we decided the dichotomous sampler particle data ought to be the principal focus of our audit.

### Original Analysis of Air Pollutants from the Dichotomous Samplers

Over the course of the study, several changes were made in operating the samplers and in the methods used to analyze the samples.

- Until and throughout most of 1981, the filters from the samplers were analyzed by an EPA laboratory in North Carolina. This laboratory determined mass by β-absorption gauge.
- In October and November 1981 (exact dates varied in each city), the analysis of the filters was transferred to HSPH until 1984. The HSPH laboratory used standard gravimetric analysis in which the filters were weighed before and after exposure. (Courtney and colleagues [1982] found no significant bias between the two methods of sample analysis when they applied them to air quality samples [not from the Six Cities Study] collected in North Carolina.)
- In January and February 1984, the analysis of the filters was transferred from HSPH back to the EPA laboratory in North Carolina; the mass was again measured using the same methods as before.
- Also in January and February 1984, the filters on the coarse particle channel were oiled to improve particle adhesion. This action was taken in response to a discovery that substantial and variable particle losses had been occurring in transit and handling (Dzubay and Barbour 1983; Spengler and Thurston 1983). Oiling the filters would have increased the levels of coarse particle mass but would not have affected measurements of fine particle mass.
- In March and April 1984, new inlets were installed that reduced the 50% sampling cutoff for particle size from 15 μm to 10 μm. This action would have resulted

**Table 6.** Changes in Dichotomous Sampler Configurations and Analysis Methods in the Six Cities Study

| Factor Changed | Epoch 1 (1979–1981) | Epoch 2 (1981–1984) | Epoch 3 (1984–1984[a]) | Epoch 4 (1984–1988[b]) |
|---|---|---|---|---|
| Inlet size cutoff[c] | 15 | 15 | 15 | 10 |
| Coarse filter | Dry | Dry | Oiled | Oiled |
| Type of analysis | β Gauge | Gravimetric | β Gauge | β Gauge |
| Analysis laboratory | EPA | HSPH | EPA | EPA |

[a] At the longest, this epoch lasted from January through April of 1984.

[b] The data from 1986–1988 were not used in the epidemiologic analysis published in NEJM.

[c] From the coarse particle channel of the size-selective impactor.

in lower levels of coarse particle mass but would not have affected measurements of fine particle mass.

The Audit Team used these transitions to partition the dichotomous sampler measurements into four distinct epochs, as summarized in Table 6.

### Data Transmission, Electronic Recording, and Contemporary Quality Assurance

Quality assurance of data gathering procedures was centrally coordinated at HSPH. As they were being applied in 1982, QA procedures were described in a paper presented at the annual meeting of the Air Pollution Control Association (Briggs et al 1982). A contemporary QA manual (Harvard School of Public Health Air Quality Group 1982) was also available. Both of these documents had been written before any of the changes had been instituted in how the dichotomous samplers were operated and how the samples were analyzed.

From 1979 through the summer of 1981 (Briggs et al 1982), filters from the six cities were returned to the EPA laboratory for analysis. These shipments were accompanied by standard forms (EPA 3B) that supplied information (such as total flow rate and the duration of the sample run) needed to convert the filter loadings to ambient concentrations. The EPA laboratory performed the analysis and the calculations of concentration and returned concentrations corrected for blank filter values. Meanwhile, HSPH collected weekly field logs and calibration records directly from the sampler operators.

The EPA data were screened for encoding and transmission errors, compliance with standard operating procedures and criteria, and statistical anomalies (outliers), and then merged with other study records at HSPH into a master data file. Briggs and colleagues (1982) outlined a review process that augmented each record with diagnostic variables (referred to as "flags") that indicated whether procedures and data were within acceptable ranges.

In the summer of 1982, the Quality Assurance Division of the EPA's Environmental Monitoring Systems Laboratory organized and coordinated a thorough systems audit carried out through personnel of the Research Triangle Institute (Eaton et al 1982).

No updated documentation was located for the years after 1982. The Audit Team assumed that the same procedures were used but likely were modified when gravimetric measurements were made at HSPH.

In addition to the 1982 systems audit described above, the Office of Scientific Integrity (OSI) conducted an external and independent review in response to an internal accusation of misconduct in the processing of ozone measurements. The OSI scrutinized the gas concentration data in detail and concluded that their "exhaustive inquiry resulted in a 'clean bill of health' for the study and for the Six Cities scientists" (SW Hadley, written communication, November 1990).

### Data Provided and Source Documents Accessible for the Reanalysis

The Audit Team expected to have available a master electronic database of all air pollution measurements for the entire Six Cities Study; however, master data files were not found. Instead, various data files contained different data subsets, which appeared to have been selected from a common database according to different screening criteria. The efforts to reconstruct the data used to produce the results published in the NEJM are discussed in the next sections.

The primary data that seemed to be missing from the master database were the dichotomous sampler data. Several records documenting original dichotomous sampler measurements and analyses were accessible for some time periods from some cities: laboratory (both EPA and HSPH) transmittals of filter sample measurements and concentration calculations (both electronic and hard copies), some

HSPH data files, and field logs from the dichotomous sampler operators. However, there was no city or time period for which all of these records could be located.

### Audit Objectives for Data from Dichotomous Samplers

The Audit Team arrived at the following decisions regarding the scope of the audit for the air quality data:

- We decided not to conduct an audit of the gases because data on gases ($SO_2$, $NO_2$, and $O_3$) had been appropriately checked by external contemporary audits and the 1990 OSI investigation; therefore, no further review was warranted.
- Data on aerosol acidity had not been collected over a common time period for all six cities, and the data had not been necessarily connected to concurrent particle measurements; therefore, an audit was not required.
- The particle data from high-volume samplers had been collected and analyzed with Federal Reference Methods and subjected to contemporary external audits; no further review seemed necessary.
- The particle datasets from dichotomous samplers had been acquired and analyzed with different methods and procedures at different times; these warranted the primary attention and resources of the Audit Team.

Our audit of the air quality data had three broad objectives:

1. verify the conversion of primary filter measurements of air pollutants into concentrations;
2. evaluate the procedures for validating and archiving the concentrations; and
3. clarify how the published means had been derived and evaluate how sensitive the means may be to computational procedures and data selection criteria.

Dr Warren White of the Audit Team conducted two site visits at HSPH on March 8 through 12 and April 12 through 16, 1999. Two years earlier, Dr White had acquired from Dr Dockery a computer spreadsheet containing various particle mass concentrations for 1979–1986: (1) TSP data from high-volume samplers; (2) inhalable particle data from high-volume samplers with SSIs (these data had been recorded every sixth day and had not been used in the air pollution analyses for the NEJM article); and (3) fine and coarse particle data from dichotomous samplers. This extracted dataset (referred to hereafter as 1997.file) had been assembled specifically for Dr White and the data included had not necessarily been selected according to the same criteria used for the epidemiologic analysis of mortality and air pollution. In preparing for the Audit Team's site visit, Dr White used this 1997.file to guide which measurement locations (cities) and periods would be appropriate to review in detail at HSPH.

#### Objective 1. Verify Conversion of Primary Filter Measurements into Concentrations

To convert a simple filter measurement to an ambient mass concentration, one generally needs four numbers: the mass of the filter with the sample, the mass of the (blank) filter without the sample, the sampler flow rate, and the sampling duration. We wanted to recalculate a few filter measurements to establish the following points.

- The correctness of the calculation, which is significantly more complex for a sample from a dichotomous filter than one from a simple filter. The Audit Team also noted that the equation for this calculation had been reported incorrectly in HSPH's QA Manual for Air Quality Assessment (section III, chapter 6, page 4, C_MASS formula, May 1982); therefore, we wanted to verify the actual methods used for these calculations.
- The handling of the blank correction factor and its effect on uncertainty. The QA Manual states (in section I, chapter 10, page 1, March 1982) that the first filter in each tray of 36 was to be used as a blank in the analysis, but it also indicates (in section III, chapter 6, pages 3 and 4) that mass concentrations were to be calculated from β-absorption gauge measurements with no blank corrections.
- The reporting convention for concentrations: ambient conditions, standard temperature and pressure, or something else?

***Extant Original Records by Epoch*** The archival master electronic data files described by Briggs and colleagues (1982) were not found for epoch 1 (1979–1981). Contemporary hard copies were located for at least some of the concentration transmittals received at HSPH from the EPA laboratory during epoch 1 (1979–1981), and the Audit Team was able to review several monthly records from Harriman (1980), Portage (1980), Steubenville (1980), and St Louis (1980). The EPA transmittals describe data before they were subjected to the screening process described by Briggs and colleagues (1982) and are therefore unflagged.

Similarly, master data files for epoch 2 (1981–1984) were not found. The only laboratory records available for inspection for epoch 2 were those from the HSPH laboratory.

Printouts of the master data files were located for epochs 3 and 4 (1984–1988). These printouts had been produced at HSPH in the late 1980s and accounted for essentially all of the observations recorded in the site operator logs the Audit Team reviewed (Harriman 1985; Topeka 1984, 1985,

**Table 7.** Original Records for Dichotomous Samplers Examined in the Audit of the Six Cities Study[a]

| City | 1979–1981 | 1982–1983 | 1984–1988[b] |
|---|---|---|---|
| Harriman | EPA Lab | | Field logs, HSPH MF |
| Portage | EPA Lab | | |
| Steubenville | EPA Lab | | HSPH MF |
| St Louis | EPA Lab | Field logs, HSPH Lab | HSPH MF |
| Topeka | Field logs | | Field logs, HSPH MF |
| Watertown | | | Field logs, HSPH MF |

[a] Individual entries in columns represent samples of records spanning several weeks to several months, not all of the years mentioned. Different datasets were available in different years. EPA Lab = EPA laboratory transmittals; HSPH Lab = HSPH weighing laboratory records; HSPH MF = HSPH master data files; and field logs are from dichotomous sampler operators.

[b] The data from 1986–1988 were not used in the epidemiologic analysis published in NEJM.

and 1988; Watertown 1985). The printouts were of data files that had been subjected to the QA procedures described by Briggs and colleagues (1982) and included flagged data fields.

The Audit Team received no response to a request to visit the EPA contract laboratory in North Carolina. Table 7 summarizes the original records the Audit Team examined during the site visits at HSPH. We did not randomly sample cities and periods, as we did with individual health records, because air quality data records were not uniformly available.

***Audit Team's Recalculations of Concentrations*** We could not recalculate the measurements made during epochs 1, 3, and 4 because records of the analyses completed at the EPA laboratory were not available at HSPH. These data conversions should not be of concern, however, because the EPA laboratory was the leading practitioner of these methods at the time.

The Audit Team was successful in recalculating concentrations from primary filter measurements for some of the analyses conducted at HSPH during epoch 2. Figure 1 shows results obtained for 30 observations of concentrations for St Louis from May through July 1983. The Audit Team found no indication that adjustments were made for variations in temperature and pressure. The root-mean-square difference between calculated and reported concentrations is 0.7 μg/m$^3$ for fine particles and 1.0 μg/m$^3$

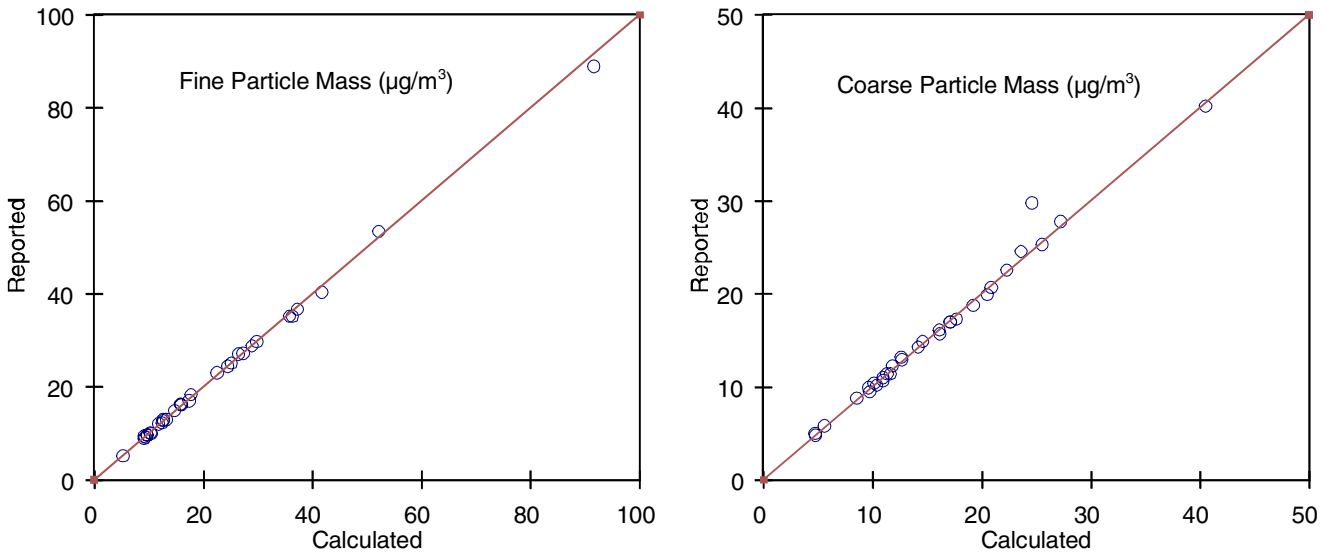



**Figure 1. Agreement between reported and newly calculated fine (left panel) and coarse (right panel) particle mass concentrations in St Louis May–July 1983.** The straight line in each panel defines perfect agreement.

for coarse particles. This level of discrepancy could arise from minor uncertainties as to the exact procedure used in the original conversion.

**Objective 2. Evaluate Procedures for Validating and Archiving Concentration Measurements**

The written procedures used to validate and document laboratory transmittals and the computerized and manual review processes used to inspect the data and input them into the master air pollution files are described in the section Data Transmission, Electronic Recording, and Contemporary Quality Assurance. That section also references a contemporary QA manual (Harvard School of Public Health Air Quality Group 1982); the Audit Team found some of the formulas and descriptions in that manual to be clearly erroneous. The manual refers to an additional report documenting procedures at the EPA contract laboratory, but no copy of that report could be located at HSPH.

One set of records the Audit Team examined included hard-copy transmittals from the EPA laboratory of data from Steubenville for the period April 1979 through February 1981. This period had been discussed in some detail by Briggs and colleagues (1982) to illustrate the conventions for validating data. According to Briggs, during the period of September 16 through 24, 1980, the samples for all 9 days had been noted by the site operator as "suspect" because of repairs to the roof on which the sampler was located. Concentrations for all of these samples were included in the EPA transmittal to HSPH, as they should have been. According to Briggs' documentation, the data were not voided but were archived and coded with a "suspect" flag.

**Objective 3: Clarify Derivation of Published Means and Evaluate Their Sensitivity to Computational Procedures and Data Selection Criteria**

***Air Quality Dataset*** The master air pollution data files were no longer accessible on the HSPH computer system and the staff of HSPH were unable to locate a copy of this file. Various electronic data files examined during the first visit were found to contain different data subsets and appeared to have been selected from a common database according to different screening criteria. However, one source of potential problems was that different values were sometimes reported in different files for the same observation.

During the first site visit, Dr Dockery produced a provisional and incomplete reconstruction of the air quality data used in the NEJM analysis; he supplemented these data with dichotomous sampler mass concentrations used in a time-series analysis published in a 1996 article in the *Journal of the Air and Waste Management Association* (JAWMA; Schwartz et al 1996; hereafter, the electronic file containing the data published in JAWMA is referred to as JAWMA.file). None of the data files found on the HSPH computer and none of the reconstructed databases could produce the exact air pollution concentration averages reported in the NEJM article. Before the second onsite audit, Dr Dockery produced an improved reconstruction of the NEJM analytical file (hereafter referred to as Reconstruct.file), which was the one the Audit Team used to compare with all other original records of air pollution transmittals. The Reconstruct.file likely comprised electronic data files extracted from the master air pollution files in different years, according to criteria that evolved with time.

*Comparison of Original Records with Reconstruct.file* The Audit Team verified the fine particle mass concentrations in the Reconstruct.file with some of the original records described in Table 7 for each of the epochs described in Table 6; the results are summarized in Table 8. The Audit Team could account for all but 3 of the 1,010 values examined in the Reconstruct.file (in Table 8, see the column "NEJM vs Original Records" under "Number Unmatched"); these 3 data points could simply have been missed in the audit.

*Comparison of Original Records with JAWMA.file* Although the JAWMA air data were not formally audited, Table 8 includes results of a similar comparison for the JAWMA.file because it is discussed below as an alternative representation of the dichotomous sampler data. A significantly larger number (64 of 1,191) of the JAWMA values that were examined could not be accounted for and some of them are from dates when field logs indicate that no samples were taken.

***Criteria for Selecting Data for the Mortality and Air Pollution Analysis*** No contemporary account could be found of the criteria used to select data for the mortality and air pollution analyses. Nevertheless, the Audit Team was able to infer some of the criteria used by comparing the Reconstruct.file with available earlier records. This comparison clearly reflected that some selection criteria had changed over the years, as described in the next sections.

*Restriction on Coarse/Fine Mass Ratio* Data from epoch 1 (1979–1981) were systematically excluded whenever the coarse/fine mass ratio was less than 0.3 or greater than 1.3. This restriction reflects early EPA guidance; Briggs and colleagues (1982) noted that it does not allow for actual variations in particle size distributions: thus, it "appears to be an undesirable check for bad values in its present form. … [I]f this criterion were employed to void data, it would likely introduce bias into the datasets." Data from later

years (1982 on) were included regardless of coarse/fine mass ratios in accordance with the recommendation of Briggs and colleagues. The abrupt elimination of the coarse/fine mass ratio restriction is shown in the time-series ratios reported for Portage, which are plotted in Figure 2 from the Reconstruct.file. A similar pattern was found in all six cities.

Even during the time it was applied, however, the coarse/fine mass ratio restriction did not greatly affect the fine particle concentrations for Portage in any obvious manner. This effect is shown in Figure 3, which compares the Reconstruct.file data from HSPH for Portage in 1980 with the values reported by the EPA contract laboratory. The EPA data points that are unmatched by HSPH data points are those values that HSPH excluded because the coarse/fine mass ratio fell outside the applied boundaries.

The Audit Team also assessed the empirical effect of the coarse/fine mass ratio restriction on average concentrations by applying the restriction to otherwise unrestricted data in the Reconstruct.file for 1982 and later years (Table 9). Had the restriction been applied to the data in these years, the greatest impact would have been seen in Topeka, where Briggs and colleagues (1982) reported the average measured ratio would have fallen outside the "appropriate" range.

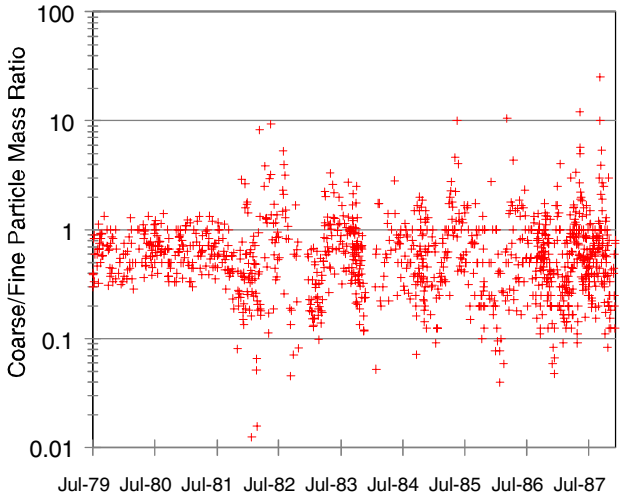



**Figure 2. Time-series data from Reconstruct.file for Portage 1979–1987.** The scattering of data points shows that data from epoch 1 (1979–1981) were systematically excluded whenever the coarse/fine mass ratio was less than 0.3 or greater than 1.3.

*Exclusion of Samples Collected from Multiple Filters*

Another selection criterion employed was the exclusion of concentrations measured with more than one set of filters. Samples were sometimes collected over multiple filters because the Beckman dichotomous samplers automatically switched to a new filter pair whenever the fine particle

**Table 8.** Comparability of Dichotomous Sampler Fine Particle Mass Concentrations from Original Records Inventoried in Table 7, Reconstruct.file (NEJM), and JAWMA.file for the Six Cities Study

| | Period Audited | | Number of Values | | | Number Unmatched[a] | | | | Mean Value (μg/m$^3$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| City | Start | End | Original Records | NEJM | JAWMA | Original Records vs NEJM | NEJM vs Original Records | Original Records vs JAWMA | JAWMA vs Original Records | Original Records | NEJM | JAWMA |
| Harriman | 01/30/80 | 05/06/80 | 69 | 51 | 67 | 18 | 0 | 2 | 0 | 23.0 | 22.9 | 22.5 |
| | 02/12/85 | 12/17/85 | 205 | 205 | 217 | 0 | 0 | 0 | 12 | 20.2 | 20.1 | 19.7 |
| Portage | 02/27/80 | 07/16/80 | 68 | 36 | 69 | 32 | 0 | 1 | 2 | 13.3 | 14.3 | 13.3 |
| Steubenville | 05/01/80 | 08/03/80 | 64 | 26 | 60 | 38 | 0 | 4 | 0 | 48.0 | 29.8 | 46.6 |
| | 01/19/84 | 07/11/84 | 84 | 82 | 84 | 2 | 0 | 0 | 0 | 26.1 | 26.6 | 26.1 |
| St Louis | 03/20/80 | 09/08/80 | 97 | 70 | 96 | 27 | 0 | 1 | 0 | 23.7 | 25.3 | 23.5 |
| | 03/10/82 | 04/01/82 | 12 | 12 | 12 | 0 | 0 | 0 | 0 | 14.3 | 13.8 | 13.8 |
| | 05/12/83 | 08/01/83 | 30 | 30 | 30 | 0 | 0 | 0 | 0 | 22.2 | 22.8 | 22.8 |
| | 02/18/85 | 01/01/86 | 157 | 153 | 173 | 4 | 0 | 3 | 19 | 17.5 | 17.9 | 17.6 |
| Topeka | 02/21/84 | 08/01/84 | 96 | 96 | 97 | 1 | 1 | 0 | 1 | 12.6 | 12.7 | 12.6 |
| | 02/03/85 | 05/22/85 | 72 | 72 | 76 | 0 | 0 | 0 | 4 | 10.4 | 10.4 | 11.0 |
| Watertown | 01/10/85 | 12/31/85 | 203 | 177 | 210 | 28 | 2 | 19 | 26 | 14.2 | 14.6 | 14.9 |
| Totals | | | 1,157 | 1,010 | 1,191 | 150 | 3 | 30 | 64 | | | |

[a] The number of entries in the first file for which no corresponding entries were found in the second.

**Table 9**. Effects of Excluding Observations Outside the Acceptable Range of Coarse/Fine Particle Mass Ratio (0.3–1.3) in the Six Cities Study[a]

| | Number of Observations | | Average Fine Particle Concentration (μg/m$^3$) | | |
|---|---|---|---|---|---|
| City | All Data[b] | Restricted[c,d] | All Data[b] | Restricted[c] | Percentage of Change[e] |
| Harriman | 699 | 546 (78%) | 19.6 | 19.2 | –2 |
| Portage | 508 | 310 (61%) | 10.5 | 10.5 | 0 |
| Steubenville | 541 | 424 (78%) | 26.1 | 26.6 | 2 |
| St Louis | 588 | 443 (75%) | 17.8 | 18.0 | 1 |
| Topeka | 557 | 270 (48%) | 11.7 | 13.5 | 15 |
| Watertown | 602 | 399 (66%) | 14.1 | 14.1 | 0 |

[a] All data in the Reconstruct.file for 1982–1985.

[b] Values for all days (observations) regardless of the coarse/fine mass ratio value.

[c] Values for days (observations) on which the coarse/fine mass ratio fell within the range.

[d] Percentage of all observations in parentheses.

[e] This was calculated as [(Restricted – Whole)/Restricted] × 100%.

flow dropped below a specified rate (14.25 L/min, from a nominal 16.7 L/min). As Briggs and colleagues (1982) noted, "This can be expected to happen during very polluted days, when the filters become heavily loaded.... [This condition] (multiple samples in a day) does not indicate questionable data." Rejecting these observations could have incorrectly attenuated high concentrations.

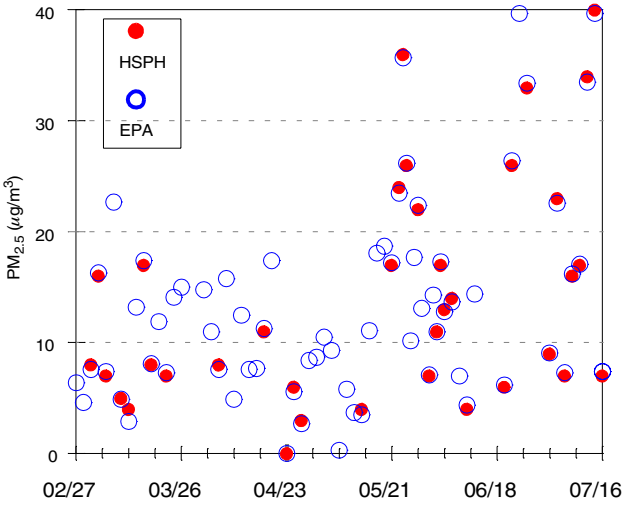



**Figure 3. Data for Portage from 2/27/80 to 7/16/80 restricted due to coarse/fine mass ratio.** Open circles are data transmitted from the EPA laboratory and filled circles are data from the HSPH Reconstruct.file. Misalignment of coincident EPA and HSPH values reflects numerical rounding of the HSPH values. The EPA data points that have no matching HSPH data points were data excluded from the HSPH files because the coarse/fine mass ratio fell outside the acceptable range of 0.3–1.3. Average fine particle mass was 13.3 μg/m$^3$ for the 68 EPA measurements and 14.3 μg/m$^3$ for the 36 HSPH values.

Figure 4 compares the data in the Reconstruct.file with the values reported to HSPH by the EPA laboratory in Steubenville in 1980 that included high concentrations of fine particles. As suggested by Briggs and colleagues (1982), concentrations were generally higher on days when multiple filters were used. The EPA laboratory

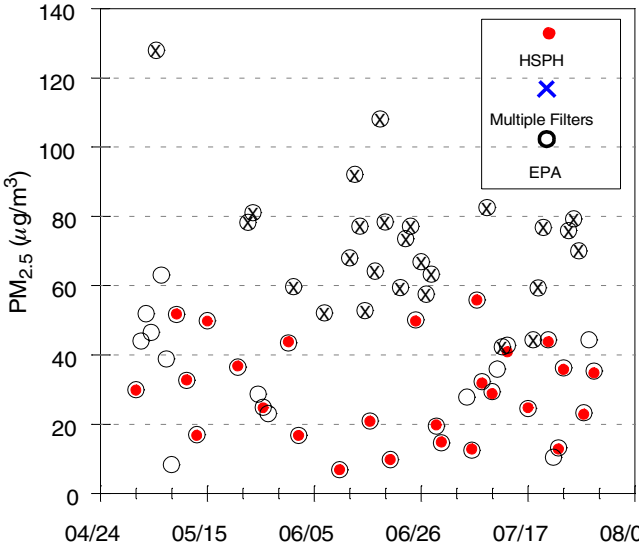



**Figure 4. Fine particle levels for a period of time in Steubenville in 1980 that included high concentrations of fine particles.** Open circles are values reported to HSPH by the EPA contract laboratory; an ⊗ indicates a value obtained from multiple filters; filled circles are data in the HSPH Reconstruct.file. The recordings of higher concentrations were generally on days when multiple filters were used. Of the 64 EPA laboratory observations, 26 measurements had been acquired with multiple filters and were excluded from the HSPH analysis. The HSPH Reconstruct.file reports 26 concentrations, all from single filters.

**Table 10.** City Mean Particle Concentrations Published in NEJM and Recalculated from Reconstruct.file for Indicated Years of the Six Cities Study[a]

| City | Published (NEJM)[b] | Mean of All Observations | Mean of Annual Averages | Mean of Quarterly Averages |
|---|---|---|---|---|
| **Fine Particles (1979–1985)** | | | | |
| Harriman | 20.8 | 20.9 | 20.8 | 20.9 |
| Portage | 11.0 | 11.0 | 11.0 | 11.0 |
| Steubenville | 29.6 | 29.6 | 29.7 | 29.6 |
| St Louis | 19.0 | 19.0 | 19.7 | 19.0 |
| Topeka | 12.5 | 12.5 | 12.9 | 12.5 |
| Watertown | 14.9 | 14.9 | 15.2 | 14.9 |
| **Inhalable Particles (1979–1985)** | | | | |
| Harriman | 32.5 | 32.6 | 32.5 | 32.6 |
| Portage | 18.2 | 18.2 | 18.2 | 18.1 |
| Steubenville | 46.5 | 46.5 | 46.4 | 46.4 |
| St Louis | 31.4 | 31.4 | 33.0 | 31.3 |
| Topeka | 26.4 | 26.4 | 26.3 | 26.4 |
| Watertown | 24.2 | 24.2 | 24.6 | 24.1 |
| **Total Particles (1977–1985)** | | | | |
| Harriman | 49.4 | 49.4 | 49.4 | 49.9 |
| Portage | 34.1 | 33.4 | 34.1 | 32.0 |
| Steubenville | 89.9 | 92.4 | 89.9 | 91.2 |
| St Louis | 72.5 | 68.7 | 72.5 | 68.3 |
| Topeka | 56.6 | 56.2 | 56.6 | 54.3 |
| Watertown | 49.2 | 46.6 | 49.2 | 46.3 |

[a] Values are given as means in $\mu g/m^3$.

[b] See Table 1 in Dockery et al 1993.

reported values for 64 observations for which the average fine particle mass concentration was 48 $\mu g/m^3$. Of those 64, 26 measurements had been acquired with multiple filters; with those 26 values eliminated, the fine particle mass concentration was 32 $\mu g/m^3$ for the 38 observations from single filters. The Reconstruct.file reports values for 26 observations [from single filters] for which the average fine particle mass concentration was 30 $\mu g/m^3$. Multiple-filter observations became less frequent in later years.

***Reproducing the Published Statistics*** Table 10 shows mean concentrations for fine, inhalable, and total particles from the NEJM publication and for three different calculations from data in the Reconstruct.file. The first calculation (Mean of All Observations) averages all observations within the indicated time periods. The second calculation (Mean of Annual Averages) represents an average of yearly concentrations. The third calculation (Mean of Quarterly Averages) represents an average of quarterly mean concentrations. The recalculated Means of Annual Averages exactly match the published means for total particles at all six cities. However, the corresponding means for fine and inhalable particles differ significantly from the NEJM values at St Louis, Topeka, and Watertown. Conversely, the recalculated Means of All Observations exactly match or are within 0.1 $\mu g/m^3$ (Harriman) of the NEJM values for fine and inhalable particles, but are significantly different for total particles at all cities except Harriman.

**Table 11**. City Mean Particle Concentrations Calculated from All Observations for 1979–1985 in Reconstruct.file and in JAWMA.file for the Audit of the Six Cities Study

| | Concentration ($\mu g/m^3$) | | Number of Observations | |
|---|---|---|---|---|
| City | Reconstruct[a] | JAWMA | Reconstruct | JAWMA |
| **Fine Particles** | | | | |
| Harriman | 20.9 | 21.0 | 1,029 | 1,552 |
| Portage | 11.0 | 11.5 | 771 | 975 |
| Steubenville | 29.6 | 30.8 | 994 | 1,145 |
| St Louis | 19.0 | 18.9 | 868 | 1,046 |
| Topeka | 12.5 | 12.5 | 728 | 938 |
| Watertown | 14.9 | 15.7 | 850 | 1,139 |
| **Inhalable Particles** | | | | |
| Harriman | 32.6 | 33.0 | 1,026 | 1,151 |
| Portage | 18.2 | 18.5 | 737 | 925 |
| Steubenville | 46.5 | 48.3 | 987 | 1,143 |
| St Louis | 31.4 | 31.7 | 852 | 1,043 |
| Topeka | 26.4 | 28.3 | 720 | 938 |
| Watertown | 24.2 | 24.5 | 836 | 1,139 |

[a] Referred to as the Mean of All Observations in Table 10.

***Other Evidence for the Quality of the NEJM Air Pollution Data***

*Comparison of Reconstruct.file with the JAWMA.file* The three recalculated means in Table 10 are all derived from the Reconstruct.file. All three therefore reflect the same selection criteria for the inclusion or exclusion of observations. To understand the effects of altering these criteria, the Audit Team compared the Means of All Observations shown in Table 10 with the same statistics calculated for data in the JAWMA.file (Schwartz et al 1996), the results of which are shown in Table 11. (This comparison does not include total particle concentrations because the JAWMA.file included data from dichotomous samplers only, which provide fine and coarse particle levels.)

The selection criteria used to extract the data in the JAWMA.file were undocumented, but probably were based on less stringent criteria than those used in the Reconstruct.file. Averaging all observations in the JAWMA.file for the 1979–1985 period does not yield the means published in NEJM, even though averaging all observations including those from later years does yield exactly the time-series means published in JAWMA (data

not shown). As noted in Table 8, about 5% of the examined JAWMA data could not be accounted for in the original records we audited.

*Comparison of Reconstruct.file Dichotomous Sampler Data with Data from Size-Selective High-Volume Samplers in 1997.file* The high-volume samplers with SSIs measured particles only every sixth day (for 24 hours) during the period 1980 through 1986. These samplers directly measured inhalable particles (fine + coarse) and did not separate fine from coarse. The high-volume samplers' SSIs were different from the dichotomous samplers' SSIs in that (1) they were designed for much higher sample flow rates, and (2) they remained at a 15-μm cutpoint, whereas the dichotomous SSIs changed to a 10-μm cutpoint in early 1984.

The data from the high-volume samplers with SSIs had not been used either in the cross-sectional analysis published in NEJM or in the time-series analysis published in JAWMA due to the low frequency of the measurements. The data had, however, been quality assured along with the other particle measurements (Spengler et al 1986). The SSI high-volume sampler had been operated independently from the dichotomous sampler; not only were the particles sized and the airflows controlled separately, but different filter media and analytic procedures had been used. The data from the SSI high-volume samplers could thus be used to corroborate the data from the dichotomous samplers in that agreement between two independent measurements provides evidence of the quality of both sets of measurements. Due to the different sampling schedules, this comparison did not address the issues of data selection and file integrity.

The paragraphs that follow adopt a temporary convention restricting the use of the term "inhalable particles". Previously, we have used the term to refer to any particles having diameters less than 10 or 15 μm. The concentrations of inhalable particles reported in NEJM, in particular, had been derived by adding together the separate concentrations obtained from the dichotomous samplers for fine (diameters < 2.5 μm) and coarse (diameters > 2.5 μm and < 10 or 15 μm) particles. *In this section only*, the term *IP* is reserved for data from the SSI high-volume samplers; data from the dichotomous samplers are distinguished as *FP*, *CP*, and *FP+CP*.

We expect the relation between concentrations from the high-volume SSI ($IP_{HV}$) and dichotomous ($FP_{DC}$+$CP_{DC}$) samplers to follow the form

$$IP_{HV} = a_0 + a_M\,(FP_{DC}+CP_{DC}),$$

**Table 12.** City-Specific Coefficients for Regressions[a] Calculated for the Six Cities Study

| City | $n$ | $r^2$ | $a_M$ (mean + SE) | $a_0$ (mean + SE) |
|---|---|---|---|---|
| Harriman | 359 | 0.78 | 0.95 ± 0.03 | 8.1 ± 0.9 |
| Portage | 283 | 0.67 | 0.95 ± 0.04 | 5.1 ± 0.9 |
| Steubenville | 316 | 0.88 | 1.02 ± 0.02 | 9.2 ± 1.0 |
| St Louis | 284 | 0.78 | 1.04 ± 0.03 | 9.5 ± 1.1 |
| Topeka | 283 | 0.71 | 0.95 ± 0.04 | 10.2 ± 1.1 |
| Watertown | 225 | 0.46 | 0.83 ± 0.06 | 11.0 ± 1.7 |

[a] Regressions took the form $IP_{HV} = a_0 + a_M\,(FP_{DC}+CP_{DC})$, where $IP_{HV}$ is from the 1997.file SSI high-volume sampler data and $FP_{DC}+CP_{DC}$ is from the JAWMA.file dichotomous sampler data. $n$ is the number of observations (number of days) for which values were available from both samplers. The estimated coefficients $a_M$ and $a_0$ are explained in the text.

where *HV* refers to the concentrations obtained from high-volume samplers and *DC* refers to the concentrations from the dichotomous samplers; the intercept $a_0 > 0$ is a measurement artifact associated with the high-volume sampler filters used in the measurement of inhalable particles; and the coefficient $a_M$ should equal unity if the dichotomous and SSI high-volume sampler measurements are equivalent. The constant $a_0$ allows for the extra mass in the $IP_{HV}$ samples contributed by artifactual sulfate (discussed in the next section). The ordinary-least-squares coefficients determined by city-specific regression of the 1997.file SSI high-volume sampler $IP_{HV}$ data on the JAWMA.file dichotomous $FP_{DC}+CP_{DC}$ data are summarized in Table 12.

Watertown stands out in Table 12 as the city with the weakest correlation ($r^2$) between $IP_{HV}$ and $FP_{DC}+CP_{DC}$, and as the only city for which the proportionality coefficient $a_M$ differs significantly from 1. The distinctive character of the Watertown measurements is also evident in data plots such as Figure 5. Each point in the plot represents a pair of measurements at the same time and same place, one by SSI high-volume sampler ($IP_{HV}$) and one by dichotomous sampler ($FP_{DC}+CP_{DC}$). Measurements that agree with each other fall near the diagonal line from lower left to upper right. A relatively large fraction of the Watertown observations lie farther from this line than do the measurements for the other five cities.

We investigated whether the observed scatter in the relation between high-volume and dichotomous sampler measurements at Watertown were due to the high-volume sampler measurements or the dichotomous sampler measurements. We had a limited series of measurements at Watertown made by a high-volume sampler with a 10-μm SSI located at the same sampling site as the high-volume sampler with the 15-μm SSI. We found the 10-μm SSI measurements to be more highly correlated

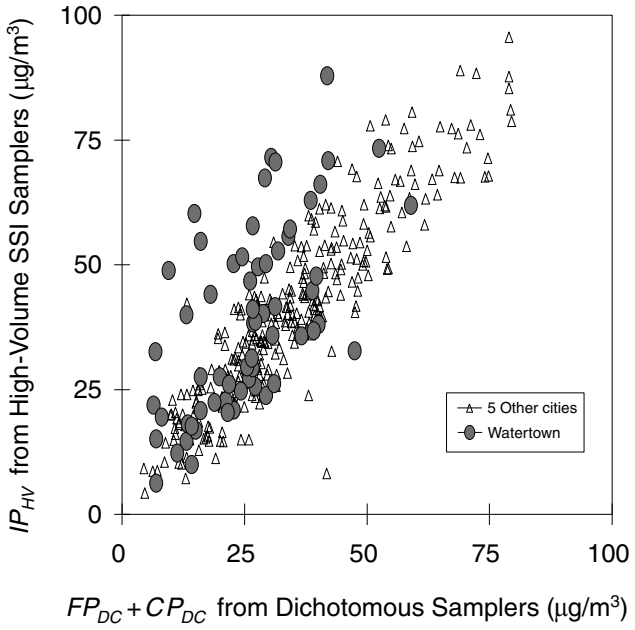



**Figure 5. Comparison of particle concentrations gathered in 1980–1981 by different types of samplers.** Each point in the plot represents a pair of measurements at the same time and place, one by an SSI high-volume sampler ($IP_{HV}$) and one by a dichotomous sampler ($FP_{DC}$+$CP_{DC}$). Measurements that agree with each other fall near the diagonal line from lower left to upper right. The correspondence between $IP_{HV}$ and $FP_{DC}$+$CP_{DC}$ measurements in Watertown is noticeably poorer than it is in the other five cities, as evidenced by the relatively large fraction of Watertown observations that lie farther from this line than measurements for the other cities.

with the 15-µm SSI high-volume sampler values than with either the high-volume or the dichotomous sampler measurements. Therefore, we concluded that whatever errors might have occurred in either of the high-volume sampler measurements, they were small compared with the measurement errors in the dichotomous sampler measurements. Furthermore, field logs indicated that the Watertown dichotomous sampler experienced more operational problems and was serviced by more operators than samplers in the other five cities, which supports the contention that the dichotomous sampler measurements were the source of the anomalous values at Watertown.

The SSI high-volume sampler data can also be examined for evidence of the effects from the changes in the dichotomous sampler configurations and the filter analysis methods that differentiated the measurement epochs (described in Table 6). (The SSI high-volume sampler filters were always weighed, whereas the dichotomous filters were sometimes weighed and sometimes analyzed by β attenuation; therefore, the high-volume sampler filter measurements offer a stable reference against which to compare the dichotomous filter measurements.) Because of the anomalous scatter noted above, Watertown has been excluded from this analysis. Table 12 suggests the high-volume sampler artifact (the $a_0$ column) varies with city but the incremental sensitivity to dichotomous mass (the $a_M$ column) does not. We expect the effects of the changes in sampler configurations and methods to take the approximate form:

$$IP = a_{city} + a_{FP}FP_{DC} + a_{CP}CP_{DC} + d_{grav}(FP_{DC_2} + CP_{DC_2} + b_2) + d_{loss}CP_{DC_{3,4}} + d_{inlet}CP_{DC_4},$$

where $FP_{DC_k}$, $CP_{DC_k}$, and $b_k$ take the values $FP_{DC}$, $CP_{DC}$, and $b$ during the $k^{\text{th}}$ measurement epoch and 0 otherwise. The quantity $a_{city}$ is a city-specific value for the artifact term, $a_0$. The baseline coefficients $a_{FP}$ and $a_{CP}$ describe the relation of high-volume sampler mass measurements to dichotomous sampler mass measurements during epoch 1, when the dichotomous samplers were operated with unoiled coarse filters and 15-µm inlets and the filters were analyzed by β-absorption gauge. The correction $d_{loss}$ is $-F/(1-F)$, where $F$ is the fractional loss from unoiled coarse filters. Similarly, $d_{inlet}$ is $(R^{-1} - 1)$, where $R = CP_{10}/CP_{15}$ is the ratio of the two definitions of $CP$ mass. Finally, $d_{grav}$ and $b$ describe potential calibration and blank differences between the gravimetric and β-absorption gauge analyses.

Regressions were calculated with various subsets of the above model. Out of 1,525 simultaneous SSI high-volume and JAWMA dichotomous sampler datasets collected in the five cities under examination, only 39 were taken during the few months of epoch 3. The near coincidence of coarse filter oiling at the end of epoch 2, which increased measured $CP$ mass, with the switch from a 15-µm to a 10-µm cutpoint at the start of epoch 4, which decreased measured $CP$ mass, therefore confounded the two changes' opposing effects. The oiling term $d_{loss}$ and the 39 epoch-3 observations were accordingly dropped from the regression, leaving the coefficient $d_{inlet}$ to represent the net effect of the transition from epoch 2 to epoch 4. A small, barely significant calibration effect was associated with the gravimetric analysis, but it was confined to fine particles only. The only robust coefficient was $d_{inlet}$; Table 13 summarizes results from the regression model setting $d_{loss}$, $d_{grav}$, and $b$ equal to zero. The high-volume sampler offset $a_{city}$ was then 6.8, 3.6, 10.4, 10.6, and 7.7 µg/m$^3$ at Harriman, Portage, Steubenville, St Louis, and Topeka, respectively.

Recall that $d_{inlet}$ in Table 13 represents the net of two effects: postsampling losses were cut by oiling the coarse filters at the same time that the largest particles were dropped from sampling by the more restrictive inlet. Thus the baseline $CP$ coefficient $a_{CP}$ = 1.08 was greater than 1

**Table 13.** Results and Parameter Estimates from Ordinary-Least-Squares Regressions[a] of *IP* on *FP* and *CP*[b] Calculated for the Six Cities Study

| | | Epoch 1 ($n$ = 325) | Epoch 2 ($n$ = 450) | Epoch 3 ($n$ = 711) |
|---|---|---|---|---|
| Variable | $t$ | μg(high-volume)/μg(dichotomous) | | |
| ***FP* Total** | 4.1 | 0.91 | 0.91 | 0.91 |
| *CP* | 3.0 | 1.08 | 1.08 | 1.08 |
| $D_{inlet}$ | 5.8 | | | 0.19 |
| ***CP* Total** | | 1.08 | 1.08 | 1.27 |
| $e_{IP}$ (μg/m$^3$) | | 7.7 | 7.5 | 9.7 |

[a] $R^2 = 0.84$.

[b] *IP* values are from the 1997.file SSI high-volume sampler data, and *FP* and *CP* values are from the JAWMA.file dichotomous sampler data. Student $t$ values are based on standard errors from classical theory; coefficients for *FP* and *CP* are tested against unity, and the adjustment $D_{inlet}$ is tested against zero. *IP* prediction error ($e_{IP}$) is the root-mean-square difference between observed and predicted *IP* concentrations during indicated measurement epochs.

even in the early years, when the high-volume and dichotomous filters sampled the same particle size range, because it had to account for coarse particles retained by the high-volume sampler filters but lost from the unoiled dichotomous sampler filters. In the absence of such losses, random error in the dichotomous sampler measurements would be expected to attenuate $a_{CP}$ to a value less than 1 in the same way it attenuates $a_{FP}$.

*Comparison of Sulfate Concentrations Measured with High-Volume Samplers and Those Measured with Dichotomous Samplers* The sulfate particle data used in the original investigation came from analyses of the high-volume sampler filters. Sulfate particle concentrations were also determined by x-ray fluorescence of the fine and coarse dichotomous sampler filters during the years 1979–1981 and 1984–1988. Table 14 summarizes city-specific regression coefficients between the high-volume and dichotomous determinations for coincident samples (1979–1984). The dichotomous values represent inhalable (fine + coarse) particles; as indicated in the right-hand column, the bulk of inhalable sulfate is in the fine particle fraction. Even perfectly accurate high-volume and dichotomous sampler sulfate values need not be identical because high-volume samples, but not dichotomous samples, could include sulfate carried by "non-inhalable" particles larger than 10 or 15 μm in diameter. The effect of this discrepancy in sampled size ranges is expected to be tiny, however, because the dichotomous samplers found little sulfate in particles larger than 2.5 μm. Figure 6 depicts the correlation between dichotomous and high-volume sampler levels of sulfate for each of the six cities.

Standard high-volume sampler filters are known to react with ambient sulfur dioxide, yielding some artifactual sulfate (Coutant 1977). The Teflon filters used by the dichotomous samplers are inert, thus avoiding this artifact. The expected relation of sulfate measurement from dichotomous samplers to high-volume samplers is thus of the approximate form

$$\text{dichotomous } SO_4^{2-} = b(\text{high-volume } SO_4^{2-} - a),$$

**Table 14.** Sulfate Concentrations from High-Volume and Dichotomous[a] Particle Samplers for the Six Cities Study

| | | | Regression Coefficients[b] | | 1979–1984 Interpolated Mean Sulfate | | |
|---|---|---|---|---|---|---|---|
| City | $n$ | $r^2$ | Dichotomous ÷ High-Volume | Artifact | Observed High-Volume Sampler Data | Estimated Dichotomous[c] Sampler Data | Percentage from Fine Particle Channel of Dichotomous Samplers |
| Harriman | 334 | 0.58 | 1.21 | 1.6 | 8.1 | 7.9 | 93 |
| Portage | 228 | 0.81 | 1.23 | 1.5 | 5.3 | 4.7 | 92 |
| Steubenville | 312 | 0.79 | 1.24 | 1.9 | 12.8 | 13.5 | 88 |
| St Louis | 217 | 0.76 | 1.10 | 1.0 | 8.0 | 7.6 | 92 |
| Topeka | 143 | 0.88 | 1.13 | 0.9 | 4.8 | 4.4 | 94 |
| Watertown | 246 | 0.71 | 1.23 | 1.7 | 6.5 | 5.9 | 90 |

[a] Values for dichotomous samplers represent inhalable (FP + CP) particles.

[b] Model: dichotomous $SO_4^{2-}$ = (dichotomous/high-volume)(high-volume $SO_4^{2-}$ – artifact). Equal error variances are assumed for dichotomous and high-volume sampler measurements.

[c] Calculated from observed high-volume sampler mean sulfate and the relation of dichotomous sampler to high-volume sampler data described in footnote b.

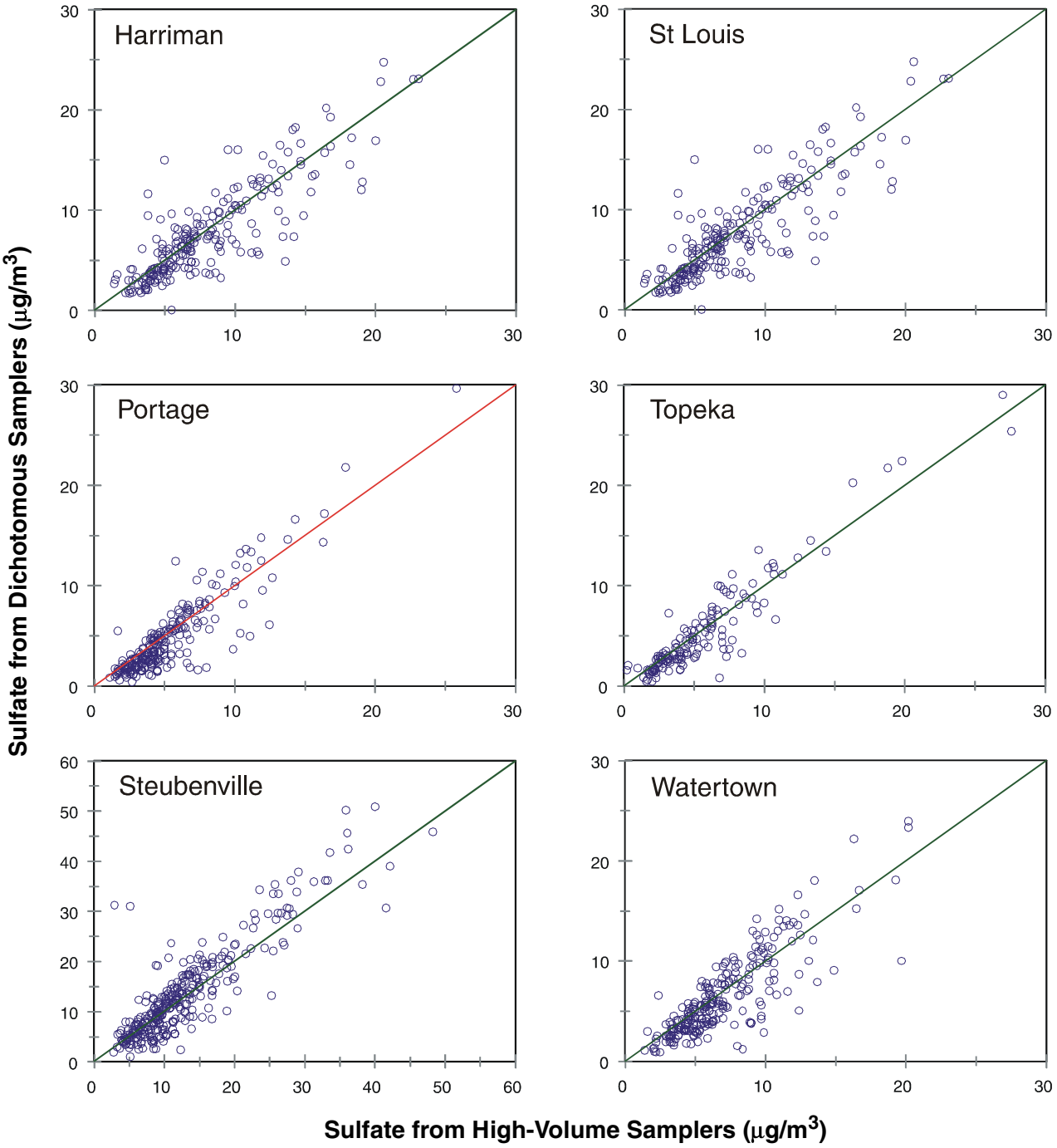



**Figure 6. Sulfate determinations by high-volume and dichotomous (fine + coarse) samplers.** Note the compressed scale on the Steubenville panel.

where $a \geq 0$ is the characteristic magnitude of the artifact, and $b \leq 1$ is the ratio of incremental dichotomous sulfate to incremental high-volume sulfate. Table 14 gives city-specific coefficients for this relation from least-squares fits with equal weighting of dichotomous and high-volume errors.

The empirical values of high-volume artifact and dichotomous/high-volume slope are reasonably consistent across cities. The apparent artifacts are of plausible magnitude; but the high dichotomous/high-volume slopes are difficult to explain as other than indicators of a systematic error in one of the two determinations. The dichotomous

excess in these coefficients is statistically significant at each city and is evident in data cross-plots.

The empirical relation of *dichotomous* $SO_4^{2-}$ = *b*(*high-volume* $SO_4^{2-}$ – *a*), derived from limited coincident measurements, can be combined with the full data series from the high-volume samplers to estimate the 1979–1984 sulfate averages that would have been obtained from the dichotomous samplers if the 1982–1983 samples had been chemically analyzed. (Ordinary least-squares regression yields essentially the same estimates for 1979–1984 dichotomous sulfate averages, differing by no more than 0.1 μg/m$^3$.) Table 14 shows the average difference between observed high-volume and estimated dichotomous sulfate to be no more than about 10% because the apparent discrepancy between the high-volume and dichotomous sampler calibrations compensates for the high-volume sampler artifact.

*Comparison of Reconstruct.file Total Suspended Particulate Data with the Same Data from 1997.file*

The 1997.file includes TSP data for the years 1979–1986, and the NEJM results were based on TSP data for years 1977–1985; therefore, we have restricted our comparisons to the individual years contained in both datasets (1979–1985).

Table 15 summarizes the annual mean TSP concentrations at each city from the 1997.file and from the Reconstruct.file. The column of New TSP concentrations refers to values in the Reconstruct.file but not in the 1997.file. The column of total TSP concentrations

**Table 15.** Annual Mean TSP and Sulfate Concentrations Calculated from the 1997.file and the Reconstruct.file for the Six Cities Study[a]

| | 1997.file | | Reconstruct.file | | | | | |
|---|---|---|---|---|---|---|---|---|
| City and Year | TSP | *n* | New TSP[b] | *n* | Total TSP | *n* | $SO_4^{2-}$ | *n* |
| **Harriman** | | | | | | | | |
| 1979 | 55.7 | 170 | 48.9 | 60 | 48.9 | 60 | 7.9 | 170 |
| 1980 | 65.3 | 177 | 49.0 | 61 | 49.0 | 61 | 9.9 | 177 |
| 1981 | 52.2 | 166 | 52.3 | 39 | 52.1 | 193 | 6.7 | 166 |
| 1982 | 49.1 | 170 | 43.0 | 1 | 49.0 | 171 | 7.3 | 170 |
| 1983 | 45.7 | 131 | 43.8 | 5 | 45.6 | 136 | 8.9 | 131 |
| 1984 | 46.7 | 122 | | 0 | 46.7 | 122 | 7.8 | 122 |
| 1985 | 51.5 | 111 | | 0 | 51.5 | 111 | | |
| **Portage** | | | | | | | | |
| 1979 | 36.5 | 137 | 38.1 | 39 | 36.3 | 156 | 5.4 | 115 |
| 1980 | 33.9 | 156 | 38.5 | 16 | 34.5 | 164 | 5.9 | 134 |
| 1981 | 31.0 | 144 | 25.8 | 33 | 30.1 | 171 | 4.7 | 131 |
| 1982 | 33.4 | 152 | 22.8 | 8 | 32.8 | 160 | 5.1 | 152 |
| 1983 | 33.4 | 100 | 25.0 | 1 | 33.3 | 101 | 5.3 | 100 |
| 1984 | 31.9 | 113 | | 0 | 31.9 | 113 | 5.2 | 113 |
| 1985 | 31.1 | 111 | | 0 | 31.1 | 111 | | |
| **Steubenville** | | | | | | | | |
| 1979 | 77.1 | 125 | 104.0 | 365 | 104.0 | 365 | 14.3 | 105 |
| 1980 | 74.1 | 136 | 90.8 | 366 | 90.8 | 366 | 13.1 | 131 |
| 1981 | 74.7 | 143 | 86.4 | 365 | 86.4 | 365 | 13.0 | 119 |
| 1982 | 66.1 | 165 | 82.3 | 364 | 82.3 | 364 | 12.8 | 161 |
| 1983 | 63.5 | 130 | 72.2 | 365 | 72.2 | 365 | 12.4 | 130 |
| 1984 | 70.5 | 120 | 72.0 | 182 | 72.8 | 241 | 11.3 | 120 |
| 1985 | 68.4 | 113 | | 0 | 68.4 | 113 | | |

*(Table continues next page)*

[a] Annual mean pollutant concentrations are given in μg/m$^3$.

[b] Values in the Reconstruct.file but not in the 1997.file.

represents all values in the Reconstruct.file, including the new TSP values. In the early years for all six cities, the TSP data in the 1997.file differ from those in Reconstruct.file; the "early years" vary from city to city, but are easily noted by the presence of data in the "New TSP" column. Note that, for some years at some cities, the data in the Reconstruct.file and 1997.file do not overlap at all. At Harriman, for example, 1997.file had TSP values from every-other-day sampling in 1979–1980, none of which reappear in Reconstruct.file; all of the every-sixth-day TSP values in Reconstruct.file are "new". At Steubenville, similarly, all the the daily TSP values in Reconstruct.file are "new" in the years before 1984.

The TSP values in 1997.file and the sulfate values in Reconstruct.file generally follow a common schedule in each city and appear to have come from the same high-volume sampler, whereas the TSP values in Reconstruct.file appear to include observations from a different instrument. This pattern is evident in Table 16, which compares daily data in the two files for one month at Steubenville. Note that the every-third-day TSP values in 1997.file match those in Reconstruct.file only after July 1; before that, the values for the every-third-day sequence do not match. The Audit Team inferred from this pattern that (1) Reconstruct.file took TSP values after July 1, 1984, from a high-volume that had sampled every third day since 1979 or earlier, whose filters were both weighed for TSP and chemically analyzed for sulfate ($SO_4^{2-}$ in Table 16); (2) Reconstruct.file took TSP values before July 1, 1984, from a different high-volume that had sampled daily until it was taken out of service on July 1, 1984,

**Table 15 (*continued*).** Annual Mean TSP and Sulfate Concentrations Calculated from the 1997.file and the Reconstruct.file for the Six Cities Study[a]

| | 1997.file | | Reconstruct.file | | | | | |
|---|---|---|---|---|---|---|---|---|
| City and Year | TSP | *n* | New TSP[b] | *n* | Total TSP | *n* | $SO_4^{2-}$ | *n* |
| **St Louis** | | | | | | | | |
| 1979 | 68.0 | 157 | 95.8 | 80 | 95.4 | 81 | 8.6 | 116 |
| 1980 | 78.9 | 162 | 55.8 | 9 | 79.5 | 156 | 10.4 | 92 |
| 1981 | 58.0 | 151 | 46.2 | 13 | 57.1 | 164 | 6.7 | 136 |
| 1982 | 50.5 | 174 | | 0 | 50.5 | 174 | 7.6 | 174 |
| 1983 | 50.7 | 126 | | 0 | 50.7 | 126 | 8.0 | 126 |
| 1984 | 48.4 | 117 | | 0 | 48.4 | 117 | 7.5 | 116 |
| 1985 | 53.9 | 117 | | 0 | 53.9 | 117 | | |
| **Topeka** | | | | | | | | |
| 1979 | 44.7 | 47 | 56.3 | 95 | 52.5 | 142 | 5.2 | 40 |
| 1980 | 63.8 | 78 | 87.3 | 46 | 72.6 | 124 | 4.4 | 69 |
| 1981 | 54.4 | 141 | 43.3 | 20 | 53.0 | 161 | 4.5 | 119 |
| 1982 | 52.8 | 152 | | 0 | 52.8 | 152 | 4.5 | 151 |
| 1983 | 54.5 | 126 | | 0 | 54.5 | 126 | 5.5 | 126 |
| 1984 | 50.4 | 114 | | 0 | 50.4 | 114 | 4.9 | 114 |
| 1985 | 49.5 | 111 | | 0 | 49.5 | 111 | | |
| **Watertown** | | | | | | | | |
| 1979 | 45.9 | 106 | 50.9 | 24 | 46.8 | 130 | 7.4 | 138 |
| 1980 | 55.7 | 172 | 62.2 | 1 | 55.7 | 173 | 7.7 | 138 |
| 1981 | 40.8 | 151 | 30.1 | 11 | 40.1 | 162 | 5.1 | 128 |
| 1982 | 41.3 | 157 | | 0 | 41.3 | 157 | 6.0 | 157 |
| 1983 | 39.7 | 105 | | 0 | 39.7 | 105 | 6.1 | 105 |
| 1984 | 41.9 | 108 | | 0 | 41.9 | 108 | 6.5 | 107 |
| 1985 | 39.3 | 101 | | 0 | 39.3 | 101 | | |

[a] Annual mean pollutant concentrations are given in $\mu g/m^3$.

[b] Values in the Reconstruct.file but not in the 1997.file.

**Table 16.** Comparison of One Month's Daily Air Pollutant Values for Steubenville from the 1997.file and the Reconstruct.file[a] (Six Cities Study)

| | 1997.file | Reconstruct.file | |
|---|---|---|---|
| SASDATE | TSP | TSP | $SO_4^{2-}$ |
| 15-Jun-84 | | 53 | |
| 16-Jun-84 | | 62 | |
| 17-Jun-84 | 70.6 | 101 | 18.4 |
| 18-Jun-84 | | 68 | |
| 19-Jun-84 | | 62 | |
| 20-Jun-84 | 93.3 | 66 | 9.2 |
| 21-Jun-84 | | 83 | |
| 22-Jun-84 | | 91 | |
| 23-Jun-84 | 63.3 | 87 | 16.9 |
| 24-Jun-84 | | 63 | |
| 25-Jun-84 | | 49 | |
| 26-Jun-84 | 90.4 | 66 | 17.8 |
| 27-Jun-84 | | 108 | |
| 28-Jun-84 | | 90 | |
| 29-Jun-84 | 107.5 | 92 | 24.3 |
| 30-Jun-84 | | 117 | |
| 01-Jul-84 | | | |
| 02-Jul-84 | 87 | 87 | 9.1 |
| 03-Jul-84 | | | |
| 04-Jul-84 | | | |
| 05-Jul-84 | 30 | 30 | 7.3 |
| 06-Jul-84 | | | |
| 07-Jul-84 | | | |
| 08-Jul-84 | 69 | 69 | 19 |
| 09-Jul-84 | | | |
| 10-Jul-84 | | | |
| 11-Jul-84 | 41.7 | 41.7 | 11.7 |
| 12-Jul-84 | | | |
| 13-Jul-84 | | | |
| 14-Jul-84 | 112.4 | 112.4 | 3.9 |
| 15-Jul-84 | | | |

[a] Pollutant values are given in $\mu g/m^3$.

whose filters were weighed for TSP but not chemically analyzed; and (3) Reconstruct.file consistently took sulfate values from the first sampler, thereby taking TSP and sulfate values from separate instruments before July 1, 1984, and from a common instrument after July 1, 1984.

Year-to-year variations in TSP and sulfate provide indirect support for the inference that the early TSP and sulfate data in Reconstruct.file were taken from different high-volume samplers. The notable sulfate maximal levels recorded at Harriman and St Louis in 1980 correspond to the TSP maximal levels in 1997.file that do not appear in Reconstruct.file.

## VALIDATION OF THE ORIGINAL SIX CITIES STUDY ANALYSES

We reanalyzed the dataset provided by the Original Investigators by the same methods used in the original analyses by Dockery and colleagues (1993). Specifically, we assessed the effect of air pollution on mortality using the Cox proportional-hazards regression model (Cox 1972). We conducted regression analyses after controlling for the same risk factors considered by the Original Investigators (smoking status, BMI, educational level, and occupational exposure to dusts, gases, and fumes). We stratified all Cox regression models by 5-year age groups and sex, and calculated a baseline hazard for each age-sex group. We used life-table methods to estimate the survival probabilities for each year of follow-up within each city (Cox and Oakes 1983; Lee 1992). The detailed and complete results of the reanalysis of the Six Cities Study data are contained in two appendices that are available from the Health Effects Institute upon request: Appendix E. Computer Programs Used in the Replication of the Original Analyses of the Harvard Six Cities Study; and Appendix F. Replication of the Original Analyses of the Harvard Six Cities Study.

In order to evaluate the reproducibility of the original findings, we summarized the results of the reanalysis in the same format used in the NEJM publication by Dockery and colleagues (1993). Specifically, we compared Tables 1–5 and Figures 1–3 from the publication with the corresponding results of the reanalysis and we provide a description of the findings in the sections that follow.

### Validation of the Cohort Selection Process

The Mort6C.file provided by the Original Investigators consisted of a cohort of 8,111 individuals. To replicate the analytic cohort obtained from the Original Investigators, all subjects who completed the initial questionnaire were included. We then selected all individuals who were white, who had two measures of pulmonary function, and whose height was recorded. This cohort consisted of 8,111 individuals and it was identical to the original cohort analyzed by Dockery and colleagues (1993).

### Results of the Reanalysis

During the course of the data audit, the Audit Team found that the follow-up of some individuals had been ter-

minated early. Using additional follow-up data provided by the Original Investigators, the Reanalysis Team constructed a second analytic dataset to adust for the problem of early censorship of person-years. When we compared the two cohorts, we discovered that 1% of the members of the original Six Cities cohort had been censored before being lost to follow-up.

The Reanalysis Team conducted two sets of validation analyses for the Six Cities Study. The first analysis was based on the Mort6C.file, which was one version of the Mort6C/HSPH.file used by the Original Investigators. The second analysis was based on the updated analytic cohort that the Reanalysis Team corrected for early censorship.

The results of these two sets of analyses are summarized below. Three versions of each table are shown, labeled as a, b, and c. The first (a) is an exact replica of the table published by Dockery and colleagues (1993); the second (b) presents the results of our validation analysis using the same analytic cohort the Original Investigators had used; and the third (c) presents our results using the updated analytic cohort that we corrected for early censorship. Values presented in bold italic type in the reanalysis tables indicate results different from those reported by the Original Investigators.

**Table 17a.** Characteristics of the Study Population and Mean Air Pollution Levels in the Six Cities: Original Results[a]

| Characteristic | Portage | Topeka | Watertown | Harriman | St Louis | Steubenville |
|---|---|---|---|---|---|---|
| **Study Population Variables** | | | | | | |
| Number 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 |
| Number of deaths | 232 | 156 | 248 | 222 | 281 | 291 |
| Deaths/1,000 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 (years) | 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 |
| **Air Quality Variables** | | | | | | |
| 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 |

[a] From Dockery et al 1993; corresponds to Table 1 in the original publication (Copyright © 1993, Massachusetts Medical Society, all rights reserved). 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 though 1984; and aerosol acidity, 1985 through 1988.

***Characteristics of the Study Population and Mean Air Pollution Levels in the Six Cities*** Tables 17a, 17b, and 17c provide a summary of the characteristics of the study population and the air pollution levels in each of the six cities. The study population was characterized according to sex, smoking history, education, age, BMI, and occupational exposure to dust, gases, or fumes. Air pollution was characterized in terms of TSP, inhalable particles, fine particles, sulfate particles, aerosol acidity, sulfur dioxide, nitrogen dioxide, and ozone.

The results of the reanalysis are in close agreement with the original analysis (Table 17b). We found a slight difference in average pack-years of smoking among former-smokers in Watertown; the reanalysis indicated an average of 21.0 pack-years compared with 21.8 pack-years in the original analysis. This appears to be a typographic error in the published results because the original manuscript submitted to NEJM cited the average pack-years of smoking in Watertown as 21.0. The Reanalysis Team also calculated the percentage of participants occupationally exposed to dust, gases, or fumes in Topeka to be 38%, rather than 28% as reported in the original analysis. We also found a few minor differences in estimates of some metrics of particles in Harriman and St Louis. There was a

**Table 17b.** Characteristics of the Study Population and Mean Air Pollution Levels in the Six Cities: Reanalysis Results Using the Same Analytic Cohort[a]

| Characteristic | Portage | Topeka | Watertown | Harriman | St Louis | Steubenville |
|---|---|---|---|---|---|---|
| **Study Population Variables** | | | | | | |
| Number 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 | ***17,835*** | 17,715 | 17,914 |
| Number of deaths | 232 | 156 | 248 | 222 | 281 | 291 |
| Deaths/1,000 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 | ***21.0*** | 21.1 | 22.0 | 25.0 |
| Less than high school education (%) | 25 | 12 | 22 | 35 | 45 | 30 |
| Average age (years) | 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 | ***38*** | 38 | 50 | 40 | 48 |
| **Air Quality Variables** | | | | | | |
| 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 | ***32.6*** | 31.4 | 46.5 |
| Fine particles ($\mu g/m^3$) | 11.0 | 12.5 | 14.9 | ***20.9*** | 19.0 | 29.6 |
| Sulfate particles ($\mu g/m^3$) | 5.3 | 4.8 | 6.5 | 8.1 | ***8.0*** | 12.8 |
| Aerosol acidity ($nmol/m^3$) | 10.5 | 11.6 | 20.3 | 36.1 | 10.3 | 25.2 |
| Sulfur dioxide (ppb) | ***3.7*** | ***1.5*** | ***7.6*** | 4.8 | ***9.2*** | ***23.6*** |
| Nitrogen dioxide (ppb) | 6.1 | 10.6 | 18.1 | 14.1 | ***20.9*** | 21.9 |
| Ozone (ppb) | 28.0 | 27.6 | 19.7 | 20.7 | ***19.7*** | 22.3 |

[a] Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

slightly greater discrepancy in estimates of sulfur dioxide in Portage, Watertown, and St Louis.

Table 17c reports on the characteristics of the study population when the Reanalysis Team eliminated the early censorship of person-years. We found some differences in the person-years of follow-up and the number of deaths reported originally. The person-years of follow-up increased for all six cities; increases ranged from 67 person-years in Watertown to 343 person-years in Portage. The number of deaths increased in Portage (+3), Topeka (+4), Harriman (+2), and Steubenville (+6), and decreased in Watertown (–1).

***Adjusted Mortality Rate Ratios Estimated from Cox Proportional-Hazards Models*** The Cox regression model that we used produced an estimate of the mortality rate, adjusted for age, sex, cigarette consumption, education, and BMI for the six cities. These estimates of risk were relative to Portage. (These are referred to as a mortality rate ratio.) Portage was chosen by the Original Investigators because it had the lowest levels of particles (excluding sulfate particles).

In addition, the Cox model produced estimates of the mortality rate ratio for each of the other variables included in the model (Table 18). For example, the mortality rate for

**Table 17c.** Characteristics of the Study Population and Mean Air Pollution Levels in the Six Cities: Reanalysis Results After Adjusting for Early Censoring of Person-Years[a]

| Characteristic | Portage | Topeka | Watertown | Harriman | St Louis | Steubenville |
|---|---|---|---|---|---|---|
| **Study Population Variables** | | | | | | |
| Number of participants | 1,631 | 1,239 | 1,336 | 1,258 | 1,296 | 1,351 |
| Person-years of follow-up | ***21,961*** | ***16,342*** | ***19,949*** | ***17,911*** | ***17,789*** | ***18,052*** |
| Number of deaths | ***235*** | ***160*** | ***247*** | ***224*** | 281 | ***297*** |
| Deaths/1,000 person-years | ***10.70*** | ***9.79*** | ***12.38*** | ***12.51*** | ***15.80*** | ***16.45*** |
| 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 | ***21.0*** | 21.1 | 22.0 | 25.0 |
| Less than high school education (%) | 25 | 12 | 22 | 35 | 45 | 30 |
| Average age (years) | 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 | ***38*** | 38 | 50 | 40 | 48 |
| **Air Quality Variables** | | | | | | |
| 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 | ***32.6*** | 31.4 | 46.5 |
| Fine particles ($\mu g/m^3$) | 11.0 | 12.5 | 14.9 | ***20.9*** | 19.0 | 29.6 |
| Sulfate particles ($\mu g/m^3$) | 5.3 | 4.8 | 6.5 | 8.1 | ***8.0*** | 12.8 |
| Aerosol acidity ($nmol/m^3$) | 10.5 | 11.6 | 20.3 | 36.1 | 10.3 | 25.2 |
| Sulfur dioxide (ppb) | ***3.7*** | ***1.5*** | ***7.6*** | 4.8 | ***9.2*** | ***23.6*** |
| Nitrogen dioxide (ppb) | 6.1 | 10.6 | 18.1 | 14.1 | ***20.9*** | 21.9 |
| Ozone (ppb) | 28.0 | 27.6 | 19.7 | 20.7 | ***19.7*** | 22.3 |

[a] Adjustment for early censoring was based on follow-up through March 15, 1991 for Harriman and through June 30, 1991 for all other cities, as specified by the Original Investigators. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

**Table 18a.** Adjusted Mortality Rate Ratios Estimated from Cox Proportional-Hazards Models: Original Results for the Six Cities Study[a]

| Variable | All Subjects | | Men | | Women | |
|---|---|---|---|---|---|---|
| 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[b] | 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[c] | 1.00 | (—) | 1.00 | (—) | 1.00 | (—) |
| Topeka | 1.01 | (0.82–1.24) | 1.04 | (0.79–1.36) | 0.97 | (0.71–1.34) |
| Harriman | 1.17 | (0.97–1.41) | 1.21 | (0.96–1.54) | 1.07 | (0.79–1.45) |
| Watertown | 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 | 1.26 | (1.06–1.50) | 1.29 | (1.03–1.62) | 1.23 | (0.93–1.61) |

[a] From Dockery et al 1993; corresponds to Table 2 in the original publication (Copyright © 1993, Massachusetts Medical Society, all rights reserved). Values are rate ratios (95% CIs). 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).

[b] This actually corresponds to 20 pack-years of smoking. The value 10 in this table was a typographical error in the original paper.

[c] City-specific rate ratios are all expressed in relation to Portage.

**Table 18b.** Adjusted Mortality Rate Ratios Estimated from Cox Proportional-Hazards Models: Reanalysis Results for the Six Cities Study Using the Same Analytic Cohort[a]

| Variable | All Subjects | | Men | | Women | |
|---|---|---|---|---|---|---|
| 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) | ***1.26*** | ***(1.13–1.41)*** | 1.18 | ***(0.99***–1.41**)** |
| Former-smoker | 1.20 | (1.01–1.43) | 1.17 | (0.93–1.48) | 1.34 | (1.02–1.77) |
| 20 Pack-years of smoking | ***1.16*** | ***(1.09***–1.23**)** | ***1.17*** | ***(1.10***–1.25**)** | ***1.14*** | **(**0.97–***1.35***) |
| 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) | ***1.12*** | (1.03–1.20) |
| City | | | | | | |
| Portage[b] | 1.00 | (—) | 1.00 | (—) | 1.00 | (—) |
| Topeka | 1.01 | (0.82–1.24) | 1.04 | (0.79–1.36) | 0.97 | (0.71–1.34) |
| Harriman | 1.17 | (0.97–1.41) | 1.21 | (0.96–1.54) | 1.07 | (0.79–1.45) |
| Watertown | 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 | 1.26 | (1.06–1.50) | 1.29 | (1.03–1.62) | 1.23 | (0.93–1.61) |

[a] Values are rate ratios (95% CIs). 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). Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

[b] City-specific rate ratios are all expressed in relation to Portage.

**Table 18c.** Adjusted Mortality Rate Ratios Estimated from Cox Proportional-Hazards Models: Reanalysis Results for the Six Cities Study After Adjusting for Early Censoring of Person-Years[a]

| Variable | All Subjects | | Men | | Women | |
|---|---|---|---|---|---|---|
| Current-smoker | ***1.61*** | **(*1.33–1.95*)** | ***1.77*** | **(*1.34–2.34*)** | ***1.56*** | **(*1.18–2.06*)** |
| 25 Pack-years of smoking | 1.26 | **(*1.15–1.37*)** | 1.25 | (1.12–***1.40***) | 1.18 | **(*0.99*–1.41)** |
| Former-smoker | ***1.21*** | **(*1.02*–1.43)** | 1.17 | **(*0.92–1.47*)** | ***1.37*** | **(*1.04–1.80*)** |
| 20 Pack-years of smoking | 1.15 | (1.08–1.23) | ***1.17*** | (1.09–1.25) | ***1.14*** | **(*0.96–1.34*)** |
| Less than high school education | 1.19 | **(*1.07*–1.33)** | ***1.23*** | **(**1.06–***1.42*)** | ***1.14*** | **(*0.96–1.36*)** |
| Body mass index | 1.08 | (1.02–1.14) | 1.03 | (0.95–1.12) | ***1.12*** | **(*1.04–1.21*)** |
| City[b] | | | | | | |
| Portage | 1.00 | (—) | 1.00 | (—) | 1.00 | (—) |
| Topeka | ***1.03*** | **(*0.84–1.26*)** | ***1.09*** | **(*0.83–1.42*)** | ***0.96*** | **(*0.70–1.31*)** |
| Harriman | ***1.19*** | **(*0.99–1.43*)** | ***1.24*** | **(*0.98–1.57*)** | 1.07 | **(**0.79–***1.44*)** |
| Watertown | 1.07 | **(**0.89–***1.29*)** | 0.94 | (0.73–1.20) | 1.22 | (0.93–1.61) |
| St Louis | ***1.15*** | **(**0.96–***1.37*)** | ***1.16*** | **(*0.93–1.46*)** | ***1.12*** | **(*0.84–1.47*)** |
| Steubenville | ***1.28*** | **(*1.08–1.52*)** | ***1.30*** | **(*1.04–1.63*)** | ***1.26*** | **(*0.96–1.66*)** |

[a] Values are rate ratios (95% CIs). 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). Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

[b] City-specific rate ratios are all expressed in relation to Portage.

subjects with less than high school education was divided by the mortality rate for those with high school education or more, and this had the value of 1.19 meaning that there was a 19% increase in mortality among the less educated relative to the more highly educated. The adjusted mortality rate ratios are summarized in Tables 18a, 18b, and 18c. In the original version of this table (Table 18a), mortality rate ratios are reported for subjects with 25 and 10 pack-years of smoking. During the course of the reanalysis, we discovered that the rate ratios given for 10 pack-years of smoking actually corresponded to 20 pack-years instead of 10 (Table 18b). We confirmed this with the Original Investigators; it appears this discrepancy was due to a typographic error in the NEJM article.

When the Reanalysis Team adjusted for early censoring of person-years, we found some small changes in the mortality rate ratios (Table 18c); although small, the changes are almost all in an upward direction.

***Adjusted Mortality Rate Ratios for the Most-Polluted City Versus the Least-Polluted City Studied*** Tables 19a, 19b, and 19c present adjusted mortality rate ratios for the most-polluted versus least-polluted city using fine particles as the indicator of air pollution (ie, the mortality rate ratio was calculated for an increase in fine particle concentrations across the range of values represented by the cities; thus, subjects in Steubenville were all assigned a value of 29.6 $\mu g/m^3$, those in Portage 11.0 $\mu g/m^3$, those in Topeka 12.5 $\mu g/m^3$, those in Watertown 14.9 $\mu g/m^3$, those in Harriman 20.9 $\mu g/m^3$, those in St Louis 19.0 $\mu g/m^3$; and

**Table 19a.** Adjusted Mortality Rate Ratios for the Most-Polluted Versus Least-Polluted Cities Studied by Smoking Status, Sex, and Occupational Exposure: Original Results for the Six Cities Study[a]

| Group of Subjects | Number of Subjects | Number of Deaths | Rate Ratio (95% CI) |
|---|---|---|---|
| All | 8,096 | 1,429[b] | 1.26 (1.08–1.47) |
| Nonsmokers | 3,266 | 431 | 1.19 (0.90–1.57) |
| Women | 2,280 | 292 | 1.15 (0.82–1.62) |
| Men | 986 | 139 | 1.29 (0.80–2.09) |
| Former-smokers | 1,934 | 432 | 1.35 (1.02–1.77) |
| Women | 670 | 106 | 1.48 (0.82–2.66) |
| Men | 1,264 | 326 | 1.31 (0.96–1.80) |
| Current-smokers | 2,896 | 566 | 1.32 (1.04–1.68) |
| Women | 1,478 | 201 | 1.23 (0.83–1.83) |
| Men | 1,418 | 365 | 1.42 (1.05–1.92) |
| No occupational exposure[c] | 4,455 | 686 | 1.17 (0.93–1.47) |
| Women | 3,151 | 417 | 1.13 (0.85–1.50) |
| Men | 1,304 | 269 | 1.27 (0.85–1.92) |
| Occupational exposure[c] | 3,641 | 743 | 1.35 (1.10–1.65) |
| Women | 1,277 | 182 | 1.32 (0.86–1.50) |
| Men | 2,364 | 561 | 1.35 (1.07–1.69) |

[a] From Dockery et al 1993; corresponds to Table 3 in the original publication (Copyright © 1993, Massachusetts Medical Society, all rights reserved). Fine particle concentration was used as the indicator of air pollution. The highest pollution level was in Steubenville and the lowest in Portage. Rates have been adjusted for age, sex, smoking, education, and body mass index. Fifteen subjects were excluded because of missing data on weight.

[b] Although Table 17a indicates a total of 1,430 deaths, the 15 excluded subjects (noted in footnote a) included one death.

[c] To gases, fumes, or dust.

**Table 19b.** Adjusted Mortality Rate Ratios for the Most-Polluted City Versus Least-Polluted City Studied by Smoking Status, Sex, and Occupational Exposure: Reanalysis Results for the Six Cities Study Using the Same Analytic Cohort[a]

| Group of Subjects | Number of Subjects | Number of Deaths | Rate Ratio (95% CI) |
|---|---|---|---|
| All | 8,096 | 1,429 | 1.26 (1.08–1.47) |
| Nonsmokers | ***3,265*** | 431 | 1.19 (0.90–1.57) |
| Women | 2,280 | 292 | 1.15 (0.82–1.62) |
| Men | ***985*** | 139 | 1.29 (0.80–2.09) |
| Former-smokers | 1,934 | 432 | 1.35 (1.02–1.77) |
| Women | 670 | 106 | 1.48 (0.82–2.66) |
| Men | 1,264 | 326 | 1.31 **(**0.96–***1.79*****)** |
| Current-smokers | ***2,897*** | 566 | 1.32 (1.04–1.68) |
| Women | 1,478 | 201 | 1.23 (0.83–1.83) |
| Men | ***1,419*** | 365 | 1.42 (1.05–1.92) |
| No occupational exposure[b] | 4,455 | 686 | 1.17 (0.93–1.47) |
| Women | 3,151 | 417 | 1.13 (0.85–1.50) |
| Men | 1,304 | 269 | 1.27 (0.85–1.92) |
| Occupational exposure[b] | 3,641 | 743 | 1.35 (1.10–1.65) |
| Women | 1,277 | 182 | 1.32 **(**0.86–***2.04*****)** |
| Men | 2,364 | 561 | 1.35 (1.07–1.69) |

[a] Fine particle concentration was used as the indicator of air pollution. The city with the highest pollution level was Steubenville and that with the lowest was Portage. Rates have been adjusted for age, sex, smoking, education, and body mass index. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

[b] To gases, fumes, or dust.

**Table 19c.** Adjusted Mortality Rate Ratios for the Most-Polluted City Versus Least-Polluted City Studied by Smoking Status, Sex, and Occupational Exposure: Reanalysis Results for the Six Cities Study After Adjusting for Early Censoring of Person-Years[a]

| Group of Subjects | Number of Subjects | Number of Deaths | Rate Ratio (95% CI) |
|---|---|---|---|
| All | 8,096 | ***1,443*** | ***1.28* (*1.10–1.48*)** |
| Nonsmokers | ***3,265*** | ***433*** | ***1.22* (*0.92–1.60*)** |
| Women | 2,280 | ***293*** | ***1.21* (*0.86–1.70*)** |
| Men | ***985*** | ***140*** | ***1.26* (*0.78–2.04*)** |
| Former-smokers | 1,934 | ***435*** | ***1.33* (*1.01–1.75*)** |
| Women | 670 | ***107*** | ***1.54* (*0.86–2.75*)** |
| Men | 1,264 | ***328*** | ***1.28* (*0.94–1.75*)** |
| Current-smokers | ***2,897*** | ***575*** | ***1.34* (*1.06–1.70*)** |
| Women | 1,478 | ***205*** | ***1.25* (*0.85–1.85*)** |
| Men | ***1,419*** | ***370*** | ***1.43* (*1.06–1.93*)** |
| No occupational exposure[b] | 4,455 | ***694*** | ***1.21* (*0.96–1.53*)** |
| Women | 3,151 | ***421*** | ***1.19* (*0.90–1.58*)** |
| Men | 1,304 | ***273*** | ***1.29* (*0.86–1.93*)** |
| Occupational exposure[b] | 3,641 | ***749*** | ***1.34* (**1.10–*1.64*)** |
| Women | 1,277 | ***184*** | ***1.33* (**0.86–*2.04*)** |
| Men | 2,364 | ***565*** | ***1.33* (*1.06–1.67*)** |

[a] Fine particle concentration was used as the indicator of air pollution. The city with the highest pollution level was Steubenville and that with the lowest was Portage. Rates have been adjusted for age, sex, smoking, education, and body mass index. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

[b] To gases, fumes, or dust.

the regression model included a term for fine air particles instead of the variable representing cities). The rate ratios are reported by smoking status, sex, and occupational exposure, and are adjusted for age, sex, smoking, education, and BMI. The reanalysis (Table 19b) indicated that the total number of male current-smokers should be 1,419 rather than 1,418 as reported in the NEJM article. The Original Investigators explained that information on weight was missing for one male smoker, so that subject had not been used in this analysis. The Reanalysis Team found an apparent discrepancy in the 95% upper confidence limit on the mortality rate ratio for occupational exposure to gases, fumes, or dust among women; the reanalysis produced an upper limit of 2.04 compared with the original value of 1.50 (Table 19b).

Again, when the Reanalysis Team eliminated the early censorship of person-years (Table 19c), some slight changes in the mortality rate ratios resulted. We did not consider these changes to be of epidemiologic importance.

***Estimated Mortality Rate Ratios for the Most-Polluted City Versus the Least-Polluted City in Selected Analytic Models*** In Tables 20a, 20b, and 20c different analytic models are applied to calculate the mortality rate ratios for the most-polluted city (Steubenville) versus the least-polluted city (Portage) using fine particles as the indicator of air pollution. All rate ratios are adjusted for age and sex. The reanalysis produced results identical to those reported by the Original Investigators (Table 20b).

When the Reanalysis Team corrected for early censorship of person-years, some slight changes were found in all

**Table 20a.** Estimated Mortality Rate Ratios for the Most-Polluted City Versus the Least-Polluted City Using Selected Models: Original Results for the Six Cities Study[a]

| Model Number | Variables Included[b] | 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 exposures | 1.26 (1.08–1.46) |
| 6 | Model 5 excluding 1,439 subjects with hypertension | 1.25 (1.04–1.50) |
| 7 | Model 5 excluding 561 subjects with diabetes | 1.29 (1.09–1.52) |

[a] From Dockery et al 1993; corresponds to Table 4 in the original publication (Copyright © 1993, Massachusetts Medical Society, all rights reserved). Fine particle concentration was used as the indicator of air pollution. The city with the highest pollution level was Steubenville and that with the lowest was Portage. In addition to the variables specified, rates have been adjusted for age and sex.

[b] Subjects with hypertension 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.

**Table 20b.** Estimated Mortality Rate Ratios for the Most-Polluted City Versus the Least-Polluted City Using Selected Models: Reanalysis Results for the Six Cities Study Using the Same Analytic Cohort[a]

| Model Number | Variables Included[b] | 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 exposures | 1.26 (1.08–1.46) |
| 6 | Model 5 excluding 1,439 subjects with hypertension | 1.25 (1.04–1.50) |
| 7 | Model 5 excluding 561 subjects with diabetes | 1.29 (1.09–1.52) |

[a] Fine particle concentration was used as the indicator of air pollution. The city with the highest pollution level was Steubenville and that with the lowest was Portage. In addition to the variables specified, rates have been adjusted for age and sex.

[b] Subjects with hypertension 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.

**Table 20c.** Estimated Mortality Rate Ratios for the Most-Polluted City Versus the Least-Polluted City Using Selected Models: Reanalysis Results for the Six Cities Study After Adjusting for Early Censoring of Person-Years[a]

| Model Number | Variables Included[b] | Rate Ratio (95% CI) |
|---|---|---|
| 1 | Fine particles | ***1.32*** (***1.14–1.54***) |
| 2 | Model 1 + all smoking variables | ***1.30*** (***1.12–1.51***) |
| 3 | Model 2 + high school education | ***1.28*** (***1.10–1.48***) |
| 4 | Model 3 + body mass index | ***1.28*** (***1.10–1.48***) |
| 5 | Model 4 + occupational exposures | ***1.27*** (***1.10–1.48***) |
| 6 | Model 5 excluding 1,439 subjects with hypertension | ***1.28*** (***1.07–1.53***) |
| 7 | Model 5 excluding 561 subjects with diabetes | ***1.30*** (***1.11–1.53***) |

[a] Fine particle concentration was used as the indicator of air pollution. The city with the highest pollution level was Steubenville and that with the lowest was Portage. In addition to the variables specified, rates have been adjusted for age and sex. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

[b] Subjects with hypertension 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.

**Table 21a.** Adjusted Mortality Rate Ratios for Current-Smokers, Former-Smokers, and for Both Smoking Groups in the Most-Polluted City Versus the Least-Polluted City by Cause of Death: Original Results for the Six Cities Study[a]

| Cause of Death | Percent of Total Deaths | Current-Smoker[b] | Former-Smoker[c] | Most- vs Least-Polluted City |
|---|---|---|---|---|
| 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) |

[a] From Dockery et al 1993; corresponds to Table 5 in the original publication (Copyright © 1993, Massachusetts Medical Society, all rights reserved). Values are rate ratios (95% CIs). Fine particle concentration was used as the indicator of air pollution. The city with the highest pollution level was Steubenville and that with the lowest was Portage. Rates have been adjusted for age, sex, smoking, education, and body mass index.

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

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

of the mortality rate ratios (maximum difference 0.03 [Table 20c]).

***Adjusted Mortality Rate Ratios for Current-Smokers, Former-Smokers, and for the Most-Polluted City Versus the Least-Polluted City by Cause of Death*** Tables 21a, 21b, and 21c show adjusted mortality rate ratios for current-smokers and former-smokers, each compared with nonsmokers, and then both smoker groups residing in the most-polluted city versus those in the least-polluted city (with fine particle concentration being used as the indicator of air pollution). For the former two analyses, these rate ratios are adjusted for age, sex, smoking, education, and BMI. These mortality rate ratios represent risk of death for a current-smoker with 25 pack-years of smoking and a former-smoker with 20 pack-years of smoking (the average pack-years at enrollment for each group) compared with never-smokers. The adjusted mortality rate ratios for current-smokers were estimated by multiplying the risk ratio for current-smokers by the risk ratio for the number of pack-years smoked (25). The rate ratios for former-smokers were calculated in a similar fashion.

The Original Investigator determined 95% confidence intervals (CIs) by using the following formula:

$$95\ \%\ \text{CI for RR (Current-Smoker)} = \exp\{\beta_1 + \beta_2 + \beta_3 \pm 1.96\ [\text{Var}(\beta_1) + \text{Var}(\beta_2) + \text{Var}(\beta_3)]^{1/2}\}$$

where $\beta_1$, $\beta_2$, and $\beta_3$ are the estimates of the logarithm of the relative risk for the indicator variable representing current smoking, number of pack-years of cigarettes smoked, and number of years of smoking, respectively, and with the

**Table 21b.** Adjusted Mortality Rate Ratios for Current-Smokers, Former-Smokers, and for Both Smoking Groups in the Most-Polluted City Versus the Least-Polluted City by Cause of Death: Reanalysis Results for the Six Cities Study Using the Same Analytic Cohort[a]

| Cause of Death | Percent of Total Deaths | Current-Smoker[b] | Former-Smoker[c] | Most- vs Least-Polluted City |
|---|---|---|---|---|
| All | 100 | 2.00 (***1.74–2.31***) | 1.39 (***1.20–1.61***) | 1.26 (1.08–1.47) |
| Lung cancer | 8.4 | 8.00 (***3.85–16.63***) | ***2.55*** (***1.12–5.80***) | 1.37 (0.81–***2.32***) |
| Cardiopulmonary disease | 53.1 | 2.30 (***1.88–2.82***) | 1.52 (***1.23–1.87***) | 1.37 (1.11–1.68) |
| All others | 38.5 | 1.46 (***1.17–1.82***) | 1.17 (***0.93–1.48***) | 1.01 (0.79–1.30) |

[a] Values are rate ratios (95% CIs). Fine particle concentration was used as the indicator of air pollution. The city with the highest pollution level was Steubenville and that with the lowest was Portage. Rates have been adjusted for age, sex, smoking, education, and body mass index. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

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

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

**Table 21c.** Adjusted Mortality Rate Ratios for Current-Smokers, Former-Smokers, and for Both Smoking Groups in the Most-Polluted City Versus the Least-Polluted City by Cause of Death: Reanalysis Results for the Six Cities Study After Adjusting for Early Censoring of Person-Years[a]

| Cause of Death | Percent of Total Deaths | Current-Smoker[b] | Former-Smoker[c] | Most- vs Least-Polluted City |
|---|---|---|---|---|
| All | 100 | ***2.03*** (***1.76–2.33***) | 1.39 (***1.20–1.61***) | ***1.28*** (***1.10–1.48***) |
| Lung cancer | ***8.2*** | ***8.07*** (***3.89–16.75***) | ***2.52*** (***1.10–5.74***) | ***1.43*** (***0.85–2.41***) |
| Cardiopulmonary disease | ***51.7*** | 2.30 (***1.88–2.82***) | 1.52 (***1.23–1.87***) | ***1.38*** (***1.12–1.69***) |
| All others | ***37.6*** | ***1.44*** (***1.16–1.80***) | 1.17 (***0.94–1.47***) | 1.01 (0.79–1.30) |

[a] Values are rate ratios (95% CIs). Fine particle concentration was used as the indicator of air pollution. The city with the highest pollution level was Steubenville and that with the lowest was Portage. Rates have been adjusted for age, sex, smoking, education, and body mass index. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

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

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

corresponding estimates of variance denoted by Var(β•). Interval estimation using this approach assumes that the parameter estimates are statistically independent, though these parameters are actually correlated.

When recalculating CIs for current- and former-smokers, the Reanalysis Team incorporated statistical dependence between the parameter estimates into the calculation of the CI by applying the formula:

$$95\%\ \text{CI for RR (Current-Smoker)} = \exp(\beta_1 + \beta_2 + \beta_3 \pm 1.96\ \{\text{Var}(\beta_1) + \ldots + \text{Var}(\beta_3) + 2[\text{Cov}(\beta_1, \beta_2) + \ldots + \text{Cov}(\beta_1, \beta_3)]\}^{1/2})$$

where $\text{Cov}(\beta_1,\beta_2)$ is the estimated covariance between the parameter estimates. (We refer to this as a direct method.) Covariances were estimated using the SAS procedure for the Cox proportional-hazards model. The CIs are narrower using this approach than those determined by the method the Original Investigators used (Table 21b).

Once again, when the Reanalysis Team corrected for the early censorship of person-years, we noted slight increases in the risk ratios (Table 21c).

***Annual Average Concentrations of Total Particles, Fine Particles, and Sulfate Particles in the Six Cities*** Figures 7 through 9 show the levels of TSP, fine particles, and sulfate particles in each city. In seeking to validate the original results on the basis of air quality data provided by the Original Investigators, the Reanalysis Team found some discrepancies in what had been published in the NEJM article. The Reanalysis Team received directly from Dr Dockery on July 29, 1999, the dataset we used to recompute the long-term means published by Dockery and colleagues. The dataset was used by the Reanalysis Team to reproduce the long-term averages and annual average concentrations of pollutants cited in the original paper.

The Reanalysis Team noted a number of discrepancies among the published averages, those received from Dr Dockery (personal communication from Douglas Dockery to the Reanalysis Team on March 31, 1999) and the ones we computed. The results of this step are summarized in Tables 17a, 17b, and 17c.

For all gaseous pollutants other than sulfur dioxide, the discrepancies the Reanalysis Team noted were minor and could be attributed to approximations in intermediate steps or to use of different software or procedures within the same software. For St Louis, the mean concentrations for nitrogen dioxide and ozone were apparently reversed in the NEJM article. This was either a typographic or transcription error in the article.

We were not able to reproduce the mean concentrations for sulfur dioxide except for Harriman. The discrepancies in means ranged from 0.1 $\mu g/m^3$ for Topeka to 4.9 $\mu g/m^3$ for St Louis. The published means for both TSP and sulfur dioxide were computed from annual averages (personal communication from Douglas Dockery to the Reanalysis Team on March 31, 1999). The Reanalysis Team followed the same procedures. We calculated annual averages first and then used those

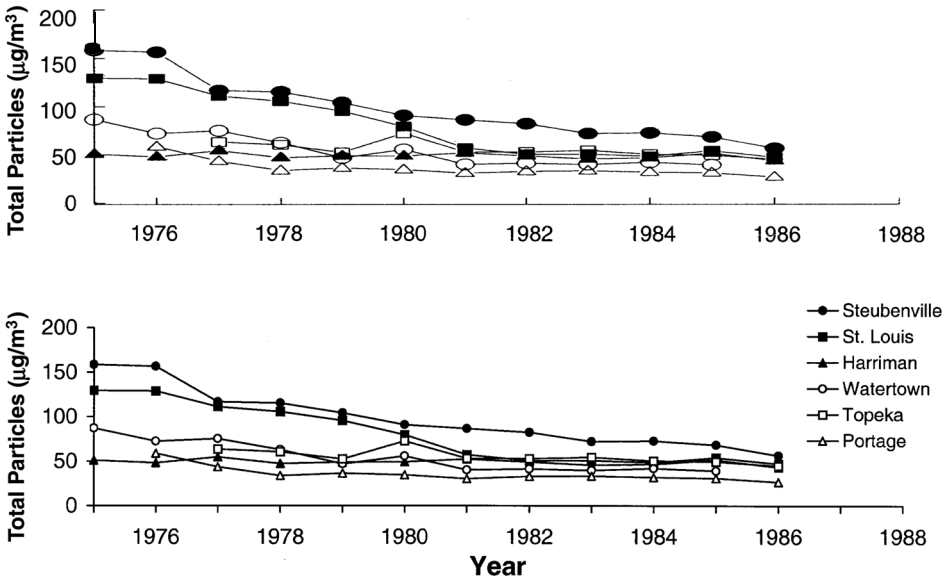



**Figure 7. Annual Average Concentrations of Total Particles in the Six Cities.** Top panel: Original results from Dockery and associates 1993 (Figure 1 top panel; Copyright © 1993, Massachusetts Medical Society, all rights reserved). Bottom panel: Reanalysis Team's results.

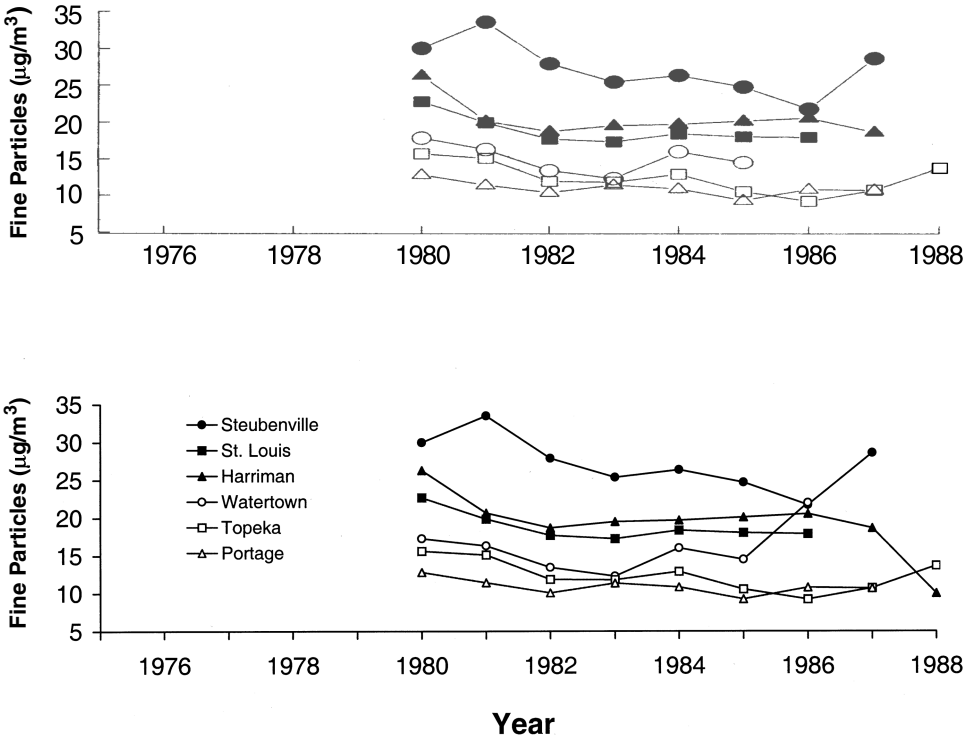



**Figure 8. Annual Average Concentrations of Fine Particles in the Six Cities.** Top panel: Original results from Dockery and associates 1993 (Figure 1 middle panel; Copyright © 1993, Massachusetts Medical Society, all rights reserved). Bottom panel: Reanalysis Team's results. (Note: The Original Investigators did not use the 1986 data for Watertown or the 1988 data for Kingston-Harriman because only one measurement was taken in these two cities in those years.)

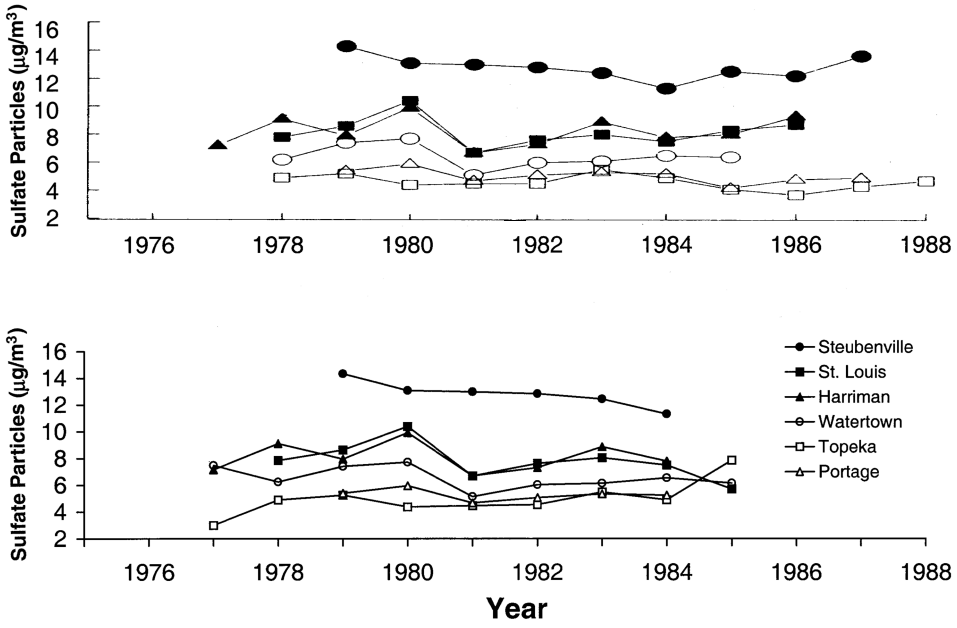



**Figure 9. Annual Average Concentrations of Sulfate Particles in the Six Cities.** Top panel: Original results from Dockery and associates 1993 (Figure 1 bottom panel; Copyright © 1993, Massachusetts Medical Society, all rights reserved). Bottom panel: Reanalysis Team's results.

to compute long-term average concentrations. However, the discrepancies still persisted.

Some discrepancies are noticeable in the graphic plots as well. Figures 7, 8, and 9 show differences in years of coverage between the published and the computed plots. First, for TSP (Figure 7), data entries prior to 1975 (1973 and 1974 data mostly) were not used in the original publication; from 1975 on, the original and reanalysis plots are consistent. Second, the data points for fine particles (Figure 8) prior to 1980 were omitted from the original graph. These data exist for all cities except Harriman. In addition, fine particle data for later years were not shown in the original plots; these are Harriman in 1988 and Watertown in 1986, as shown in Figure 8. Third, data for sulfate particles before 1978 were not used in the original analyses, except for Harriman, where the data start in 1977 (Figure 9). In the original figure, data are plotted for all cities (except Watertown) beyond 1985. However, the Reanalysis Team found no data entries for the years 1986–1988 in the data file; in fact, we found data for 1985 only for St Louis, Topeka, and Watertown.

***Crude Probability of Survival in the Six Cities by Years of Follow-up*** Figure 10 (which was Figure 2 in NEJM) illustrates the crude probability of survival in each of the six cities according to the number of years of follow-up. The Reanalysis Team found no differences between our results and those reported by the Original Investigators.

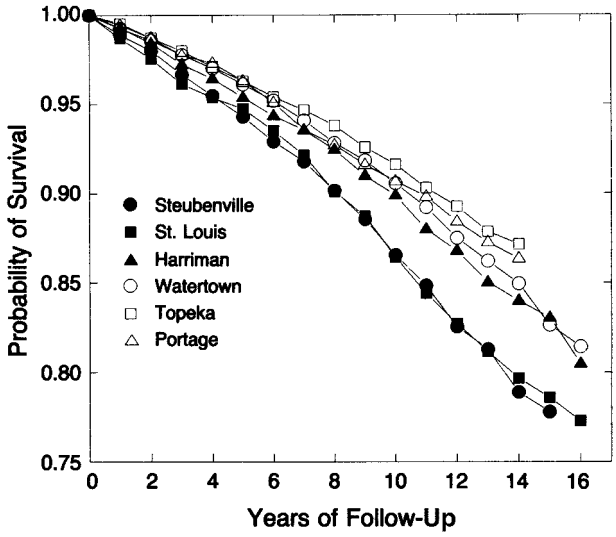



**Figure 10. Crude Probability of Survival in the Six Cities, According to Years of Follow-Up.** Original results from Dockery and associates 1993 (Figure 2; Copyright © 1993, Massachusetts Medical Society, all rights reserved).

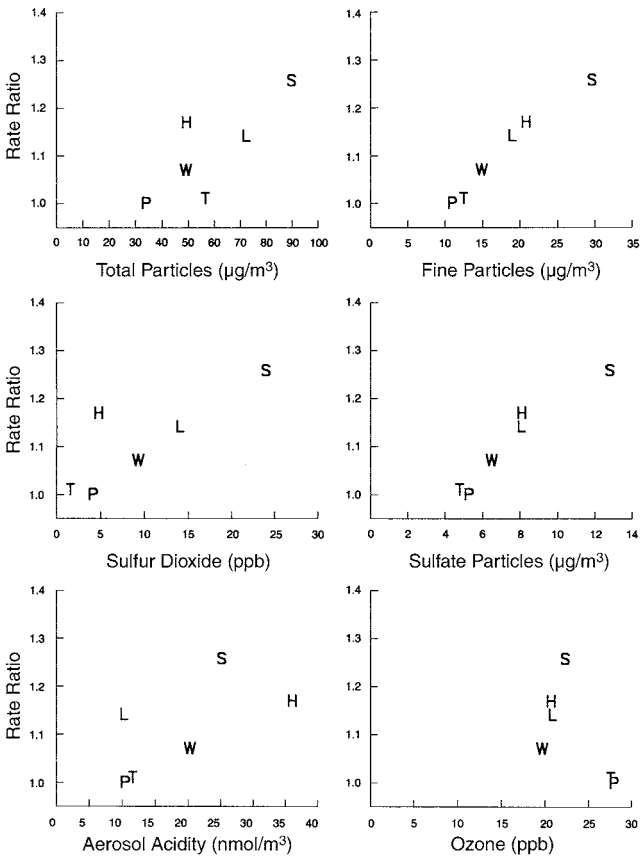



**Figure 11. Estimated Adjusted Mortality Rate Ratios and Pollution Levels in the Six Cities.** Original results from Dockery and associates 1993 (Figure 3; Copyright © 1993, Massachusetts Medical Society, all rights reserved). P = Portage, T = Topeka, W = Watertown, L = St Louis, H = Harriman, and S = Steubenville.

***Estimated Adjusted Mortality Rate Ratios and Pollution Levels in the Six Cities*** Each panel of Figure 11 (which was Figure 3 in the NEJM) shows the relation between mortality rate ratios in each city on the basis of one measure of air pollution: TSP, fine particles, sulfur dioxide, sulfate particles, aerosole acidity, or ozone. The reanalysis revealed no discrepancies in the original findings.

## THE AMERICAN CANCER SOCIETY STUDY

In 1982, the ACS initiated a large prospective cohort study, which involved subjects from all 50 United States, the District of Columbia, and Puerto Rico, known as the Cancer Prevention Study II (CPS-II). Enrollment had been restricted to persons who were at least 30 years of age and who were members of households with at least one individual 45 years of age or older. Each participant had completed a four-page questionnaire (see Appendix D), which included items 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 aspects of exercise and health-related behaviors.

Vital status for all CPS-II participants, from September 1, 1982, through December 31, 1989, had been determined using personal inquiries and automated record linkage to the NDI. Death certificates had been subsequently obtained from state health departments and coded by a nosologist. The nosologist coded the underlying cause of death according to the ICD-9.

From the CPS-II cohort of approximately 1.2 million adults, Pope and colleagues (1995) included all subjects who had no missing data for a specific set of variables obtained from the questionnaire, and for whom a death certificate had been obtained if they were deceased. Two subsets of this population were defined if they had resided, at the time of enrollment, in (1) one of 151 metropolitan areas (MAs) for which sulfate particle measurements had been collected during the years 1980–1982, or (2) one of 50 MAs for which fine particle measurements had been collected during the years 1979–1983. (The 151 MAs with sulfate measurements included all but three of the 50 MAs with fine particle measurements; thus, data were collected for 154 total cities.) The population subset with exposure to sulfate particles totaled 552,138 adult subjects (referred to as the sulfate cohort), of which 295,223 subjects were also in the population subset with exposure to fine particles (referred to as the fine particle cohort). Risk factor data for individuals were obtained from the CPS-II. (Hereafter, the study by Pope and associates [1995], as published in the *American Journal of Respiratory and Critical Care Medicine* [AJRCCM], is referred to as the ACS Study.[†])

A total of 38,963 deaths were recorded in the sulfate cohort and 20,765 deaths in the fine particle cohort. Separate analyses were performed for deaths from: all causes combined, lung cancer, cardiopulmonary disease, and all others.

Two measures of air pollution, fine particles and sulfate, were modeled. The mean concentration of sulfate air pollution by MA during 1980 was estimated using data from the EPA Aerometric Information Retrieval System (AIRS) database. These means were calculated as the averages of annual arithmetic mean 24-hour sulfate values for all monitoring sites in the 151 MAs. Mean sulfate concentrations averaged 11 $\mu g/m^3$ and ranged from 3.6 to 23.5 $\mu g/m^3$. The median concentration of fine particles between 1979 and 1983 was estimated from the

[†] The original article appears in its entirety at the end of this Special Report.

EPA's dichotomous sampler network by Lipfert and colleagues (1988). These estimates of fine particle levels had been used previously in a population-based cross-sectional mortality study of 50 MAs. The average median fine particle concentration was 18.2 $\mu g/m^3$ and overall values ranged from 9.0 to 33.5 $\mu g/m^3$ (Lipfert 1993).

Cox proportional-hazards regression models were used to calculate adjusted mortality risk ratios. The time axis was defined using calendar time from the date of enrollment. Statistical adjustments were made for several covariates that included, among others, smoking, education, BMI, and alcohol consumption. In addition, the potential confounding influence of occupational exposures on the estimates of air pollution, such as diesel engine exhaust, wood dust, and fumes, was evaluated. All models were stratified by 5-year age categories, gender, and race, which allowed each sex-age-race stratum to have its own baseline hazard. To determine the extent to which the results were confounded by differences in climates across the MAs, variables that accounted for relatively hot or cold conditions were added to the models. Cox proportional-hazards models were estimated separately for all causes of death combined and the three cause-of-death subcategories: lung cancer (ICD-9 code 162), cardiopulmonary disease (ICD-9 codes 401–440 and 460–519), and all others.

Both sulfate and fine particle exposures were found to be associated with an excess risk of all-cause mortality. The ratio of the mortality risk for all causes of death for subjects in the most-polluted city relative to those in the least-polluted city was estimated to be 1.15 (95% CI: 1.09–1.22) for the sulfate cohort and 1.17 (95% CI: 1.09–1.26) for the fine particle cohort.

## AUDIT OF STUDY POPULATION DATA

### Data Provided and Source Documents Accessible for the Data Audit

In the absence of a study protocol, we audited the data against the study methods and results as presented in the publication by Pope and colleagues (1995). Because of space limitations at the ACS offices, most of the Audit Team's activities were conducted offsite.

One of the difficulties the Audit Team faced was that the original staff of the ACS Study who managed the data collection and databases were no longer employed by ACS. Dr Eugenia Calle of the ACS facilitated contacts with Ms Cathy Lally, who had been employed by ACS after the data collection and much of the programming had been completed. (Ms Lally was no longer employed by ACS, but performed work on a periodic consulting basis.) She assisted the Audit Team with issues about coding and programming.

The ACS staff reconstructed SAS datasets corresponding to the analytic files that had been used by the Original Investigators (hereafter, these electronic datasets are referred to collectively as Analytic.files). These datasets contained all of the variables derived from the questionnaires used in the original analysis (see Appendix D), vital status of the participants, and average annual sulfate and particle levels in the cities.

The Audit Team relied on code books, copies of microfilmed records, and printouts of computer programs provided to the Reanalysis Team. This database has continued to be updated for use in other studies. Therefore, the Audit Team worked with the reconstructed version of the database, as it existed at the time of study publication. From discussions the Audit Team had with Ms Lally, it was clear that, while reconstructing the database for transfer to the Reanalysis Team, she had carefully examined the computer programs and quality control process and responded to any issues that she uncovered. This process was important to the audit, but was not formalized.

### Sampling the Dataset and Assessing Error Rates in the Original Data: Subsets of Study Population and Deceased Subjects

The original study cohort included 552,138 men and women who filled out questionnaires on health and lifestyle. As in the audit of the Six Cities Study, we randomly selected questionnaires for 250 subjects. The Audit Team coordinator met with the Reanalysis Team and identified variables from the questionnaires to be verified and used in the sensitivity analyses (Table 22).

Records of vital status had been lost when the ACS offices moved from New York to Atlanta. For 44 of the 250 subjects in the audit sample, the Audit Team ascertained vital status from a later American Cancer Society Nutrition Survey; for these subjects, vital status could be positively confirmed because they were alive at a date later than the termination date for follow-up in the cohort used in the ACS Study. For the remaining 206 subjects, the Audit Team ascertained vital status by checking the NDI; in addition, we searched the Social Security Death Index available on the Internet (http://www.ancestry.com).

The total number of deaths used in the ACS Study analyses was 51,137; from this group of deceased subjects, the Audit Team randomly selected a second 250-subject subset of death certificates. The ACS Original Investigators provided the Audit Team with a list containing full names and dates of birth for these 250 deceased subjects.

For each death certificate, the Audit Team's nosologist coded the underlying cause of death according to the ICD-9 and compared it with the code that had been used in

**Table 22.** List of Variables for Reanalysis Team to Audit and the Criteria for Declaring Errors in the ACS Study

| Original Questionnaire Variable | Subvariable | Criteria |
|---|---|---|
| Subject identification number | | Any difference |
| Age at enrollment | | Any difference |
| Sex | | Any difference |
| Race | | Any difference |
| Vital status | Death month and year if applicable | Any difference |
| Survival time from date of enrollment | Survival censored at end of study, 12/31/89 | Any difference |
| Cigarette smoking status | Current and former | Any difference |
| Pipe and cigar smoking status | Current and former | Any difference |
| Years smoked | Current and former | Any difference |
| Cigarettes per day | Current and former | Any difference |
| Hours per day exposed to passive smoke | | Any difference |
| Height | | Any difference |
| Weight | | Any difference |
| Number of alcoholic drinks per day | | Any difference |
| Education | | Any difference |
| Occupational exposure to asbestos, chemicals/solvents/acids, coal/stone dust, tar/pitch/asphalt, diesel exhaust, formaldehyde | | Any difference |

original analysis. The Audit Team identified possible cases in which an ICD-9 code for an immediate or contributing cause of death had been used rather than the ICD-9 code for the underlying cause. From the microfilm copies of each of the death certificates, the Audit Team also tracked the notation of the ICD-9 code through its entry into the Analytic.files and noted any transcription errors.

Printouts of the Analytic.files provided to the Reanalysis Team were used to check specific data points for each variable in the subsets of questionnaires and death certificates.

**Subset of Study Population: Questionnaires**

***Questionnaire Variables*** All original questionnaires and death certificates had been destroyed after filming because of storage space considerations. Questionnaires were found on the microfilm for 249 out of 250 subjects. One microfilm copy of a questionnaire could not be located because the roll and frame numbers were missing. The Audit Team could not determine if this missing record was due to an error in microfilming or in the actual retrieval and data management of the study.

*Questionnaire Validation Variable for SID Number* We matched each 14-digit SID number from the Analytic.files with the 14-digit identification number on the questionnaire. Errors were found in 3 (1.2%) of the 249 questionnaires: one in the division number, one in the unit number, and one in the group number.

*Sex and Race* We found no inconsistencies in the recording of sex or race.

*Age at Enrollment* The Audit Team noted one minor inconsistency in recording the age at enrollment in that the age had been rounded up to the next year.

*Height and Weight* We detected no errors in the presentation of height and weight.

*Smoking Status and Passive Exposure to Smoke* Information on active smoking and passive exposure to smoke was contained in 11 variables. The Original Investigators had recorded total years of smoking for current- and former-smokers directly from the questionnaire responses. The participants' answer to "total years of smoking" did not always match the number of years calculated from their responses to "age began smoking" and "age quit smoking". Other coding conventions limited the hours per day of passive exposure to smoke.

The Audit Team found good consistency between the Analytic.files and the questionnaires. We found no inconsistencies for five of the eight smoking variables; the other three had one error per variable. Likewise, we found no inconsistencies in two of the variables regarding passive

exposure to smoke, but found two inconsistencies for exposure to "passive smoke elsewhere".

*Alcohol Intake* Three variables provided information on intake of alcohol. We found no errors in these data.

*Occupational Exposures* Six variables were used to record occupational exposures to asbestos, chemicals/acids/solvents, coal/stone dust, coal tar/pitch/asphalt, diesel engine exhaust, and formaldehyde. These variables had then been collapsed into one variable for the statistical analyses by identifying a participant as occupationally exposed if a "1" for "yes" appeared for any one of the six variables. The Audit Team detected no errors in any of these six variables.

*Education* Although the education variable presented gradations in years of education, the final analyses compared those with and those without a high school education. We detected no errors in this latter variable.

*Vital Status and Date of Death for Deceased Members of the Questionnaire Subset* We identified 11 subjects from the questionnaire subset who were deceased. The date of death was represented by the month and year of death. We verified the vital status for members of the subset using two sources of information: a list of participants who took part in an American Cancer Society Nutrition Survey (conducted after completion of the ACS Study) and Social Security information available on the Internet.

However, to confirm that all individuals in the questionnaire subset identified as alive had indeed been alive at the ending date of the study, we needed additional information. At the request of the Audit Team, the ACS staff submitted the list of 250 names to the National Center for Health Statistics. There, technicians searched the NDI records for deaths that occurred during the study follow-up period of 1982–1989; they identified 242 records as possible matches for 71 individuals in the questionnaire subset. The Audit Team then reviewed each record, comparing the ACS and NDI entries for full name, SSN when available, date of birth (month and year), sex, race, marital status, state of residence, state of birth, and date of death (month and year).

By reviewing the NDI records, the Audit Team documented the month and year of death for the 11 individuals from this sample that had been identified as deceased by the ACS. For the other 60 individuals for whom one or more possible matches were detected, the Audit Team concluded that none of the possible NDI records represented subset members. Three cases were reviewed closely because they had no SSN in the ACS records and they matched NDI records on the basis of first and last name, birth month and year, sex, and race. However, the match was not consistent with the ACS records for state of residence or state of birth. Therefore, the Audit Team concluded that these possible matches did not reflect deaths of subset members and that the ACS coding of vital status was consistent with NDI records.

Thus, the Audit Team confirmed the vital status and dates of death (for 11 individuals) for all members of the questionnaire subset.

*Survival Time* The Audit Team recalculated this variable for each subject in the questionnaire subset. We noted no errors in the calculations and no inconsistences between this variable and the ascertainment of vital status previously described.

**Subset of Deceased Subjects: Death Certificates**

We audited the data given to the Reanalysis Team against source documents provided for a random sample of 250 deceased subjects.

We drew the random sample from deaths that had occurred during the first 6 years of the study, the original length of follow-up. The Original Investigators had added a seventh year of follow-up. Deaths only among men during this seventh year were included in the analysis. This oversight had been detected before the Atlanta audit and Ms Lally had completed the follow-up of women and had redone the analysis.

The Original Investigators provided the Audit Team with a listing of full names and dates of birth for the 250 subjects in the subset of deceased subjects. Of the 250 death certificates we requested, the Original Investigators retrieved 240 that had legible cause-of-death information. The ten missing or incomplete death certificates included six with missing microfiche roll and file information, one identified as "destroyed", one microfiche record that was blurred, one with an illegible cause of death, and one missing the cause-of-death section. For the 242 deaths we could verify, all had occurred before December 31, 1989, the study's ending date.

We audited the following variables by comparing information in the ACS Analysis.files to the death certificate copies:

- date of birth in Analysis.files versus date of birth on the death certificate;
- date of death in Analysis.files versus the date of death on the retrieved death certificate;

- subject identification information (SID, full name, birth date) in Analysis.files versus the same information on the death certificate; and
- ICD-9 cause-of-death code in Analysis.files versus code interpreted by the Audit Team nosologist from the death certificate.

***Date of Birth*** The Audit Team found 11 dates of birth on death certificates that did not match the dates of birth in the Analysis.files, which had been derived from the participant's own entry on the questionnaire.

***Date of Death*** We noted two inconsistencies, one in the month and one in the year of death.

***Correct Death Certificate*** Due to variations in spelling of last names, or differences in dates of birth, or both, the Audit Team could not verify 15 death certificates as pertaining to the study subjects identified. We forwarded the SID numbers for these individuals to Dr Calle, who returned addresses, states of birth, names of spouses, and SSNs when available. We were then able to verify that all but one death certificate represented the appropriate study participant. That one death certificate clearly did not represent the intended study subject because the match had been based only on the phonetic spelling of the last name and the state of death. The Audit Team tracked the actual subject using Social Security information available on the Internet.

***Cause-of-Death Codes*** As described for the Six Cities Study, the Audit Team nosologist compared the cause-of-death code with the one in the Analysis.files.

The variable containing cause-of-death information included either a two-digit CPS-II code (code book provided by Dr Calle) or a four-digit ICD-9 code. The two-digit code was a consolidation of ICD-9 codes. If a two-digit entry appeared, the Audit Team nosologist converted her ICD-9 code to the broader two-digit code on the basis of entries in the code book and then compared her code with that in the Analysis.files.

In 15 (6.3%) of the 240 death certificates with legible cause-of-death information, the Audit Team's two- or four-digit code did not match the code in the Analysis.files. Broad disease categories for cause-of-death analyses had been used by the Original Investigators. In 4 (1.6%) of the 240 death certificates, using the Audit Team's code would have altered the broad disease category. Details of these and other discrepancies are shown in Table 23.

The Audit Team next tracked how information had been incorporated into the broad disease categories used in the original analyses. Ms Lally again provided programming documentation. The program identified the cause-of-death code as codetype=1 (the two-digit CPS-II code) or codetype=2 (the four-digit ICD-9 code) and then proceeded with the following algorithm:

- asthma deaths were identified if code1 = 16 or 4930–4939;
- cardiopulmonary deaths were identified if code1 = 01, 03, 04, 05, 06, 07, 13, 14, 15, 16, 17, 18, 4010–4059, 4100–4179, 4200–4389, 4400–4409, 4800–4969, 4600–4789, or 5000–5199; due to the "else if" command used in each section, asthma deaths would not be included in this category because they had already been identified in an earlier step as belonging to the category of asthma deaths;
- lung cancer deaths were identified if code1 = 62 or 1620–1629; and
- all deaths not belonging to the first three groups were classified as "other".

The Audit Team detected a minor error in the computer program: the two-digit codes of 0A and 0B were coded as "other". However, as 0A referred to ICD-9 code 416.9, chronic pulmonary heart disease unspecified, and 0B referred to 440.9, generalized and unspecified atherosclerosis, these deaths should have been coded as cardiopulmonary, yet the program assigned them to the default "other" category. The Audit Team brought this to the attention of Dr Calle and Ms Lally, who searched the databases for individual records with a code 0A or 0B. For the total cohort, 16 deaths had been coded as 0A and 55 deaths had been coded as 0B. These 71 deaths had been grouped with "other" deaths rather than with cardiopulmonary deaths. The Audit Team concluded that this small number of additional cardiopulmonary deaths would not have affected the original results from the ACS Study.

## AUDIT OF AIR QUALITY DATA

The ACS Study was not originally designed as an air pollution study. The air quality monitoring data used for the ACS analyses came from various sources, some of which are now technologically difficult to access. Documentation of the statistical reduction procedures has been lost. Summary statistics for different groups of standard metropolitan statistical areas had been derived by different investigators. These data sources do not indicate whether the tabulated values refer to all or a subset of monitors in a region or whether they represent means or medians. Values of sulfate for some cities could have come from several different sources. No information was available on any procedures that may have been applied to screen data. It

**Table 23.** Discrepancies in Codes Assigned to Causes of Death on Death Certificates Used by the ACS Study

| Code in Analytic.files | Causes of Death on Death Certificate | Comments | Code by Audit Team's Nosologist |
|---|---|---|---|
| 59 (159): Malignant neoplasm of other/ill-defined sites within digestive organs | Line a: Metastasis adenocarcinoma (primary unknown) | Adenocarcinoma does not necessarily originate in digestive organs (eg, lung adenocarcinoma) | 99 (199.0): Malignant neoplasm without specification of site, disseminated |
| 10: Thrombosis | Line a: Acute pulmonary embolism<br>Line b: Thrombophlebitis, lower extremities<br>Line c: Severe hypercalcemia with venous stasis | One other case also had pulmonary embolism (line a) and venous stasis (line b) on death certificate, yet had been coded as a 4 rather than as a 10 like this case | 4 (415.1): Pulmonary embolism[a] |
| 01: Ischemic heart disease | Line a: Septic shock<br>Line b: Overwhelming septicemia | | 28 (038.9): Septicemia[a] |
| 57: Cancer of pancreas | Line a: Cancer, liver with hepatic coma; pancreatitis | | 55 (155.2): Liver cancer |
| 05: Other forms of heart disease (includes congestive heart failure) | Line a: Cardiopulmonary arrest<br>Line b: Class IV congestive heart failure<br>Line c: Renal failure | | 23 (586): Renal failure[a] |
| 22: All other digestive diseases | Line a: Gangrene of large and small bowel<br>Line b: Portal vein thrombosis<br>Line c: Lactic acidosis | | 10 (453.8): Thrombosis of other specified veins |
| 01: Ischemic heart disease | Line a: Bronchopneumonia | Atherosclerotic heart disease was listed in Part II (other significant conditions) | 13: Pneumonia |
| 414.0: Coronary atherosclerosis | Line a: Intracerebral hemorrhage (days)<br>Line b: Atherosclerotic heart disease (years) | | 06 (431.0): Cardiovascular aneurysm (stroke) |
| 73: Cancer of skin | Line a: Metastatic squamous cell carcinoma | Squamous cell carcinoma does not necessarily originate from skin (eg, lung squamous cell carcinoma) | 99 (199.0): Malignant neoplasm without specification of site, disseminated |
| 54: Cancer of rectum | Line a: Disseminated intravascular coagulopathy<br>Line b: Colon cancer with liver metastasis | | 53: Cancer of colon |

*(Table continues next page)*

[a] If the Audit Team's code were used, the grouping of diseases would have changed in the final analysis.

**Table 23 (*continued*).** Discrepancies in Codes Assigned to Causes of Death on Death Certificates Used by the ACS Study

| Code in Analytic.files | Causes of Death on Death Certificate | Comments | Code by Audit Team's Nosologist |
|---|---|---|---|
| 410.0: Acute mycocardial infarction | Line a: Cardiopulmonary arrest<br>Line b: Acute myocardial infarction<br>Line c: Atherosclerotic heart disease<br>Line d: Acute myelogenous leukemia | | 36 (205.0): Acute myelogenous leukemia (leukemia)[a] |
| 53: Colon cancer | Line a: Adenocarcinoma, abdomen, generalized | Adenocarcinoma in abdomen of woman is not necessarily colon cancer, could also be endometrial (uterus) or other parts of digestive tract | 59 (159): Malignant neoplasm within digestive organs and peritoneum |
| 05: Heart disease | "Deferred", then in different writing, the notation "4292"; "Pending" was written in the block for "Suicide, homicide, undetermined or pending investigation" | This would be the correct group for 429.2, cardiovascular disease, unspecified | Could not code, because a cause of death had not been determined |
| 01: Ischemic heart disease | Line a: Cardiorespiratory arrest<br>Line b: Arteriosclerotic heart disease<br>Line c: Cardiovascular aneurysm | | 06: Cardiovascular aneurysm (stroke) |
| 03: Hypertension | Line a: Congestive heart failure<br>Line b: ACVD | | 05: Other forms of heart disease, includes congestive heart failure |
| 20: Cirrhosis of liver | Line a: Sepsis<br>Line b: Intestinal infarction | Part II (other significant conditions) noted alcoholic cirrhosis, but this section is not coded as the underlying cause of death | 22 (557.0): Vascular insufficiency of intestine |

[a] If the Audit Team's code were used, the grouping of diseases would have changed in the final analysis.

was not possible to audit instrument operating logs, filter weights, or other raw data records.

### VALIDATION OF THE ORIGINAL ACS STUDY ANALYSES

The Reanalysis Team completed the validation using the SAS datasets provided by the Original Investigators. We used the same variables, the same criteria, and the same methods to replicate the results reported by Pope and colleagues (1995).

We estimated the mortality risk ratios with multiple regression analyses using the Cox proportional-hazards regression model (Cox 1972) as implemented in the SAS program. We computed mortality risk ratios (and their associated 95% CIs) due to sulfate and fine particle air pollution for lung cancer, cardiopulmonary disease, and all-cause mortality. As in the original analyses, we controlled for smoking, education, BMI, and other risk factors. We stratified all analyses by 5-year age categories, gender, and race (white, black, and other) and calculated separate baseline hazards for each age-sex-race stratum.

The complete results of the reanalysis are included in two appendices, which are available from the Health Effects Institute upon request: Appendix G. Computer Programs Used in the Replication of the American Cancer Society Study, and Appendix H. Replication of the Original Analysis of the American Cancer Society Study (Based on the Subcohort Used by the Original Investigators).

**Validation of the Cohort Selection Process**

The CPS-II cohort included 1,185,102 participants. Because only a subset of that cohort was used in the ACS Study, the Reanalysis Team first replicated the selection process. We selected all participants who lived within each MA for which data on sulfate or fine particle pollutants were available. To do this, we used a program that mapped the participants' ZIP codes onto MAs (see Part II for a further discussion of these methods). This procedure resulted in two population subcohorts, those used for the sulfate analyses (referred to as the sulfate cohort) and those used for the fine particle analyses (referred to as the fine particle cohort). Next, we excluded those participants for whom relevant information was missing. Using these two procedures, the Reanlysis Team selected 559,049 individuals for the sulfate cohort and 298,817 individuals for the fine particle cohort. Because a number of the MAs had pollution data regarding both fine particles and sulfate, some participants were members of both cohorts.

We found a different number of subjects than had been reported by the Original Investigators: 552,138 individuals in the sulfate cohort and 295,223 individuals in the fine particles cohort. Thus, the Reanalysis Team assigned 6,911 more subjects to the sulfate cohort and 3,594 more individuals to the fine particle cohort. The Original Investigators confirmed that this discrepancy was due to a typographic error in coding the formula used to determine the number of years that female former-smokers had been free of smoking. Consequently, the original SAS program had assigned a "missing" value to this variable and mistakenly excluded these individuals (7,706 female former-smokers in total).

When we began the reanalysis, the Original Investigators pointed out two other oversights in the original analyses. First, whereas the original publication had reported that deaths had been determined until December 31, 1989, only women who died before September 1, 1988, were included, thus excluding 5,421 female deaths. Second, they had intended that deaths from asthma would be categorized with deaths from cardiopulmonary disease. Instead, a computing error included these subjects in the all-cause mortality group. Because of this error, 83 asthma deaths (in men and women) had been coded incorrectly.

**Results of the Reanalysis**

For the first part of the validation analysis, we used the same cohort that the Original Investigators had used. For the second part, we included the 7,706 female former-smokers and the 5,421 female deaths that had been inadvertently left out of the original analyses. We also treated the 83 asthma deaths as cardiopulmonary deaths in this analysis.

***Characteristics of Subjects in the ACS Analytic Cohort and Air Pollution Levels*** The Reanalysis Team assessed the following characteristics of the study population and the air pollution indices: number of MAs for each pollutant index, number of subjects, number of deaths, mean age at enrollment, sex, race, a profile of subjects' smoking experiences (cigarettes/day, number of years smoked, pipe/cigar smoker, and passive exposure to smoke), occupational exposure, education level, BMI, alcohol use, and exposure to air pollutants.

To compare the Original Investigators' results with those of the Reanalysis Team, Table 24 provides summary profiles of the original analytic cohort derived from CPS-II and the two indices of exposure to particulate air pollution: mean concentrations of sulfate particles for 1980 in the participants' areas of residence (derived from the US EPA's AIRS database) and median fine particle concentrations for 1979 through 1983 (calculated from the EPA's dichotomous sampler network). (The original results were presented in Table 1 of the AJRCCM publication.)

Although we confirmed the mean concentration of sulfate particles to be 11.0 $\mu g/m^3$, we calculated the SD to be 3.3 $\mu g/m^3$ rather than 3.6 $\mu g/m^3$. We also found the SD for fine particles to be 4.4 $\mu g/m^3$, slightly lower than the Original Investigators' value of 5.1 $\mu g/m^3$.

In the second part of the validation, which included the 7,706 female former-smokers and the additional 5,421 female deaths, we calculated a total of 43,361 deaths in the revised sulfate cohort of 559,049 individuals and 23,093 deaths among 298,817 individuals in the revised fine particle cohort. The percentage of females increased from 56.0% to 56.6% in the sulfate cohort and from 55.9% to 56.4% in the fine particle cohort. The percentages of current-smokers decreased slightly in both cohorts, whereas the percentage of former-smokers increased slightly. We also noted some small differences in the duration and intensity of smoking among former-smokers. The percentage of individuals subject to occupational exposures decreased slightly in both cohorts.

**Table 24.** Summary Characteristics of Subjects in the ACS Study's Analytic Cohort and in the Reanalysis Cohort

| Characteristic | Original Analysis[a] | | Validation Reanalysis[b] | |
|---|---|---|---|---|
| | Analysis with Sulfate Particles | Analysis with Fine Particles | Analysis with Sulfate Particles | Analysis with Fine Particles |
| Number of metropolitan areas | 151 | 50 | 151 | 50 |
| Number of subjects | 552,138 | 295,223 | ***559,049*** | ***298,817*** |
| Number of deaths | 38,963 | 20,765 | ***43,361*** | ***23,093*** |
| Age at enrollment (mean) | 56.5 | 56.6 | ***56.6*** | 56.6 |
| Sex (% female) | 56.0 | 55.9 | ***56.6*** | ***56.4*** |
| Race (%) | | | | |
| White | 94.2 | 94.0 | 94.2 | 94.0 |
| Black | 4.1 | 4.1 | 4.1 | 4.1 |
| Other | 1.7 | 1.9 | 1.7 | 1.9 |
| Current cigarette smokers (%) | 22.0 | 21.6 | ***21.7*** | ***21.4*** |
| Cigarettes/day (mean) | 22.0 | 22.1 | 22.0 | 22.1 |
| Years smoked (mean) | 33.5 | 33.5 | 33.5 | 33.5 |
| Former cigarette smokers (%) | 29.1 | 29.4 | ***30.0*** | ***30.2*** |
| Cigarettes/day (mean) | 22.0 | 22.0 | ***21.5*** | ***21.6*** |
| Years smoked (mean) | 22.3 | 22.2 | ***22.2*** | ***22.0*** |
| Pipe/cigar smokers only (%) | 4.1 | 3.9 | ***4.0*** | 3.9 |
| Passive smoke (mean hours/day) | 3.2 | 3.2 | 3.2 | 3.2 |
| Occupational exposure (%) | 20.0 | 19.5 | ***19.8*** | ***19.4*** |
| Less than high school education (%) | 12.3 | 11.3 | 12.3 | 11.3 |
| Body mass index (mean) | 25.1 | 25.0 | 25.1 | 25 |
| Alcohol (mean drinks/day) | 1.0 | 1.0 | 1.0 | 1 |
| Sulfate particles ($\mu g/m^3$) | | | | |
| Mean | 11.0 | | 11.0 | |
| SD | 3.6 | | ***3.3*** | |
| Range | 3.6–23.5 | | 3.6–23.5 | |
| Fine particles ($\mu g/m^3$) | | | | |
| Average median | | 18.2 | | 18.2 |
| SD | | 5.1 | | ***4.4*** |
| Range | | 9.0–33.5 | | 9.0–***33.4*** |

[a] Original results from Pope et al 1995; corresponds to Table 1 in the original publication (reprinted with permission from the *American Journal of Respiratory and Critical Care Medicine,* the Official Journal of the American Thoracic Society; Copyright © 1995 American Lung Association).

[b] Reanalysis results based on revised ACS cohort. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

### *Adjusted Mortality Risk Ratios by Cause of Death for Cigarette Smoking and for a Difference in Pollution*

Mortality risk ratios were calculated by replacing the variable representing the city (MA) in the statistical model with a continuous, linear variable representing either the mean of ambient sulfate or the median of fine particles. In this way, an exposure-response pattern was estimated according to level of pollution. Following the Original Investigators, we expressed the mortality risk ratios for an increase in particles across their entire ranges (Table 24). For sulfate particles, this factor was 19.9 $\mu g/m^3$ and for fine particles it was 24.5 $\mu g/m^3$.

The relative risk of mortality among current-smokers was derived by multiplying the relative risks associated with a series of smoking variables. These variables included indicators for current smoking status, daily consumption of cigarettes, and number of pack-years. In practice, this summary measure of risk was calculated by taking the exponential of the sum of the logarithm of the individual risks associated with these variables. The risk of mortality calculated in this manner assumed that, on average, a current-smoker consumed 20 cigarettes a day and had 25 pack-years at enrollment compared with a never-smoker.

**Table 25a.** Adjusted Mortality Risk Ratios by Cause of Death for Cigarette Smoking and for a Difference in Pollution: Original Result of the ACS Study[a]

| Cause of Death | Current-Smoker[b] | Sulfate[c] (19.9 μg/m$^3$) | Fine Particles[c] (24.5 μg/m$^3$) |
|---|---|---|---|
| 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 disease | 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) |

[a] From Pope et al 1995; corresponds to Table 2 in the original publication (reprinted with permission from the *American Journal of Respiratory and Critical Care Medicine,* the Official Journal of the American Thoracic Society; Copyright © 1995 American Lung Association). The difference in pollution equals the most-polluted areas compared with the least-polluted areas using either the sulfate or fine particle concentration as the measure of combustion-source air pollution. Values are risk ratios (95% CIs), which have been adjusted for age, sex, race, exposure to passive cigarette smoke, body mass index, drinks per day of alcohol, education, and occupational exposure.

[b] 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 years of smoking 20 cigarettes per day compared with a never-smoker.

[c] Risk ratios have also been adjusted for cigarette smoking.

**Table 25b.** Adjusted Mortality Risk Ratios by Cause of Death for Cigarette Smoking and for a Difference in Pollution: Renalysis Results for the ACS Study Using the Same Analytic Cohort[a]

| Cause of Death | Current-Smoker[b] | Sulfate[c] (19.9 μg/m$^3$) | Fine Particles[c] (24.5 μg/m$^3$) |
|---|---|---|---|
| All | 2.07 ***(1.98–2.16)*** | 1.15 (1.09–1.22) | 1.17 (1.09–1.26) |
| Lung cancer | 9.73 ***(8.31–11.39)*** | 1.36 (1.11–1.66) | 1.03 (0.80–1.33) |
| Cardiopulmonary disease | 2.28 ***(2.14–2.43)*** | 1.26 (1.16–1.37) | 1.31 (1.17–1.46) |
| All other | 1.54 ***(1.44–1.64)*** | 1.01 ***(0.93***–1.11**)** | 1.07 ***(0.95–1.21)*** |

[a] The difference in pollution equals the most-polluted areas compared with the least-polluted areas using either the sulfate or fine particle concentration as the measure of combustion-source air pollution. Values are risk ratios (95% CIs), which have been adjusted for age, sex, race, exposure to passive cigarette smoke, body mass index, drinks per day of alcohol, aducation, and occupational exposure. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

[b] 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 years of smoking 20 cigarettes per day compared with a never-smoker.

[c] Risk ratios have also been adjusted for cigarette smoking.

**Table 25c.** Adjusted Mortality Risk Ratios by Cause of Death for Cigarette Smoking and for a Difference in Pollution: Reanalysis Results for the ACS Study Based on the Revised ACS Cohort[a]

| Cause of Death | Current-Smoker[b] | Sulfate[c] (19.9 μg/m$^3$) | Fine Particles[c] (24.5 μg/m$^3$) |
|---|---|---|---|
| All | ***2.06*** **(*1.97–2.14*)** | ***1.16*** **(*1.10–1.23*)** | ***1.18*** **(*1.10–1.27*)** |
| Lung cancer | ***10.13*** **(*8.73–11.76*)** | 1.36 **(*1.13–1.65*)** | ***1.02*** **(**0.80–***1.30*)** |
| Cardiopulmonary disease | ***2.31*** **(*2.17–2.46*)** | ***1.28*** **(*1.19–1.39*)** | ***1.32*** **(*1.19***–1.46**)** |
| All other | ***1.50*** **(*1.41–1.60*)** | ***1.02*** **(*0.93***–1.11**)** | ***1.09*** **(*0.98–1.22*)** |

[a] The difference in pollution equals the most-polluted areas compared with the least-polluted areas using either the sulfate or fine particle concentration as the measure of combustion-source air pollution. Values are risk ratios (95% CIs), which have been adjusted for age, sex, race, exposure to passive cigarette smoke, body mass index, drinks per day of alcohol, aducation, and occupational exposure. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

[b] 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 years of smoking 20 cigarettes per day compared with a never-smoker.

[c] Risk ratios have also been adjusted for cigarette smoking.

Tables 25a, 25b, and 25c present adjusted mortality risk ratios (and 95% CIs) by cause of death for current-smokers and for an increase of 19.9 $\mu g/m^3$ sulfate or an increase of 24.5 $\mu g/m^3$ fine particles (Table 25a gives original results as they were presented in Table 2 of the original publication; Table 25b shows the Reanalysis Team's results using the same cohort; and Table 25c shows results using the revised cohort). The mortality risk ratios were adjusted for age, sex, race, cigarette smoking, passive exposure to cigarette smoke, BMI, drinks per day of alcohol, education, and occupational exposure.

The Original Investigators used a conservative method of calculating CIs on the mortality risk ratios for current-smokers. (For a complete description of the different formulas to calculate CIs used by the Original Investigators and by the Reanalysis Team, see the Six Cities Study section Adjusted Mortality Rate Ratios for Current-Smokers, Former-Smokers, and for the Most-Polluted Versus the Least-Polluted City by Cause of Death.) Using the method preferred by the Reanalysis Team, the CIs for current-smokers were somewhat narrower (see Table 25c) than those calculated by the Original Investigators. For example, the original 95% CI of 5.96–15.9 for lung cancer mortality among current-smokers decreased in width to 95% CI: 8.31–11.4.

When we included additional data in the second part of the validation analysis, the mortality risk ratios for both sulfate and fine particle exposure tended to increase. For example, the mortality risk ratio for deaths from cardiopulmonary disease associated with sulfate exposure increased from 1.26 (95% CI: 1.16–1.37) to 1.28 (95% CI: 1.19–1.39).

***Adjusted Mortality Risk Ratios for the Most-Polluted Areas Compared with the Least-Polluted Areas for Deaths from All Causes, Lung Cancer, and Cardiopulmonary Disease by Gender and Smoking Status*** Tables 26 and 27 summarize the adjusted mortality risk ratios by gender and smoking status for an increase in particles across their ranges for deaths due to all causes, lung cancer, and cardiopulmonary disease. The mortality risk ratios were adjusted for age, sex, race, cigarette smoking, passive exposure to cigarette smoke, BMI, drinks per day of alcohol, education, and occupational exposures. (Tables 26a and 27a give original results as they were presented in Table 3 of the AJRCCM publication; Tables 26b and 27b show the Reanalysis Team's results using the same cohort; and Tables 26c and 27c show the Reanalysis Team's results using the revised cohort.)

Although the first part of the validation analysis produced only trivial discrepancies between the Reanalysis Team's results and those of the Original Investigators (Tables 26b and 27b), including additional data in the second part of the validation analyses again tended to increase the estimates of the mortality risk ratios. For example, the mortality risk ratios for female ever-smokers increased in three analyses: (1) for all causes of death associated with sulfate exposure (Tables 26a and 26c), it increased from 1.14 (95% CI: 0.97–1.33) to 1.18 (95% CI: 1.04–1.35); (2) for cardiopulmonary deaths associated with sulfate exposure it increased from 1.30 (95% CI: 1.01–1.66) to 1.44 (95% CI: 1.17–1.78); and (3) for cardiopulmonary deaths associated with fine particle exposure (Tables 27a and 27c), it increased from 1.27 (95% CI: 0.92–1.74) to 1.32 (95% CI: 1.01–1.72).

**Table 26a.** Adjusted Mortality Risk Ratios for the Most-Polluted Areas Compared with the Least-Polluted Areas for Deaths from All Causes, Lung Cancer, and Cardiopulmonary Disease by Gender and Smoking Status for Sulfate (19.9 $\mu g/m^3$): Original Results of the ACS Study[a]

| Study Group | All Causes | Lung Cancer | Cardiopulmonary Disease |
|---|---|---|---|
| All combined | 1.15 (1.09–1.22) | 1.36 (1.11–1.66) | 1.26 (1.16–1.37) |
| Women | 1.18 (1.06–1.30) | 1.17 (0.80–1.72) | 1.39 (1.20–1.61) |
| Men | 1.14 (1.06–1.23) | 1.43 (1.13–1.81) | 1.20 (1.08–1.33) |
| Never-smokers | 1.18 (1.06–1.30) | 1.51 (0.73–3.11) | 1.36 (1.19–1.58) |
| Women | 1.20 (1.06–1.36) | 1.61 (0.66–3.92) | 1.44 (1.20–1.74) |
| Men | 1.14 (0.97–1.34) | 1.36 (0.40–4.66) | 1.28 (1.03–1.58) |
| Ever-smokers | 1.14 (1.06–1.23) | 1.35 (1.10–1.66) | 1.20 (1.08–1.33) |
| Women | 1.14 (0.97–1.33) | 1.10 (0.72–1.68) | 1.30 (1.01–1.66) |
| Men | 1.14 (1.05–1.24) | 1.44 (1.14–1.83) | 1.17 (1.05–1.32) |

[a] From Pope et al 1995; corresponds to the left half of Table 3 in the original publication (reprinted with permission from the *American Journal of Respiratory and Critical Care Medicine,* the Official Journal of the American Thoracic Society; Copyright © 1995 American Lung Association). Values are risk ratios (95% CIs), which 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 26b.** Adjusted Mortality Risk Ratios for the Most-Polluted Areas Compared with the Least-Polluted Areas for Deaths from All Causes, Lung Cancer, and Cardiopulmonary Disease by Gender and Smoking Status for Sulfate (19.9 μg/m$^3$): Renalysis Results for the ACS Study Using the Same Analytic Cohort[a]

| Study Group | All Causes | Lung Cancer | Cardiopulmonary Disease |
|---|---|---|---|
| All combined | 1.15 (1.09–1.22) | 1.36 (1.11–1.66) | 1.26 (1.16–1.37) |
| Women | 1.18 (***1.07***–1.30) | 1.17 (0.80–1.72) | 1.39 (1.20–***1.62***) |
| Men | 1.14 (***1.05–1.22***) | 1.43 (1.13–1.81) | 1.20 (1.08–1.33) |
| Never-smokers | 1.18 (***1.07***–1.30) | 1.51 (0.73–3.11) | ***1.38*** (***1.20***–1.58) |
| Women | 1.20 (1.06–***1.37***) | 1.61 (0.66–3.92) | ***1.45*** (***1.21–1.75***) |
| Men | 1.14 (0.97–1.34) | 1.36 (0.40–4.66) | 1.28 (1.03–1.58) |
| Ever-smokers | 1.14 (1.06–1.23) | 1.35 (1.10–1.66) | 1.20 (1.08–1.33) |
| Women | ***1.15*** (***0.98–1.34***) | 1.10 (0.72–1.68) | 1.30 (1.01–1.66) |
| Men | 1.14 (1.05–***1.23***) | 1.44 (***1.13***–1.83) | 1.17 (1.05–1.32) |

[a] Values are risk ratios (95% CIs). 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. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

**Table 26c.** Adjusted Mortality Risk Ratios for the Most-Polluted Areas Compared with the Least-Polluted Areas for Deaths from All Causes, Lung Cancer, and Cardiopulmonary Disease by Gender and Smoking Status for Sulfate (19.9 μg/m$^3$): Reanalysis Results for the ACS Study Based on the Revised ACS Cohort[a]

| Study Group | All Causes | Lung Cancer | Cardiopulmonary Disease |
|---|---|---|---|
| All combined | ***1.16*** (***1.10–1.23***) | 1.36 (***1.13–1.65***) | ***1.28*** (***1.19–1.40***) |
| Women | ***1.20*** (***1.10***–1.30) | ***1.22*** (***0.87–1.70***) | ***1.42*** (***1.25–1.62***) |
| Men | 1.14 (***1.05–1.22***) | 1.43 (1.13–1.81) | 1.20 (1.08–***1.31***) |
| Never-smokers | ***1.19*** (***1.08***–1.30) | ***1.87*** (***0.95–3.69***) | ***1.37*** (***1.20–1.56***) |
| Women | ***1.21*** (***1.08***–1.36) | ***2.17*** (***0.96–4.88***) | ***1.42*** (1.20–***1.67***) |
| Men | 1.14 (0.97–1.34) | 1.36 (0.40–4.66) | 1.28 (1.03–1.58) |
| Ever-smokers | ***1.15*** (***1.07–1.24***) | ***1.33*** (***1.09–1.62***) | ***1.23*** (***1.12–1.34***) |
| Women | ***1.18*** (***1.04–1.35***) | ***1.09*** (***0.75–1.57***) | ***1.44*** (***1.17–1.78***) |
| Men | 1.14 (1.05–***1.23***) | 1.44 (***1.13***–1.83) | 1.17 (1.05–1.32) |

[a] Values are risk ratios (95% CIs) which 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. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

**Table 27a.** Adjusted Mortality Risk Ratios for the Most-Polluted Areas Compared with the Least-Polluted Areas for Deaths from All Causes, Lung Cancer, and Cardiopulmonary Disease by Gender and Smoking Status for Fine Particles (24.5 μg/m$^3$): Original Results of the ACS Study[a]

| Study Group | All Causes | Lung Cancer | Cardiopulmonary Disease |
|---|---|---|---|
| All combined | 1.17 (1.09–1.26) | 1.03 (0.80–1.33) | 1.31 (1.17–1.46) |
| Women | 1.16 (1.02–1.32) | 0.90 (0.56–1.44) | 1.45 (1.20–1.78) |
| Men | 1.18 (1.07–1.30) | 1.10 (0.81–1.47) | 1.24 (1.08–1.41) |
| Never-smokers | 1.22 (1.07–1.39) | 0.59 (0.23–1.52) | 1.43 (1.18–1.72) |
| Women | 1.21 (1.02–1.43) | 0.65 (0.21–2.06) | 1.57 (1.23–2.01) |
| Men | 1.24 (1.00–1.54) | 0.49 (0.09–2.66) | 1.24 (0.93–1.67) |
| Ever-smokers | 1.15 (1.05–1.26) | 1.07 (0.82–1.39) | 1.24 (1.08–1.42) |
| Women | 1.10 (0.90–1.33) | 0.95 (0.57–1.58) | 1.27 (0.92–1.74) |
| Men | 1.16 (1.05–1.29) | 1.12 (0.83–1.52) | 1.23 (1.06–1.43) |

[a] From Pope et al 1995; corresponds to the right half of Table 3 in the original publication (reprinted with permission from the *American Journal of Respiratory and Critical Care Medicine,* the Official Journal of the American Thoracic Society; Copyright © 1995 American Lung Association). Values are risk ratios (95% CIs), which 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.

The Original Investigators reported that lung cancer mortality had not been associated with combustion-source air pollution when fine particles (in 50 MAs) were used as the pollution index; however, they had found an association when sulfate (in 151 MAs) was used as the index. The Original Investigators had considered whether the difference in MAs might account for the different findings. To test this hypothesis, they had restricted their analyses to the 47 MAs for which both sulfate and fine particle data were available. Again, no association was found when fine particles were used as the pollution index. However, when sulfate was used as the index, the adjusted mortality risk ratio for lung cancer was 1.20 (95% CI: 1.08–1.34) and for cardiopulmonary disease it was 1.44 (95% CI: 1.11–1.86). Using the same dataset as the Original Investigators, the Reanalysis Team reproduced these results.

The Original Investigators had also reported that high, low, and mean temperatures were not correlated with either sulfate or fine particle pollution. However, they had found that sulfate particle levels were slightly lower in both relatively cold (normal mean temperatures lower than 50°F) and relatively hot (normal mean temperatures higher than 60°F) MAs. When these weather indicator variables were included in the risk models, the adjusted mortality risk

**Table 27b.** Adjusted Mortality Risk Ratios for the Most-Polluted Areas Compared with the Least-Polluted Areas for Deaths from All Causes, Lung Cancer, and Cardiopulmonary Disease by Gender and Smoking Status for Fine Particles (24.5 μg/m$^3$): Reanalysis Results for the ACS Study Using the Same Analytic Cohort[a]

| Study Group | All Causes | Lung Cancer | Cardiopulmonary Disease |
|---|---|---|---|
| All combined | 1.17 (1.09–1.26) | 1.03 (0.80–1.33) | 1.31 (1.17–1.46) |
| Women | 1.16 (1.02–1.32) | 0.90 (0.56–1.44) | ***1.46*** (1.20–***1.77***) |
| Men | 1.18 (1.07–***1.29***) | 1.10 (0.81–***1.48***) | 1.24 (1.08–1.41) |
| Never-smokers | 1.22 (1.07–1.39) | 0.59 (0.23–1.52) | 1.43 (1.18–1.72) |
| Women | 1.21 (1.02–***1.44***) | 0.65 (0.21–2.06) | ***1.58*** (1.23–***2.02***) |
| Men | 1.24 (1.00–1.54) | 0.49 (0.09–2.66) | 1.24 (0.93–***1.66***) |
| Ever-smokers | 1.15 (1.05–1.26) | 1.07 (0.82–1.39) | 1.24 (1.08–1.42) |
| Women | 1.10 (0.90–1.33) | 0.95 (0.57–1.58) | 1.27 (0.92–1.74) |
| Men | 1.16 (1.05–1.29) | 1.12 (0.83–1.52) | 1.23 (1.06–1.43 ) |

[a] Values are risk ratios (95% CIs), which 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. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

**Table 27c.** Adjusted Mortality Risk Ratios for the Most-Polluted Areas Compared with the Least-Polluted Areas for Deaths from All Causes, Lung Cancer, and Cardiopulmonary Disease by Gender and Smoking Status for Fine Particles (24.5 μg/m$^3$): Reanalysis Results for the ACS Study Based on the Revised ACS Cohort[a]

| Study Group | All Causes | Lung Cancer | Cardiopulmonary Disease |
|---|---|---|---|
| All combined | ***1.18 (1.10–1.27)*** | ***1.02*** (0.80–***1.30***) | ***1.32 (1.19***–1.46) |
| Women | ***1.19 (1.06–1.33)*** | ***0.89 (0.59–1.34)*** | 1.45 (***1.22–1.71***) |
| Men | 1.18 (1.07–***1.29***) | 1.10 (0.81–***1.48***) | 1.24 (1.08–1.41) |
| Never-smokers | ***1.24 (1.10–1.40)*** | ***0.73 (0.30–1.80)*** | 1.43 (***1.20–1.70***) |
| Women | ***1.25 (1.07–1.45)*** | ***0.87 (0.30–2.52)*** | ***1.54 (1.24–1.92)*** |
| Men | 1.24 (1.00–1.54) | 0.49 (0.09–2.66) | 1.24 (0.93–***1.66)*** |
| Ever-smokers | 1.15 (1.05–1.26) | ***1.04 (0.81–1.34)*** | ***1.25 (1.10***–1.42) |
| Women | ***1.12 (0.95–1.32)*** | ***0.88 (0.56–1.39)*** | ***1.32 (1.01***–***1.72***) |
| Men | 1.16 (1.05–1.29) | 1.12 (0.83–1.52) | 1.23 (1.06–1.43) |

[a] Values are risk ratios (95% CIs), which 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. Values in bold italics show Reanalysis Team results that differ from those reported by the Original Investigators.

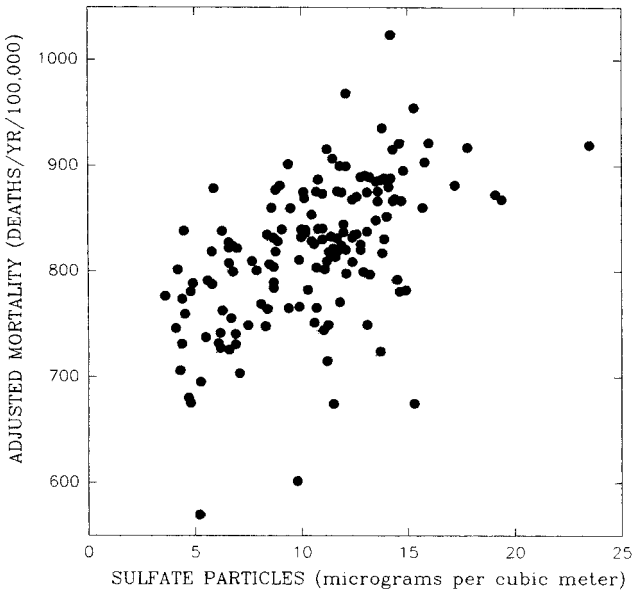



**Figure 12. Age-, sex-, and race-adjusted population-based mortality rates for 1980 plotted against mean sulfate air pollution levels for 1980.** Data are from metropolitan areas that correspond approximately to areas used in the prospective cohort analysis. Original results from Pope and colleagues 1995 (Figure 1; reprinted with permission from the *American Journal of Respiratory and Critical Care Medicine*, the Official Journal of the American Thoracic Society; Copyright © 1995 American Lung Association).

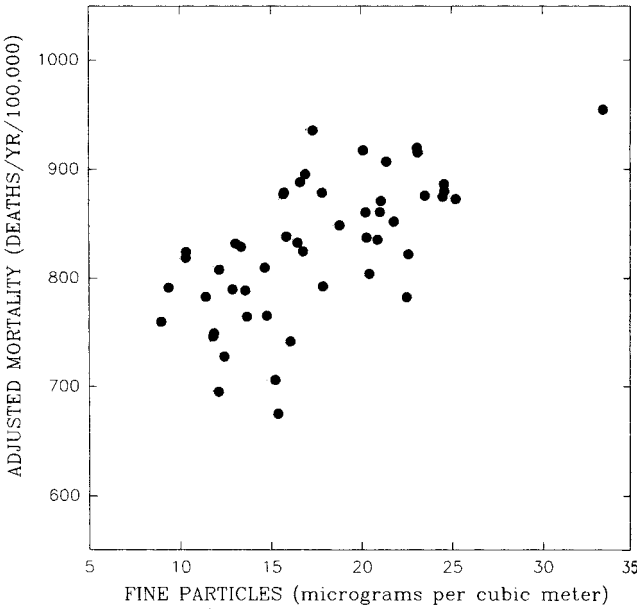



**Figure 13. Age-, sex-, and race-adjusted population-based mortality rates for 1980 plotted against median** [*not* mean, *as in the original publication*] **fine particulate air pollution levels for 1979 to 1983.** Data are from metropolitan areas that correspond approximately to areas used in the prospective cohort analysis. Original results from Pope and colleagues 1995 (Figure 2; reprinted with permission from the *American Journal of Respiratory and Critical Care Medicine*, the Official Journal of the American Thoracic Society; Copyright © 1995 American Lung Association).

ratios for deaths from lung cancer and cardiopulmonary disease were 1.36 (95% CI: 1.11–1.66) and 1.23 (95% CI: 1.13–1.34), respectively, when sulfate was used as the pollution index, and 1.05 (95% CI: 0.82–1.36) and 1.26 (95% CI: 1.13–1.40), respectively, when fine particles were used as the index. Aside from a minor difference in the risk ratio for cardiopulmonary mortality of 1.24 (95% CI: 1.14–1.35), the Reanalysis Team reproduced these results using the same dataset as the Original Investigators.

When asthma deaths were included in cardiopulmonary deaths, the risk ratio from sulfate changed marginally from 1.26 to 1.25 (95% CI: 1.15–1.36) and that from fine particles changed from 1.31 to 1.30 (95% CI: 1.16–1.44).

We also replicated their figures (Figures 1 and 2 in the AJRCCM publication) using population-based mortality rates for 1980 (adjusted for age, sex, and race) that were provided by the Original Investigators and found no discrepancies (Figures 12 and 13).

## SUMMARY AND CONCLUSIONS

In Part I of the reanalysis of the Six Cities and ACS studies, we used two methods to ensure the validity of the original studies' results: a data quality audit and a series of validation analyses. As might be expected in studies as large and broad as these, we found some small discrepancies during the reanalysis. These discrepencies do not alter in any substantive fashion the results of the original analyses; thus, the Reanalysis Team is satisfied that the objectives of this reanalysis have been satisfied and that the original results are indeed correct as published.

The validation analysis subsequently conducted on both studies using the same data and the same methods the Original Investigators had used resulted in nearly complete agreement with the original findings. Discrepancies in the Six Cities Study were minor.

- Some typographic errors were found in the summary table in the Six Cities Study as reported in the NEJM. However, because those values had not been used in subsequent calculations, they had no effect on the findings of the study.
- Most of the discrepancies noted by the Reanalysis Team pertained to the estimates of pollutant levels; some of these are likely due to subtle differences in the order of calculations performed or in the software used.
- The validation analysis of the key results from the Six Cities Study attained complete agreement with all of the point estimates of the various rate ratios calculated. The only discrepancy we found was a minor typographic error in reporting the number of pack-years smoked.
- The Reanalysis Team updated the Six Cities cohort to include the missing person-years of observation identified through the data quality audit. Adding 928 person-years of observation resulted in an increase of 14 deaths in the six cities. Using the same methods of analysis as had been applied to the original cohort led to mortality rate ratios associated with exposure to fine particulate matter that were higher than those reported. For example, the original relative risk of 1.26 for all-cause mortality increased to 1.28 after adjusting for early censoring of person-years. This adjustment increased the mortality rate ratio for cardiopulmonary disease from 1.37 to 1.43.

While reconstructing the ACS database to match the information used in the original analysis, ACS staff and the Reanalysis Team noted three errors in computer programming: asthma deaths had been excluded from the total cardiopulmonary deaths, a group of female former-smokers had been excluded from the subcohort, and female deaths had been censored earlier than they should have been.

The Reanalysis Team reproduced the ACS results when we used the same data as those used to derive the findings reported in the AJRCCM. However, when we included the group of female former-smokers and the female deaths and asthma deaths that had been excluded, several differences became apparent.

- The mortality risk ratios due to both sulfate and fine particle exposure increased slightly.
- The mortality risk ratios increased when we compared the most-polluted city with the least-polluted city.
- The mortality risk ratio due to sulfate exposure became significant for all causes of death for female ever-smokers.

One further discrepancy the Reanalysis Team noted in both studies was that the methods the Original Investigators used to calculate CIs for mortality risk estimates related to tobacco consumption were incorrect. These methods had not been used for mortality risk estimates for ambient air pollution in either of the two studies. The Reanalysis Team chose to use a direct method, which emphasized the dependence between the parameter estimates, to calculate CIs on risk estimates for the effect of tobacco consumption on mortality. The direct method noticeably narrowed the CIs for the mortality estimates for both studies.

**Table 28.** Errors in the Data Used in the Six Cities Study and the ACS Study Found by the Reanalysis Team

| Finding | Magnitude of Potential Impact | Effects on Validity | How Addressed in Part I[a] |
|---|---|---|---|
| Six Cities: Early censorship of time-on-study for some participants in some cities | Loss of approximately 1% of person-years, effect of which was greatest in Portage and Topeka; no early censorship in Watertown | Minor | Recalculated |
| ACS: Exclusion of a group of female former-smokers who met selection criteria | 7,706 Women excluded | Small increase in mortality risk ratios for sulfate and fine particles | Recalculated |
| ACS: Follow-up of women curtailed on 9/1/88 rather than the correct date of 12/31/89 | 5,421 Deaths among women excluded from analysis | Small increase in mortality risk ratios for sulfate and fine particles | Recalculated |
| ACS: Asthma deaths included in "other" category, rather than as cardiopulmonary deaths | 83 Asthma deaths excluded from cardiopulmonary category | Minor | Recalculated |
| ACS: Computer programming error resulted in two ICD-9 codes reflecting cardiopulmonary diseases not included in cardiopulmonary category | 71 Deaths added to "other" rather than cardiopulmonary category | Minor | Recalculated |

[a] The Reanalysis Team recalculated relative risks on the basis of including the data that had been excluded by the Original Investigators.

Overall, the Audit Team found that both studies had been well conducted and well documented. The minor errors that we found in the data would not have materially impacted the data as published or the Original Investigators' conclusions. The variables used in the original publications were valid. The error rate we calculated for each variable in each study was less than 5% and not critical from an epidemiologic standpoint with regard to changing the estimates of relative risk. The audits of both studies uncovered some systematic errors (Table 28). However, the Reanalysis Team was able to reconstitute the cohorts using the information from the data audits and carry out detailed reanalyses that showed minor differences from original findings.

The Reanalysis Team analyzed most of the data twice using different statistical packages (S-PLUS and SAS) and obtained the same results. This indicates that the numerical results were not dependent upon the computer programs that were used to fit the Cox proportional-hazards regression models in the Original Investigations.

Although Part I of the reanalysis of these two important cohort mortality studies effectively confirms the numerical results reported by the Original Investigators, a final assessment of these two studies was conducted in Part II. Whereas Part I of the reanalysis was based on the same data and methods used by the Original Investigators, in Part II of the reanalysis we tested the robustness of these validated findings to different methods of analysis. We also included additional data not considered by the Original Investigators.

## REFERENCES

Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Lawrence Beeson W, Yang JX. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159:373–382.

Bates D, Hayes CG, Knowles M. 1985. Geographic variation in declining ischemic heart disease mortality in the United States, 1968–1978. Am J Epidemiol 122:657–672.

Briggs SLK, Thurston GD, Dumyahn TS, Evans JS, Spengler JD, Turner WA. 1982. The effectiveness of dichotomous sampler quality assurance procedures. APCA Annual Meeting, New Orleans LA.

Burnett RT, Jessiman B, Stieb D, Krewski D. 1997. Health effects of ambient particulate matter: A Canadian perspective. In: Health Effects of Particulate Matter in Ambient Air. Prague, Czech Republic. Ed Jaroslav J Vostal. April 23–25, 1997.

Cochran WG. 1977. Sampling Techniques, 3rd ed. John Wiley & Sons, New York NY.

Courtney WJ, Shaw RW, Dzubay TG. 1982. Precision and accuracy of a beta gauge for aerosol mass determinations. Environ Sci Technol 16:236–239.

Coutant RW. 1977. Effect of environmental variables on collection of atmospheric sulfate. Environ Sci Technol 11:873–878.

Cox DR. 1972. Regression models and life tables (with discussion). J R Stat Soc B34:187–200.

Cox DR, Oakes D. 1983. Analysis of Survival Data. Chapman and Hall, London, England.

Crosby PB. 1979. Quality is Free. McGraw-Hill, New York NY.

Dockery D. 1996. The air we breathe: 22 years of the Six Cities Study [Harvard School of Public Health October 4, 1996. Around the School, Web site]. Available at: http://www.hsph.harvard.edu/around/oct96/oct4/sixcity.html. Accessed March 22, 2000.

Dockery DW, Schwartz J, Spengler J. 1992. Air pollution and daily mortality: Associations with particulates and acid aerosols. Environ Res 59:362–373.

Dockery DW. 1993. Percentile curves for evaluations of repeated measures of lung function. Occup Med 8:323–338.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Dzubay TG, Barbour RK. 1983. A method to improve the adhesion of aerosol particles on Teflon filters. J Air Pollut Control Assoc 33:692–695.

Eaton WC, Arey FK, McKee JL. 1982. Systems Audit 1982: Harvard School of Public Health Six City Study. Report RTI/2218/94. Research Triangle Institute, Research Triangle Park NC.

Ferris BG, Speizer FE, Spengler JD, Dockery D, Bishop YMN, Wolfson M, Humber C. 1979. Effects of sulfur oxides and respirable particles on human health: Methodology and demography of populations in study. Am Rev Respir Dis 120:767–779.

Gamble JF. 1998. $PM_{2.5}$ and mortality in long-term prospective cohort studies: Cause-effect or statistical associations? Environ Health Perspect 106:535–549.

Harvard School of Public Health Air Quality Group. 1982. Quality Assurance Manual for Air Quality Assessment (Internal Document). Harvard School of Public Health, Boston MA.

Health Effects Institute. 1995. Particulate Air Pollution and Daily Mortality: Replication and Validation of Selected Studies, The Phase I.A Report of the Particle Epidemiology Evaluation Project. Health Effects Institute, Cambridge MA.

Health Effects Institute. 1997. Particulate Air Pollution and Daily Mortality: Analyses of the Effects of Weather and Multiple Air Pollutants, The Phase I.B Report of the Particle Epidemiology Evaluation Project. Health Effects Institute, Cambridge MA.

Hoover BK, Baldwin JK. 1984. Meeting the quality assurance challenges of the 1980's: Team auditing by toxicologists and QA professionals. J Am Coll Toxicol 3:129–139.

Hoover BK, Baldwin JK, Uelner AF, Whitmire CE, Davies CL, Bristol DW. 1986. Managing Conduct and Data Quality of Toxicology Studies. Princeton Scientific Publishers, Princeton NJ.

Hoover BK, Foliart DE, Calisti LJ, White WH. 1999. Quality assurance audits of the Harvard Six Cities and ACS Studies. The Fifteenth Health Effects Institute Annual Conference, May 9–12, La Jolla CA. Health Effects Institute, Cambridge MA.

Koenig JQ, Larson TV, Hanley QS, Rebolledo V, Dumler K. 1993. Pulmonary function changes in children associated with fine particulate matter. Environ Res 63:26–38.

Koenig JQ, Larson TV, Norris G, Claiborn C, Finn D, Zweidinger R, Lewtas J, Schwartz J. 1998. A fine particulate composition variability and exacerbation of asthma [Particulate Matter Research Activities Web site]. January 24, 2000. Available at: http://www.pmra.org/pmra/PM.nsf. Accessed March 22, 2000.

Koutrakis P, Wolfson JM, Spengler JD. 1988. An improved method for measuring aerosol strong acidity: Results from a nine-month study in St. Louis, Missouri, and Kingston, Tennessee. Atmos Environ 22:157–162.

Lave LB, Seskin EP. 1970. Air pollution and human health. Science 169:723–733.

Lee ET. 1992. Statistical Methods for Survival Data Analysis, 2nd ed. John Wiley & Sons, New York NY.

Lipfert FW. 1993. Community Air Pollution Mortality: Analysis of 1980 Data from US Metropolitan Areas, I, Particulate Air Pollution. BNL 48446-R. US Department of Energy, Brookhaven National Laboratory, Upton NY.

Lipfert FW, Malone RG, Daum ML, Mendell NR, Yang CC. 1988. A Statistical Study of the Macroepidemiology of Air Pollution and Total Mortality. BNL 52122. US Department of Energy, Brookhaven National Laboratory, Upton NY.

Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151:669–674.

Schilling EG, Sommers DJ. 1988. Acceptance sampling. In: Juran's Quality Control Handbook, 4th ed (Juran JM, Gryna FM, eds). McGraw-Hill, New York NY.

Schwartz J. 1994. What are people dying of on high air pollution days? Environ Res 64:26–35.

Schwartz J, Dockery DW, Neas LM. 1996. Is daily mortality associated specifically with fine particles? J Air Waste Manage Assoc 46:927–939.

Siconolfi RM. 1986. Statistical approaches to auditing. In: Managing Conduct and Data Quality of Toxicology Studies (Hoover BK et al, eds). Princeton Scientific Publishers, Princeton NJ.

Spengler JD, Briggs SLK, Özkaynak H. 1986. Relationships Between TSP Measurements and Size-Fractionated Particle Mass Measurements in Six Cities Participating in the Harvard Air Pollution Health Study (Report to OAQPS under EPA Cooperative Agreement CR-812667-01-0). US Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park NC.

Spengler JD, Thurston GD. 1983. Mass and elemental composition of fine and coarse particles in six US cities. J Air Pollut Control Assoc 33:1162–1171.

Spirtas R, Levin HJ. 1971. Patterns and trends in levels of suspended particulate matter. J Air Pollut Control Assoc 21:329–333.

Steelman RL. 1986. Industrial management view of quality assurance for Food and Drug Administration regulated products. In: Managing Conduct and Data Quality of Toxicology Studies (Hoover BK et al, eds). Princeton Scientific Publishers, Princeton NJ.

Venables WN, Ripley BD. 1997. Modern Applied Statistics with S-PLUS, 2nd ed. Springer-Varlag, New York NY

Wang Y, Krewski D, Bartlett S, Zielinski JM. 1994. The Effect of Record Linkage Errors on Statistical Inference in Cohort Mortality Studies. Technical Report 245. Laboratory for Research in Statistics and Probability, Carleton University, Ottawa, Ontario, Canada.

World Health Organization. 1975. *International Classification of Diseases, Ninth Revision*, Vol 1. World Health Organization, Geneva, Switzerland.

## APPENDIX A. Data Audit Standards, Goals, and Plan

The practice of team auditing, which follows published techniques (Hoover and Baldwin 1984), was selected for the Reanalysis Project due to the scope of work. It is a robust approach to auditing because it combines the resources and expertise of individuals with different qualifications so the final result is greater than any one individual with a single expertise could have accomplished working separately. Each team member was chosen for his or her expertise so the group was not limited to the employees of any one company. Preliminary results of the Reanalysis Project audit were presented at the HEI Annual Conference in La Jolla CA in May 1999 (Hoover et al 1999).

The Audit Team coordinator for the whole project was Ms Kristin Hoover. She has more than 25 years of experience in developing and managing audits of projects for organizations such as university research programs and commercial analytical chemistry laboratories on topics such as methods development, toxicology, and epidemiology. Her recent efforts have involved quality assurance monitoring and auditing for other HEI epidemiologic studies related to air pollution.

Donna Foliart, MD, MPH, has been a subcontracting consultant with Ms Hoover for previous HEI studies. Dr Foliart obtained her MD with honors from the University of California, San Francisco, in 1978, her MPH from University of California, Berkeley, in 1981, and is board certified in preventative medicine/occupational medicine (1984). She is currently with the Public Health Institute in Berkeley, where she is the principal investigator of a study of childhood leukemia.

Warren White, BSc (mathematics, California Institute of Technology), MS and PhD (mathematics, University of Wisconsin), is an expert in air pollution monitoring data. He has served in a variety of positions including OAS visiting professor at the Institute of Pure and Applied Mathematics,

National Research Council, Rio de Janeiro, Brazil; visiting professor at Brookhaven National Laboratory; and is currently at Washington University, St Louis MO. Dr White's contribution to air pollution research is well known.

Ms Linda Calisti, BSc (University of Pittsburgh, 1971) has over 20 years of experience in various types of audits such as analytical chemistry, toxicology, and human clinical research.

## GOALS AND STANDARDS

The overall objective of this audit was to conduct an independent, rigorous, retrospective, and defensible assessment of the raw data from original source documents and electronic data files from these studies to support the efforts of the Reanalysis Team. In the book *Quality is Free*, Crosby (1979) defines "quality" as conformance to requirements or standards (discussed in Hoover et al 1986). For the purposes of this audit, the standards used are described below.

### Standards for the Retrospective Audits

Standards established by the Health Effects Institute for this project were summarized in the following internal project documents:

- The Health Effects Institute Epidemiology Reanalysis Project: Project Description (March 25, 1998);
- Statement of Specifications: Epidemiology Reanalysis Project Data Quality Audit; and
- Health Effects Institute Procedures for Quality Assurance and Quality Control (February 20, 1997).

The investigators on the Reanalysis Team described the following types of documents for the Audit Team to review so we could assess the internal standards the Original Investigators had established for their own studies.

***Protocols for Each Study*** The Audit Team found no formal study protocols for either study. Instead, we audited the data against printouts of the electronic files provided to the Reanalysis Team. In the original publications, we found information that would normally be contained in a study design protocol and we audited the studies according to the published information.

***Internal Standard Operating Procedures Used in the Study*** The Audit Team found no procedural rules for either study that were formally identified as Standard Operating Procedures. Therefore, we used whatever documentation existed for each study that explained the rules for data collection, manipulation, and inclusion or exclusion for analyses. For the Six Cities Study, we obtained four notebooks of coding rules that included discussions of coding problems and associated corrective actions. We found no explanatory documentation of coding for the ACS Study. Therefore, the Audit Team determined the applied coding conventions by inference.

***Existing Quality Assurance Audits*** The Audit Team examined both internal and external audits for the Six Cities Study, but none were available for the ACS Study. However, the remaining contact at the ACS made available some computer programming documentation; this person had identified several programming problems, which were discussed in the main report.

### General Audit Plan (Applicable to Both Studies)

A detailed quality assurance plan was prepared before the audit and submitted to HEI in March of 1999. The Audit Team followed this plan for both studies with some minor exceptions related to availability of documentation or time constraints that could not have been foreseen when the plan was developed. Ms Hoover acted as the principal contact with HEI and was responsible for leading this audit program. Teams were used for each onsite audit. The Audit Team identified the following types of information as applicable for a statistically relevant subset of data.

***Organization and Personnel*** We used discussions with study personnel and written records to determine how the study had been organized and who had been responsible for management of the data. In both studies, the analyses were restricted to selected subsets of the cohort. The Audit Team determined how the questionnaires, death certificates, and air pollution data had been filed and what resources would be available to assist in the retrieval of records. The Audit Team also determined what personnel were still available who had actually worked on each study or had the greatest knowledge of procedures.

***Data Collection*** For the Six Cities Study, the Audit Team evaluated the documentation of data collection and procedural methods. We audited the data against the established coding conventions and rules, and followed any changes in coding. We examined (1) documentation of how any discrepancies in coding had been resolved; (2) field restrictions to determine how they had been utilized; and (3) the circumstances and documents about "missing" data to determine that each instance had been treated consistently.

For the ACS Study, none of these items were available and we could not perform such a thorough audit.

***Computer Processing*** The Audit Team reviewed changes to computer files to determine that they had been implemented consistently and whether the requirements as detailed in the published report had been followed. We compared changes to hard copies against the computer files and vice versa. We examined criteria for data reduction to ensure that they had been followed consistently. When we found documentation of a discrepant data element, we also examined the subsequent correction to the electronic data files. We evaluated program conventions to determine whether they had been consistently and correctly used.

***Standard Operating Procedures*** Because no documents could be identified as formal Standard Operating Procedures, the Audit Team reviewed and followed other less formal procedural documents and conventions. Ancillary documentation was largely limited to the Six Cities Study.

***Conformance with Audit Standards*** The Audit Team worked in conjunction with the rest of the Reanalysis Team to identify variables for audit in the validation and sensitivity phases. We identified two random samples from the electronic data files from the investigators: 250 individuals from each study for auditing questionnaires and study population variables, and an additional 250 individuals from each study for auditing death certificates and vital status. We compared the most original form of data (ie, questionnaires, death certificates) to a printout of the study population variables for each random sample in each study to assure the accuracy of the information in the computer file and that source records supported the coding and entry of each variable. We compared the results of this checking procedure to the published information for each study.

***Original Cohort Identification and City Selection Criteria*** The Audit Team's original intention was to inspect any records that explained criteria for including and excluding cohort members. Methods for selecting subjects in the Six Cities Study had been described in detail by Ferris and colleagues (1979). Table 1 of that publication (page 768) presented the methods for selecting subjects in each city. Subjects had been selected at random on the basis of household voting lists, private census lists, partial blocks from street lists, or alphabetized names lists.

The Audit Team could not evaluate subject selection criteria for the ACS Study because all selection of study subjects had been made by ACS volunteers who had been instructed to find subjects whom they could follow over the next 7 years. Therefore, volunteers picked relatives, neighbors, and friends whom they believed would fit the criterion of long-term follow-up. No records of selection criteria from volunteers could be found for auditing. Although we could not confirm this by our audit, it is likely that these volunteers selected individuals in similar socioeconomic groups as themselves.

***Data Audit*** The Audit Team considered a statistically based audit to be the best approach. We adopted specific procedures from methods proposed originally by Siconolfi (1986). However, that publication did not provide sufficient details as to the statistical theory behind the proposed sampling approach. Rather than relying on published tables such as those provided by Siconolfi or Schilling and Sommers (1988), the Reanalysis Team performed sample-size calculations to be used by the Audit Team.

The purpose of these calculations was to determine the optimal size of the random sample that would ensure that the true error rate in the electronic data would fall within a certain acceptable limit. We audited data for all variables used in the original publications in both the verification and the sensitivity analysis stages. The goal of the sampling was to detect errors in each variable that would meaningfully impact the interpretation of the results of the regression analyses. On the basis of discussions with the Original Investigators, we learned that the data collection and quality control measures used in each study had not changed over time in any significant way. Therefore, the Audit Team concluded that stratifying the example by city or other variable was necessary.

The Reanalysis Team investigated several aspects of the sample size issue. First, we evaluated the probability of finding errors in the data when, in fact, errors do exist. For sample sizes that range from 10 to 250, Figure A.1 shows the probability (statistical power) of detecting at least one error in the sample as a function of the error rate in the study population. For a sample size of 250, the probability of detecting an error rate of 5% is close to 100%.

Second, the Reanalysis Team calculated the power of a sample of a given size to distinguish between an error rate of 5% or less and an error rate of greater than 5%. For sample sizes that range from 50 to 1,000, Figure A.2 shows the statistical power (on the ordinate) according to the true error rate in the sample (abscissa). This figure shows that the statistical power increases as the sample size increases, although sample sizes over 250 offer very little gain. We concluded from this that a sample size of about 250 should be adequate to distinguish between an error rate of 5% or less and an error rate of 10% or more. As indicated in Figure A.3, a sample size of 250 would also be able to distinguish

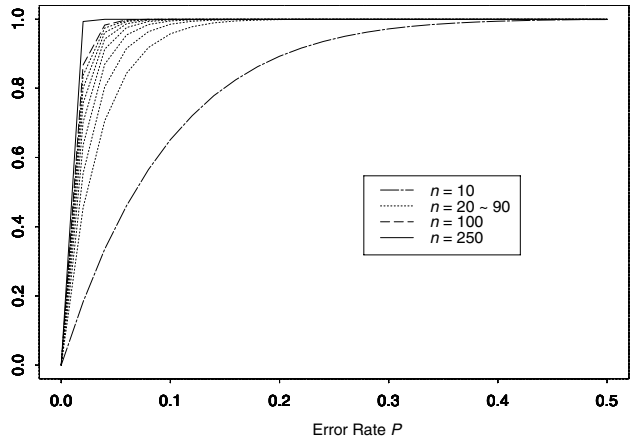



**Figure A.1. Probability (statistical power) of detecting at least one error in a sample of size *n* as a function of the error rate in the study population.**

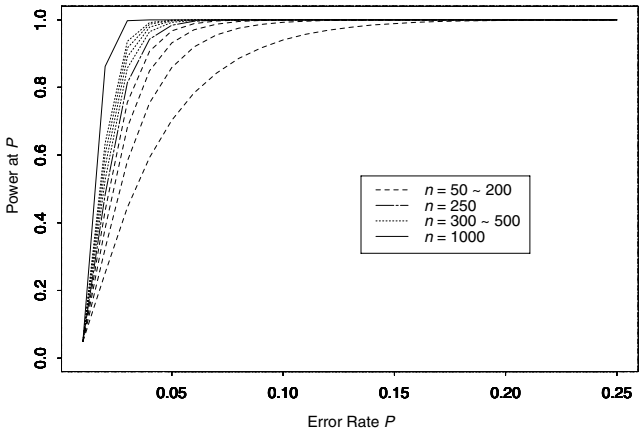



**Figure A.3. Statistical power of different sample sizes to reject the null hypothesis of the error rate in the data being less than 1%.**

between an error rate of 1% or less and error rates greater than 5% with high probability.

Third, the Reanalysis Team took a more classical approach to calculating sample size (Cochran 1977). We assumed five different levels of "statistical precision", defined as one half the CI (from 2% to 6%) at a level of statistical significance of 5%, and calculated what sample size would be necessary to achieve each of these levels of statistical precision. We considered error rates between 0% and 25%. We both included and excluded a term to correct for sampling from finite populations. Figure A.4 shows the results of these calculations. Sample sizes selected on the basis of a finite population were always larger, although very little difference is apparent for levels of statistical precision of 4% and higher.

Fourth, in addition to the above calculations, we also investigated the exact 95% CIs for sample sizes ranging from 200 to 500. The Reanalysis Team found that the CIs were very close for these sample sizes. For example, the 95% CIs for an error rate of 5% for sample sizes of 250 and 500 are 0.03–0.09% and 0.04–0.08%, respectively; for an error rate of 1%, the CIs are 0.00–0.04% and 0.00–0.03%, respectively. An important consideration in evaluating the significance of errors in the original variables is the impact of such errors on estimates of risk.

Results by Wang and colleagues (1994) for cohort mortality studies involving computerized record linkage suggest that the bias in risk estimates due to misascertainment of vital status may lead to biases in risk estimates proportional to the vital status error rate. Based on these results, the Reanalysis Team adopted a rule of thumb that error rates of less than 5% may not be of great epidemiologic importance.

In conclusion, these calculations show that a sample size of 250 was more than adequate for the purposes of this

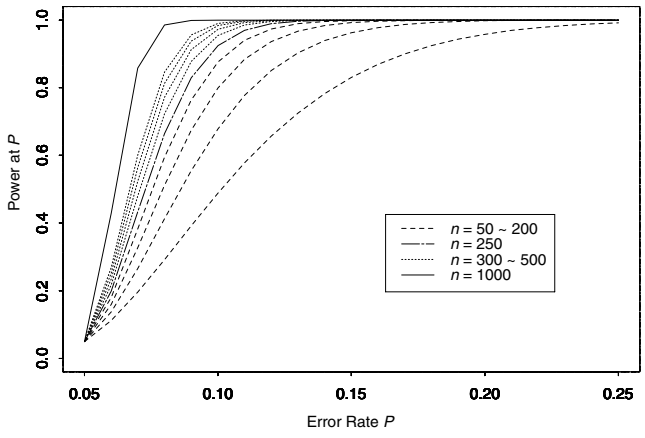



**Figure A.2. Statistical power of different sample sizes to reject the null hypothesis of errors less than 5% in the data.**

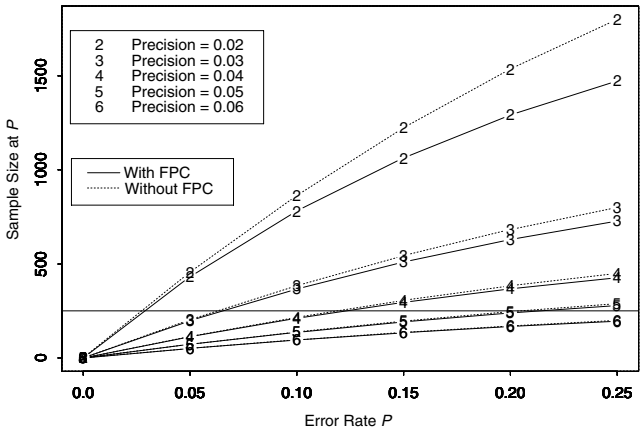



**Figure A.4. Sample sizes needed to achieve different levels of statistical precision (0.02–0.06) depending on error rate *P*.** Statistical significance was assumed to be 5%. Sample sizes were calculated both with and without a correction for sampling from a finite population (FPC).

data audit. For each of the two cohort studies, the Reanalysis Team randomly selected, without replacement, two samples of 250 each. (However, subjects selected in one sample could also be selected in the other.) We used one independent sample to audit death certificates, so that we sampled only those persons declared to be deceased in the original investigations. We selected the second independent sample from the entire cohort used in the published studies. Thus, it was possible for a subject to be included in both samples audited.

## APPENDIX B. Analytic Methods of the Harvard Six Cities Study and the American Cancer Society Study

In these original investigations survival analysis with the Cox proportional-hazards model was used to estimate relative risks of mortality associated with air pollution. In this multivariate model, the ratio of the hazard function of the unexposed population to the exposed population provides an estimate of the relative risk. Formally, this multivariate 56

model is expressed as:

$$\lambda_A(t) = \lambda_B(t) \times \exp\left(\sum_{i=1}^{k} \beta_i X_i + \gamma E\right) \quad (1)$$

where $\lambda_A(t)$ and $\lambda_B(t)$ represent the hazard rates, as functions of time, in the exposed and baseline populations, respectively; $X_i$ represents a series of potential confounding variables; and $E$ represents the exposure to air pollutants. The coefficients $\beta_i$ and $\gamma$, are estimated from the pseudolikelihood function and represent the natural logarithms of covariates. For example, $\exp(\gamma E)$ for $E$ evaluated over the entire range (for sulfate in the ACS Study this was 19.9 $\mu g/m^3$) represents the mortality risk for an increase in exposure across the range of $E$. Both the ACS and Six Cities studies used the Cox proportional-hazards model to estimate risk. The variables used in each study are outlined separately below.

### AMERICAN CANCER SOCIETY STUDY

The manuscript by the original investigators (Pope et al 1995) describes the methods used in detail. The Cox proportional-hazards model was applied using the survival time from the date of enrollment. The survival times of those who had not died were censored at the end of the study's follow-up period. The Cox proportional-hazards models were stratified by 5-year age groupings, sex, and race, which permitted a baseline hazard, $\lambda_B(t)$, to be estimated within each such stratum. A stratified Cox proportional-hazards model can be expressed by extending the formula presented in Equation 1 to read

$$\frac{\lambda_{A_s}(t)}{\lambda_{B_s}(t)} \quad (2)$$

where $s$ represents the strata defined by one or more categorical variables. This model includes separate, but not necessarily proportional, hazards for each stratum.

Separate models were fit for two air pollution variables: the mean concentration of sulfate particle pollution for 1980 in the participant's place of residence, and the median fine particle concentration for 1979–1983 calculated from the dichotomous sampler network by Lipfert and colleagues (1988). Scaling was applied so that the parameter estimates would yield a relative risk for the most-polluted area relative to the least-polluted area. For sulfate particles, this factor was 19.9 $\mu g/m^3$ and for fine particles it was 24.5 $\mu g/m^3$.

A comprehensive listing of potential confounding variables was entered into the multivariate model. The following variables were included to adjust for smoking behavior: an indicator variable for current-smokers; an indicator variable for pipe smokers, cigar smokers, or both; number of years smoked for current-smokers; cigarettes smoked daily for current-smokers; years smoked for former-smokers; cigarettes smoked daily for former-smokers; and number of hours per day passively exposed to smoke. Other risk factors that were controlled for in the analyses included BMI, drinks per day of alcohol, a dichotomous variable indicating whether high school education had been attained or not, and variables representing occupational exposure to any of several substances (asbestos, chemicals or acids or solvents, coal or stone dusts, coal tar or pitch or asphalt, diesel engine exhaust, or formaldehyde).

Cox proportional-hazards models were used to derive risk estimates for lung cancer (ICD-9 code 162), cardiopulmonary diseases (ICD-9 codes 401–440), and all causes of death. Risks were also calculated for current-smokers relative to never-smokers under the assumption that current-smokers smoked 20 cigarettes per day for a period of 25 years.

### HARVARD SIX CITIES STUDY

Similar methods were used in the Six Cities analyses (Dockery et al 1993). Cox proportional-hazards modeling was used with stratification by 5-year age groupings and sex. The series of risk factors included in these models were indicator variables for current-smokers and former-smokers; number of pack-years of smoking (for current-smokers and former-smokers separately); an indicator variable for having attained high school education or not; a

continuous-measure BMI; and binary variables denoting exposure to dusts, gases, or fumes.

Mean concentrations of fine particles and the city of residence were used as separate indicators of air pollution exposure. That means the relative risk of mortality due to air pollution exposure was evaluated in two ways. First, indicator variables were created for each city of residence by estimating the relative risk of mortality for each city using Portage, the city with the lowest concentration of fine particle air pollution, as the reference category. These relative risks by city of residence were presented separately for males and females.

Second, the Cox proportional-hazards model was used to estimate the relative risk of mortality using a continuous measure of the concentration of fine particles that included all fine particle data regardless of city or year. The logarithm estimates of relative risk were multiplied by 18.6 $\mu g/m^3$ in order to provide an estimate of the relative risk for residents of the most-polluted city (Steubenville OH) relative to residents of the least-polluted city (Portage WI).

Cox proportional-hazards models were fitted for four cause-of-death categories: all causes, lung cancer (ICD-9 code 162), cardiopulmonary disease (ICD-9 codes 400–440, 485–496), and all other causes. In a separate group-specific analysis, the Original Investigators calculated mortality risks for current-smokers, assuming these individuals had accrued 25 pack-years of smoking compared with never-smokers. Similarly, risks for former-smokers were calculated assuming 20 pack-years of smoking.

## APPENDIX C. Questionnaires and Codebook Used in the Harvard Six Cities Study

*Form 78 (1/77)*

1

### HARVARD QUESTIONNAIRE on RESPIRATORY SYMPTOMS (Adults)

I.D. (1-4) ☐☐☐☐☐ (1 2 3 4 5)

Card No.: ☐ (6)

NAME _____ (Last / First)

Soc. Sec. No.: _____ ☐☐☐☐☐☐ (7 8 9 10 11 12)

Date of Birth: _____ (7-12) Mo. Day Yr.

Tel. No. _____

Place of Birth: _____ (13-14) ☐☐ (13 14)

Address: _____

Sex (15) Male _____ 1 Female _____ 2 ☐ (15)

_____ City Zip

*(To be coded later):* S.C. _____ (16) ☐ (16)

Occupation Code: _____ (17-18-19) ☐☐☐ (17 18 19)

(20) **MARITAL STATUS:**

Single _____ 1
Married _____ 2
Widowed _____ 3
Sep/Div. _____ 4

(21) **RACE:**

Caucasian _____ 1
Negro _____ 2
Oriental _____ 3
Am. Indian/ Mexican _____ 4
Other _____ 5

☐ (20)

☐ (21)

**SPOUSE:**

Name: _____

Study No. _____ (22-25) ☐☐☐☐ (22 23 24 25)

Occupation: _____

**OCCUPATIONAL HISTORY (from time of leaving school)**

| Residences with dates | Industry | Actual Job | Materials Handled | Years of Exposure Dust | Years of Exposure Gas/Fumes |
|---|---|---|---|---|---|
| | | | | | |
| Presently: | | | | | |
| | | | TOTALS | (26-27) | (28-29) |

☐☐ (26 27)

☐☐ (28 29)

*(Be sure to get current occupation ("retired" etc.))*

(30) Number of job changes in last 10 years _____ ☐ (30)

(31) Number of residence changes (change of town) in last 10 years _____ ☐ (31)

(32-33) Number of years resident in this town _____ ☐☐ (32 33)

(34-35) Years in same part of town _____ ☐☐ (34 35)

(36)
**Highest Grade of Schooling Completed:**

| | | | |
|---|---|---|---|
| Grade school not completed | ____ 0 | Trade school or only attended college | ____ 3 |
| Grade school completed | ____ 1 | 2-yr. college or nursing graduate | ____ 4 |
| High school completed | ____ 2 | 4-yr. college graduate | ____ 5 |
| | | Post-graduate | ____ 6 |

☐ 36

**CURRENT HEALTH** *("YES" must satisfy criteria of ". . . as much as 4-6 times a day for 4 days of the week")*

**Cough**

(37) A. Do you usually have a cough? No ____ 0 Yes ____ 1 ☐ 37

(38) B. Do you cough at all on getting up, or first thing in the morning?

In winter: No ____ Yes ____ 1
In summer: No ____ Yes ____ 2
*(Add "Yes" scores)* ☐ 38

(39) C. Do you go on coughing during the day or at night?

In winter: No ____ Yes ____ 1
In summer: No ____ Yes ____ 2
*(Add "Yes" scores)* ☐ 39

**If YES to A, B, or C ask:**

D. Do you cough like this on most days for as much as 3 months at a time?

(40) No ____ 0 Yes ____ 1

E. How long have you had this cough?
Less than 3 years ____ 0
3 years or more ____ 2
N/A ____ 8
*(Add "Yes" scores)* ☐ 40

**Phlegm**

(41) A. Do you usually bring up phlegm from your chest (not from the back of your nose)?

No ____ 0 Yes ____ 1 ☐ 41

(42) B. Do you bring up phlegm at all on getting up, or first thing in the morning?

In winter: No ____ 0 Yes ____ 1
In summer: No ____ 0 Yes ____ 2
*(Add "Yes" scores)* ☐ 42

(43) C. Do you go on bringing up phlegm during the day?

In winter: No ____ 0 Yes ____ 1
In summer: No ____ 0 Yes ____ 2
*(Add "Yes" scores)* ☐ 43

**If YES to A, B, or C ask:**

D. Do you bring up phlegm like this on most days for as much as three months at a time?

(44) No ____ 0 Yes ____ 1

E. How long have you had this phlegm?
Less than 3 years ____ 0
3 years or more ____ 2
N/A ____ 8
*(Add "Yes" scores)* ☐ 44

(45) F. Do you get bouts of (increased) cough and phlegm lasting for 3 weeks each winter?

No ____ 0 Yes, last 3 winters only ____ 1 Yes, more than 3 winters ____ 2 ☐ 45

**Wheezing**

(46) A. Does your chest ever sound wheezy or whistling?

**If NO,** ask: Not even when you have a cold? No ____0 Yes ____1

**If YES,** ask: Only with colds? ____ Occasionally apart from colds? ____2

Most days or nights? ____3

*(Record highest score)*

**If YES to most days or nights,** ask:

Has this been present for the past 3 years or more? No ____ Yes ____4

46

(47) B. Have you ever had an attack of wheezing that has made you feel short of breath?

No ____0 Yes ____1

**If YES, ask:**

Have you had 2 or more such episodes? No ____0 Yes ____1

Have you ever required medicine or treatment for the(se) attack(s)? No ____0 Yes ____2

*(Add "Yes" scores)*

47

(48) **Breathlessness**

*If disabled from walking by any condition other than heart or lung disease, describe and do not ask the following questions (A-F):* ____8

Are you troubled by shortness of breath?

A. If NO, ask: Not even when hurrying on the level or walking up a slight hill?

No ____0 Yes ____1

B. If YES, ask: Do you have to walk slower than people of your age on the level because of breathlessness?

No ____ Yes ____2

C. If YES, ask: Do you ever have to stop for breath when walking at your own pace on the level?

No ____ Yes ____3

D. If YES, ask: Do you have to stop for breath after walking about 100 yards (or after a few minutes) on the level?

No ____ Yes ____4

E. If YES, ask: Are you too breathless to leave the house, or breathless on dressing or undressing?

No ____ Yes ____5

*(Record highest score)*

48

(49) **If Yes to C ask:**

Have these symptoms been present for at least the past 2 winters? No ____0 Yes ____1 N/A ____8

49

(50) **Colds**

If you get a cold, does it usually go to your chest? No ____0 Yes ____1

50

**Effect of Weather**

(51) A. Does the weather affect your chest or breathing? No ____ 0 Yes ____ 1 [51]

**If YES, ask B, C, and D.**

(52) B. Does foggy or damp weather affect it? No ____ Yes ____ 1

C. Does cold weather affect it? No ____ Yes ____ 2 *(Add "Yes" scores)* [52]

D. Does hot weather affect it? No ____ Yes ____ 4

N/A ____ 8

**(If YES to B, C, or D, ask E, F, and G.)**

(53) E. Does this weather make you short of breath? No ____ Yes ____ 1

F. Does this weather make you wheeze? No ____ Yes ____ 2 *(Add "Yes" scores)* [53]

G. Does this weather increase your cough or phlegm? No ____ Yes ____ 4

N/A ____ 8

(54) **PAST CHEST ILLNESSES**

During the past 3 years have you had any chest illness that has kept you off work, indoors at home or in bed? No ____ 0 Yes ____

**If YES, ask details of each illness; if NO, ask: "Not even flu?"**

| Year | Lasted 1 week or more? No | Lasted 1 week or more? Yes | Had increased phlegm? No | Had increased phlegm? Yes | Diagnosis | Score |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |

If YES in both columns, Score 1. Total Score (54) [54]

Has a doctor ever said you had:

| | | No | Yes |
|---|---|---|---|
| (55) | Bronchitis | 0 | 1 |
| | Emphysema | 0 | 2 |
| | Pneumonia | 0 | 4 |

*(Add "Yes" scores)* [55]

| | | No | Yes |
|---|---|---|---|
| (56) | Sinus Trouble | 0 | 1 |
| | Pulmonary Tuberculosis | 0 | 2 |
| | Hay Fever | 0 | 4 |

*(Add "Yes" scores)* [56]

(57) Bronchial Asthma No ____ 0 Yes, at present ____ 1 Yes, in past (but not now) ____ 2 [57]

(58) Other chest illness No ____ 0 Yes ____ 1 Specify _____

chest operations No ____ 0 Yes ____ 2 Specify _____

chest injury No ____ 0 Yes ____ 4 Specify _____

*(Add "Yes" scores)* [58]

5

**PAST ILLNESS – GENERAL**

(59) Has a doctor ever said you had diabetes or have you been told you had sugar in your urine (water) or too much sugar in your blood?
No ____ 0 Yes ____

If YES: Are you currently taking medication -
by injection ..... Yes ____ 1
or taking medication by mouth ..... Yes ____ 2
or controlled only by diet ..... Yes ____ 3
or none of these ..... Yes ____ 4
*(Record score)* → 59

(60) Has a doctor ever told you that you had heart trouble? No ____ 0 Yes ____ 1
If YES, ask: Have you had any *treatment* for it in the past 10 years? No ____ 0 Yes ____ 1
Has a doctor ever told you that your blood pressure was high? No ____ 0 Yes ____ 3
If YES, ask: Have you had any *treatment* for it in the past 10 years? No ____ 0 Yes ____ 3
*(Add "Yes" scores)* → 60

(61) Have you been bothered by indigestion, heartburn, or pains in the stomach in the past 10 years? No ____ 0 Yes ____ 1
If YES:
Has this been as much as twice a week for as long as a month? No ____ 0 Yes ____ 1
*(Add "Yes" scores)* → 61
Doctor's diagnosis, if given _____

(62) Have you ever vomited any blood? No ____ 0 Yes ____ 1
Have you ever been told you had stomach ulcers? No ____ 0 Yes ____ 2
*(Add "Yes" scores)* → 62

Have you ever had an operation on the abdomen or stomach for:

(63)

| | No | Yes |
|---|---|---|
| Ulcers | ____ 0 | ____ 1 |
| Appendix | ____ 0 | ____ 2 |
| Gallbladder | ____ 0 | ____ 4 |

*(Add "Yes" scores)* → 63

(64)

| | No | Yes |
|---|---|---|
| Exploratory Laparotomy | ____ 0 | ____ 1 |
| Other Intestinal | ____ 0 | ____ 2 |
| _____ | | |

*(Add "Yes" scores)* → 64

(65) Are you troubled by frequent headaches? No ____ 0 Yes ____ 1 → 65

(66) Have you ever been affected by gas or fumes at work or anywhere? No ____ 0 Yes ____
If YES, ask: Once or twice? ____ 1 More often? ____ 2 *(Record score)* → 66

(67) For any occurrence ask: Did you ever have to see a doctor? No ____ 0 Yes ____
If YES, ask: Once? ____ 1 More than once? ____ 2 N/A ____ 8 *(Record score)* → 67

(68) If doctor was seen, ask: Were you hospitalized for a day or more? No ____ 0 Yes ____
If YES, ask: Once? ____ 1 More than once? ____ 2 N/A ____ 8 *(Record score)* → 68

78 79 7 80 8

CARD 2

I.D. (1-5)

6

Card No.: 2 (6)

## DRINKING

(7) A. Do you PRESENTLY use alcoholic beverages? No ____ 0 Yes ____ 1

B. If YES, Is this as often as 1 day per week? No ____ 0 Yes ____ 1

*(Add "yes" scores)* (7)

C. *If YES to B, ask for each of beer, wine and liquor:*

"How much do you drink on an average per week?"

| (8) Beer (oz./wk.) | (9) Wine (oz./wk.) | (10) Liquor (oz./wk.) |
|---|---|---|
| None ____ 0 | None ____ 0 | None ____ 0 |
| 1-199 ____ 1 | 1-99 ____ 1 | 1-25 ____ 1 |
| 200+ ____ 2 | 100+ ____ 2 | 26+ ____ 2 |

(8) (9) (10)

[N.B.: 200 oz. = 25 8-oz. glasses 16 oz. = 1 pint
100 oz. = 25 4-oz. glasses 26 oz. = 1/5 gallon]

## TOBACCO SMOKING

(11) Have you *ever* smoked? No ____ 0 Yes ____ 1

Do you *now* smoke? No ____ 0 Yes ____ 2

(As of 1 month ago)

*(Record highest score)* (11)

*("No" means less than 20 packs of cigarettes or 12 oz. of tobacco in a lifetime.)*

*For current or ex-smokers, ask:*

(12) Have you ever been able to stop smoking cigarettes for 6 months or longer? No ____ 1 Yes ____ (12)

If YES:

Did you practice total abstinence? No ____ Yes ____ 2

Did you switch to cigar/pipe? No ____ Yes ____ 3

Did you chew or take snuff? No ____ Yes ____ 4

N/A ____ 8

*(Record score checked; if both 3 and 4 checked, record 5)*

*For current and ex-smokers, obtain the following:*

**Duration of Smoking**

| | Age Started* | Age finally stopped; if not, current age: | Years Abstinence | Total Yrs. Smoked* |
|---|---|---|---|---|
| Cigarettes | (13-14) | | | (15-16) |
| Pipe | | | | (17-18) |
| Cigars | | | | (19-20) |

(13) (14) (15) (16) (17) (18) (19) (20)

*Enter 00 for Never Smoked.*

7

## AMOUNT SMOKED

**Packs of (20) Cigarettes/week**

| | (a) (21-22) Weekly Amt. | (b) Years Duration | (a) x (b) |
|---|---|---|---|
| Present Pattern | | | |
| Past Periods | | | |
| | | | |
| | | | |
| | | | |
| Total | | | (25-28) |

**Hand-rolled tobacco oz./wk.**

| | (c) (23-24) Weekly Amt. | (d) Years Duration | (c) x (d) |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| Total | | | (29-32) |

**Pipe Tobacco oz./wk.**

| | (e) (33-34) Weekly Amt. | (f) Years Duration | (e) x (f) |
|---|---|---|---|
| Present Pattern | | | |
| Past Periods | | | |
| | | | |
| Total | | | (37-40) |

**Cigars/wk.**

| | (g) (35-36) Weekly Amt. | (h) Years Duration | (g) x (h) |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| Total | | | (41-44) |

(45) Do you smoke filter-tip cigarettes currently? *(Currently means for past month at least.)*

Never ____ 1 Less than ½ time ____ 2 ½ time + ____ 3 Always ____ 4 N/A ____ 8

How long have you been using filter-tips? ____ years

| | Slightly | Moderately | Deeply | Not at all | Never smoked |
|---|---|---|---|---|---|
| (46) Do/did you inhale the cigarette smoke? | ____ 1 | ____ 2 | ____ 3 | ____ 4 | ____ 5 |
| (47) Do/did you inhale the pipe/cigar smoke? | ____ 1 | ____ 2 | ____ 3 | ____ 4 | ____ 5 |

(48) Have you ever chewed tobacco regularly? No ____ 0 Yes ____ 1

Have you ever used snuff regularly? No ____ 0 Yes ____ 2

*(Add "Yes" scores)*

21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48

8

## ALLERGIES

*For each of the following, if response is "Yes," ask whether confirmed by doctor*

| | | None | Confirmed by Doctor: No | Confirmed by Doctor: Yes |
|---|---|---|---|---|
| Have you ever had an allergic reaction to | | | | |
| (49) | food or medicine (ingested)? | 0 | 1 | 2 |
| (50) | pollen, dust (inhaled)? | 0 | 1 | 2 |
| (51) | detergents, metals (skin contact)? | 0 | 1 | 2 |

□ □ □ 49 50 51

## FAMILY HISTORY

Were either of your natural parents ever told by a doctor that they had a chronic lung condition such as:

| | | Father | | | Mother | | |
|---|---|---|---|---|---|---|---|
| | | No (0) | Yes (1) | Don't know (2) | No (0) | Yes (1) | Don't Know (2) |
| (52) | chronic bronchitis? | | | | | | |
| (53) | emphysema? | | | | | | |
| (54) | asthma? | | | | | | |
| (55-57) | other lung disease? (specify) | | | | | | |
| | | | | | (58) | | |
| | | | | | (59) | | |
| | | | | | (60) | | |
| | | | | | (61-63) | | |

□ □ □ 52 53 54

□ □ □ 55 56 57

□ □ □ 58 59 60

□ □ □ 61 62 63

(64) PULMONARY FUNCTION

Test done _____ 1

Test not done because:

Subject could not perform test _____ 2

Refused _____ 3

Other, specify _____ 4

□ 64

(65) SELECTION: Normal _____ 0

Volunteer No _____ Yes _____ 1

Interpreter No _____ Yes _____ 2

At Home No _____ Yes _____ 4

□ 65

(66-67) INTERVIEWER _____

□ □ 66 67

(68-73) DATE OF INTERVIEW _____
Month Day Year

□ □ □ □ □ □ 68 69 70 71 72 73

□ □ □ □ □ 74 75 76 77 78

7 8 79 80

Form 82 (8/81)

1

## HARVARD QUESTIONNAIRE on RESPIRATORY SYMPTOMS (Adults)
(FOLLOW-UP)

I.D. (1-4) ☐☐☐☐☐ (1 2 3 4 5)

Card No.: ☐ (6)

NAME _____ (Last) (First)

Soc. Sec. No.: _____ ☐☐☐☐☐☐ (7 8 9 10 11 12)

Date of Birth: (7-12) _____ Mo. Day Yr.

Tel. No. _____

Sex (13) Male ____ 1 Female ____ 2

Current Address: _____ ☐☐☐ (13 14 15)

SPOUSE:

Name: _____

_____ City Zip (16-20) ☐☐☐☐☐ (16 17 18 19 20)

Study No. _____

(21) **MARITAL STATUS:** ☐☐ (21 22)

Single ____ 1 Widowed ____ 3

Married ____ 2 Sep/Div. ____ 4

(22) **RACE:**

Caucasian ____ 1 Oriental ____ 3

Black ____ 2 Am. Indian/ Mexican ____ 4

Other ____ 5

**OCCUPATIONAL HISTORY** (During the past three years)

Spouse Job Title: _____ Spouse Industry: _____

| Residences with dates | Industry | Actual Job | Materials Exposed To | Years of Exposure: Dust | Years of Exposure: Gas/Fumes |
|---|---|---|---|---|---|
| | | | | | |
| Presently: | (23-25) | (26-28) | | | |
| | | | TOTALS | (29-30) | (31-32) |

☐☐☐ (23 24 25) ☐☐☐ (26 27 28) ☐☐ (29 30) ☐☐ (31 32)

Be sure to obtain both present industry and present job (actual work activity).

(33) Number of job changes in last 3 years: ____ ☐ (33)

(34) Have you changed your address in the last three years? No ____ Yes ____ 1 ☐ (34)

If Yes, do you live in the same part of town as you did three years ago? No ____ Yes ____ 2
(Add "Yes" scores)

(35-36) How long have you lived at your current address? ____ yrs ☐☐ (35 36)

(37) What fuel do you use most to heat your home? (One only)

Oil ____ 1 Natural gas ____ 2 Bottled gas (Propane) ____ 3 Electricity ____ 4 Wood ____ 5 Coal ____ 6

Other, (Specify) _____ 7 ☐ (37)

(38-39) What other fuels are used to heat your home? (Check all appropriate.)

Oil ____ 1 Natural gas ____ 2 Bottled gas (Propane) ____ 4 Electricity ____ 8 Wood ____ 16 Coal ____ 32

Other, (Specify) _____ 0 (Add Scores) ☐☐ (38 39)

2

(40) How is heat mainly distributed to the rooms in your home? (One only)

Hot Air ___1 Hot Water ___2 Steam ___3 Fireplace ___4 Stove ___5 Space Heater ___6

Other, (Specify) _____ 7 ☐ 40

(41-42) What other heat distribution methods are used in your house? (Check all appropriate)

Hot Air ___1 Hot Water ___2 Steam ___4 Fireplace ___8 Stove ___16 Space Heater ___32

Other, (Specify) _____ 0 (Add Scores) ☐☐ 41 42

(43-44) Have you made any attempts to seal up your house for energy conservation in the last 6 years?

No ___0 Yes ___

No, house was already tight ___1 Storm windows ___2

Don't know or not applicable ___99 Caulking ___4

Insulation ___8

Flue Damper ___16

Other _____ 32 (Add Scores) ☐☐ 43 44

(45) What fuel is used for cooking? Gas ___ Coal ___ Wood ___ Electricity ___ Other _____ ☐ 45

(46) Do you have an exhaust fan for your cooking stove? No ___ Yes ___ Don't know ___ ☐ 46

(47) If yes, do you use it: Never ___ Seldom ___ Regularly ___ ☐ 47

(48) How is the exhaust fan vented? into the room ___; vented to outside ___; Don't know ___ ☐ 48

(49) Is your home air-conditioned? No ___; Yes, partially ___; Yes, completely ___ ☐ 49

The following questions apply to your HEALTH in the last three years.

Please answer Yes or No if possible.

**CURRENT HEALTH** *("YES" must satisfy criteria of ". . . as much as 4-6 times a day for 4 days of the week")*

**Cough.**

(50) A. Do you usually have a cough? No _____ 0 Yes _____ 1 ☐ 50

(51) B. Do you cough at all on getting up, or first thing in the morning?

In winter: No _____ Yes _____ 1

In summer: No _____ Yes _____ 2

*(Add "Yes" scores)* ☐ 51

(52) C. Do you go on coughing during the day or at night?

In winter: No _____ Yes _____ 1

In summer: No _____ Yes _____ 2

*(Add "Yes" scores)* ☐ 52

**If YES to A, B, or C ask:**

D. Do you cough like this on most days for as much as 3 months at a time?

(53) No _____ 0 Yes _____ 1

E. How long have you had this cough? Less than 3 years _____ 0

3 years or more _____ 2

N/A _____ 8

*(Add "Yes" scores)* ☐ 53

**Phlegm**

(54) A. Do you usually bring up phlegm from your chest (not from the back of your nose)?

No ____ 0 Yes ____ 1 □ 54

(55) B. Do you bring up phlegm at all on getting up, or first thing in the morning?

In winter: No ____ 0 Yes ____ 1
In summer: No ____ 0 Yes ____ 2
*(Add "Yes" scores)* □ 55

(56) C. Do you go on bringing up phlegm during the day?

In winter: No ____ 0 Yes ____ 1
In summer: No ____ 0 Yes ____ 2
*(Add "Yes" scores)* □ 56

**If YES to A, B, or C ask:**

(57) D. Do you bring up phlegm like this on most days for as much as three months at a time?

No ____ 0 Yes ____ 1

E. How long have you had this phlegm?

Less than 3 years ____ 0
3 years or more ____ 2
N/A ____ 8
*(Add "Yes" scores)* □ 57

(58) F. Do you get bouts of (increased) cough and phlegm lasting for 3 weeks each winter?

No ____ 0 Yes, last 3 winters only ____ 1 Yes, more than 3 winters ____ 2 □ 58

**Wheezing**

(59) A. During the past three years, has your chest ever sounded wheezy or whistling?

**If NO,** ask: Not even when you have a cold? No ____ 0 Yes ____ 1

**If YES,** ask: Only with colds? ____ Occasionally apart from colds? ____ 2
Most days or nights? ____ 3

**If YES to most days or nights,** ask:
Has this been present for the past 3 years or more? No ____ Yes ____ 4
*(Record highest score)* □ 59

(60) B. During the past three years, have you had an attack of wheezing that has made you feel short of breath?

No ____ 0 Yes ____ 1

**If YES, ask:**
Have you had 2 or more such episodes? No ____ 0 Yes ____ 1
Have you ever required medicine or treatment for the(se) attack(s)? No ____ 0 Yes ____ 2
*(Add "Yes" scores)* □ 60

(61) **Breathlessness**

*If disabled from walking by any condition other than heart or lung disease, describe and do not ask the following questions (A-F):* ____ 8

Are you troubled by shortness of breath?

A. If NO, ask: Not even when hurrying on the level or walking up a slight hill?

No ____ 0 Yes ____ 1

B. If YES, ask: Do you have to walk slower than people of your age on the level because of breathlessness?

No ____ Yes ____ 2

C. If YES, ask: Do you ever have to stop for breath when walking at your own pace on the level?

No ____ Yes ____ 3

D. If YES, ask: Do you have to stop for breath after walking about 100 yards (or after a few minutes) on the level?

No ____ Yes ____ 4

E. If YES, ask: Are you too breathless to leave the house, or breathless on dressing or undressing?

No ____ Yes ____ 5

*(Record highest score)* □ 61

4

(62) **If Yes to C ask:**

Have these symptoms been present for at least the past 2 winters? No ____ 0 Yes ____ 1 N/A ____ 8 [62]

(63) **Colds**

If you get a cold, does it usually go to your chest? No ____ 0 Yes ____ 1 [63]

**Effect of Weather**

(64) A. Does the weather affect your chest or breathing? No ____ 0 Yes ____ 1 [64]

**If YES, ask B, C, and D.**

B. Does foggy or damp weather affect it? No ____ Yes ____ 1

(65) C. Does cold weather affect it? No ____ Yes ____ 2 *(Add "Yes" scores)* [65]

D. Does hot weather affect it? No ____ Yes ____ 4

N/A ____ 8

**(If YES to B, C, or D, ask E, F, and G.)**

E. Does this weather make you short of breath? No ____ Yes ____ 1

(66) F. Does this weather make you wheeze? No ____ Yes ____ 2 *(Add "Yes" scores)* [66]

G. Does this weather increase your cough or phlegm? No ____ Yes ____ 4

N/A ____ 8

(67) **PAST CHEST ILLNESSES**

During the past 3 years have you had any chest illness that has kept you off work, indoors at home or in bed? No ____ 0 Yes ____

**If YES, ask details of each illness; if NO, ask: "Not even flu?"**

| Year | Lasted 1 week or more? No | Lasted 1 week or more? Yes | Had increased phlegm? No | Had increased phlegm? Yes | Diagnosis | Score |
|---|---|---|---|---|---|---|
| | | | | | ..... | |
| | | | | | ..... | |
| | | | | | ..... | |
| | | | | | | |

If YES in both columns, Score 1. Total Score

(67) [67]

**During the past three years, has a Doctor said you have:**

| | | No | Yes |
|---|---|---|---|
| (68) | Bronchitis | 0 | 1 |
| | Emphysema | 0 | 2 |
| | Pneumonia | 0 | 4 |

*(Add "Yes" scores)* [68]

| | | No | Yes |
|---|---|---|---|
| (69) | Sinus Trouble | 0 | 1 |
| | Pulmonary Tuberculosis | 0 | 2 |
| | Hay Fever | 0 | 4 |

*(Add "Yes" scores)* [69]

5

(70) Bronchial Asthma No ____0 Yes, at present ____1 Yes, in past (but not now) ____2 [70] [71]

(71) Other chest illness No ____0 Yes ____1 Specify ____

chest operations No ____0 Yes ____2 Specify ____

chest injury No ____0 Yes ____4 Specify ____

*(Add "Yes" scores)*

**PAST ILLNESS – GENERAL**

(72) Has a doctor ever told you that you had heart trouble? No ____0 Yes ____1

If YES, ask: Have you had any *treatment* for it in the past 3 years? No ____0 Yes ____1

Has a doctor ever told you that your blood pressure was high? No ____0 Yes ____3

If YES, ask: Have you had any *treatment* for it in the past 3 years? No ____0 Yes ____3 [72]

*(Add "Yes" scores)*

(73) Are you troubled by frequent headaches? No ____0 Yes ____1 [73]

(74) During the past three years, have you been affected by gas or fumes at work or anywhere? No ____0 Yes ____

If YES, ask: Once or twice? ____1 More often? ____2 *(Record score)* [74]

(75) For any occurrence ask: Did you ever have to see a doctor? No ____0 Yes ____

If YES, ask: Once? ____1 More than once? ____2 N/A ____8 *(Record score)* [75]

(76) If doctor was seen, ask: Were you hospitalized for a day or more? No ____0 Yes ____

If YES, ask: Once? ____1 More than once? ____2 N/A ____8 *(Record score)* [76] [77] [78]

[5] [4] [79] [80]

**CARD 2**

I.D. (1-5)

6 | 1 2 3 4 5

Card No.: 2 | 6

## TOBACCO SMOKING

(7) Have you *ever* smoked? No ____ 0 Yes ____ 1

Do you *now* smoke? No ____ 0 Yes ____ 2 *(Record highest score)*

(As of 1 month ago)

*("No" means less than 20 packs of cigarettes or 12 oz. of tobacco in a lifetime.)*

*For current or ex-smokers, ask:*

(8) Have you ever been able to stop smoking cigarettes for 6 months or longer? No ____ 1 Yes ____

7 | 8

If YES:

Did you practice total abstinence? No ____ Yes ____ 2

Did you switch to cigar/pipe? No ____ Yes ____ 3

Did you chew or take snuff? No ____ Yes ____ 4 N/A____ 8

*(Record score checked; if both 3 and 4 checked, record 5)*

*For current and ex-smokers, obtain the following:*

**Duration of Smoking**

| | Age Started* | Age finally stopped; if not, current age: | Years Abstinence | Total Yrs. Smoked* |
|---|---|---|---|---|
| Cigarettes | (9-10) | | | (11-12) |
| Pipe | | | | (13-14) |
| Cigars | | | | (15-16) |

9 | 10 | 11 | 12

13 | 14 | 15 | 16

*Enter 00 for Never Smoked.*

## AMOUNT SMOKED IN LAST THREE YEARS

**Packs of (20) Cigarettes/week**

(17-18)

| | (a) Weekly Amt. | (b) Years Duration | (a) x (b) |
|---|---|---|---|
| Present Pattern | | | |
| | | | |
| Past Three Years | | | |
| | | | |
| | | | |
| Total | | | (21-24) |

17 | 18

19 | 20

21 | 22 | 23 | 24

**Hand-rolled tobacco oz./wk.**

(19-20)

| | (c) Weekly Amt. | (d) Years Duration | (c) x (d) |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| Total | | | (25-28) |

25 | 26 | 27 | 28

**Pipe Tobacco oz./wk.**

(29-30)

| | (e) Weekly Amt. | (f) Years Duration | (e) x (f) |
|---|---|---|---|
| Present Pattern | | | |
| Past Three Years | | | |
| | | | |
| Total | | | (33-36) |

29 | 30

31 | 32

33 | 34 | 35 | 36

**Cigars/wk.**

(31-32)

| | (g) Weekly Amt. | (h) Years Duration | (g) x (h) |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| Total | | | (37-40) |

37 | 38 | 39 | 40

(41) Do you smoke filter-tip cigarettes currently? *(Currently means for past month at least.)*

Never ____1 Less than ½ time ____2 ½ time + ____3 Always ____4 N/A ____8

How long have you been using filter-tips? ____ years

☐ 41

| | | Slightly | Moderately | Deeply | Not at all | Never smoked |
|---|---|---|---|---|---|---|
| (42) | Do/did you inhale the cigarette smoke? | ____ 1 | ____ 2 | ____ 3 | ____ 4 | ____ 5 |
| (43) | Do/did you inhale the pipe/cigar smoke? | ____ 1 | ____ 2 | ____ 3 | ____ 4 | ____ 5 |

☐ 42

☐ 43

**During the last three years,**

(44) Have you ever chewed tobacco regularly? No ____0 Yes ____1

Have you ever used snuff regularly? No ____0 Yes ____2

*(Add "Yes" scores)*

☐ 44

(45) How many persons 14 years and older live in your home? (Include yourself) ____

☐ 45

(46) How many of these are smokers?

☐ 46

(47) Are you normally exposed to other smokers away from home; for example, at work? No ____

Yes, occasionally ____1 Regularly ____2

☐ 47

If YES, is your exposure to smoke at these times: Light ____0 Moderate ____4 Heavy ____6

(Add Scores)

ALLERGIES (LIFETIME)

*For each of the following, if response is "Yes," ask whether confirmed by doctor*

| During your entire lifetime have you ever had an allergic reaction to | None | *Confirmed by Doctor* No | Yes |
|---|---|---|---|
| (48) food or medicine or anything else you have ingested? | ____ 0 | ____ 1 | ____ 2 |
| (49) pollen, dust or anything else you inhaled? | ____ 0 | ____ 1 | ____ 2 |
| (50) detergents, metals or anything else you touched? | ____ 0 | ____ 1 | ____ 2 |

☐ 48 ☐ 49 ☐ 50

**FAMILY HISTORY**

Were either of your natural parents ever told by a doctor that they had a chronic lung condition such as:

| | | Father | | | Mother | | |
|---|---|---|---|---|---|---|---|
| | | No (0) | Yes (1) | Don't know (2) | No (0) | Yes (1) | Don't Know (2) |
| (51) | chronic bronchitis? | ____ | ____ | ____ | (55) ____ | ____ | ____ |
| (52) | emphysema? | ____ | ____ | ____ | (56) ____ | ____ | ____ |
| (53) | asthma? | ____ | ____ | ____ | (57) ____ | ____ | ____ |
| (54) | other lung disease? (specify) | ____ | ____ | ____ | (58) ____ | ____ | ____ |
| | | _____ | | | _____ | | |

☐ 51 ☐ 52 ☐ 53 ☐ 54

☐ 55 ☐ 56 ☐ 57 ☐ 58

(59) PULMONARY FUNCTION

Test done ____ 1

Test not done because:

Subject could not perform test ____ 2

Refused ____ 3

Other, specify _____ 4

Test done, questionable reading _____ 5
(specify)

☐ 59

8

(60) SELECTION: Normal ____ 0

Interpreter No ____ Yes ____ 2

At Home No ____ Yes ____ 4

(61-62) INTERVIEWER _____

(63-68) DATE OF INTERVIEW _____
Month Day Year

(69-70) Air Pollution Zones

60 61 62

63 64 65 66 67 68

69 70

5 79 4 80

I.D.

SPOUSE I.D.

We are attempting to identify children in the school survey who live in households with adults in this survey. If there are any children living in your home between the ages of ____ and ____, please give the following information:

| NAME | SCHOOL | GRADE |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |

NONE _____

This may be the last time we see you, but we would like to be able to keep you up to date on the results of the study. Is there someone who would know your new address if you move?

NAME _____ RELATIONSHIP _____

ADDRESS _____

Is there another person who would know your new address?

NAME _____ RELATIONSHIP _____

ADDRESS _____

## Six Cities Reanalysis
## Codebook for mort6c

| Variable name | *Meaning and response codes* |
|---|---|
| 1) ID | 5-digit ID; last digit is city code |
| 2) FVC1 | Forced vital capacity in liters |
| 3) FEV11 | Forced expiratory volume in 1 second in liters |
| 4) CURRCIG1 | Current cigarette smoker( 0 = No, 1 = Yes) |
| 5) DUST_TO1 | Total years of occupational dust exposure |
| 6) EDUC11 | Highest grade of schooling completed<br>0 = Grade school not completed<br>1 = Grade school completed<br>2 = High school completed<br>3 = Trade school or only attended college<br>4 = 2-yr college or nursing graduate<br>5 = 4-yr college graduate<br>6 = Postgraduate |
| 7) FUM_TOT1 | Total years of occupational gas or fumes exposure |
| 8) SEX1 | Sex (0 = Male, 1 = Female) |
| 9) CIG_DAY1 | Cigarettes per day |
| 10) HEIGHT1 | Height in meters |
| 11) PKYRS1 | Pack years of smoking |
| 12) WEIGHT1 | Weight in pounds |
| 13) AGE_1 | Age in years |
| 14) CITY | City<br>1 = Watertown<br>2 = Kingston/Harriman<br>4 = St. Louis<br>5 = Steubenville<br>6 = Portage<br>9 = Topeka |
| 15) INITDATE | Date of initial visit |
| 16) LASTDATE | Last date on study for mortality analysis. If patient was dead, this date is the date of death; otherwise, this date is the last date we were able to confirm the patient was alive. |
| 17) DEAD | Dead 0 = No (alive at LASTDATE), 1 = Yes |
| 18) TIMEON | Time on study in years |
| 19) DIAB | Diabetes (0 = No, 1 = Yes) |
| 20) HI_BP | High blood pressure (0 = No, 1 = Yes) |
| 21) CODE | Cause of death<br>alive = Alive<br>carp = Cardiovascular or pulmonary<br>lunc = Lung cancer<br>other = All other causes of death<br>miss = Unknown cause of death |

| Variable name | *Meaning and response codes* |
|---|---|
| 22) EDD | Less than high school education (0 = No, 1 = Yes) |
| 23) EDC | Less than 4-yr college graduate (0 = No, 1 = Yes)<br>NB: SAS label in mort6c.ssd is wrong |
| 24) ED0 | Did not complete grade school (0 = No, 1 = Yes) |
| 25) ED1 | Grade school completed and no further education (0 = No, 1 = Yes) |
| 26) ED2 | High school completed and no further education (0 = No, 1 = Yes) |
| 27) ED3 | Trade school or only attended college and no further education (0 = No, 1 = Yes) |
| 28) ED4 | 2-yr college or nursing graduate and no further education (0 = No, 1 = Yes) |
| 29) ED5 | 4-yr college graduate and no further education (0 = No, 1 = Yes) |
| 30) ED6 | Post-graduate (0 = No, 1 = Yes) |
| 31) WAT | Watertown participant (0 = No, 1 = Yes) |
| 32) KIN | Kingston / Harriman participant (0 = No, 1 = Yes) |
| 33) STL | St. Louis participant (0 = No, 1 = Yes) |
| 34) STE | Steubenville participant (0 = No, 1 = Yes) |
| 35) POR | Portage participant (0 = No, 1 = Yes) |
| 36) TOP | Topeka participant (0 = No, 1 = Yes) |
| 37) BMI | Body mass index (kg/m**2) |
| 38) FSMOKE | Former smoker but not current (0 = No, 1 = Yes) |
| 39) CPACK | Current smoker pack years |
| 40) FPACK | Former smoker pack years |
| 41) SMOKEST | Smoking status<br>cs = current smoker<br>fs = former smoker<br>ns = never smoked |
| 42) DUST | Job exposure to dust (0 = No, 1 = Yes) |
| 43) FUME | Job exposure to fumes (0 = No, 1 = Yes) |
| 44) OCCU | Occupational exposure to dust or fumes (0 = No, 1 = Yes) |
| 45) SO4 | SO4/8 (ug/m3) |
| 46) PM15 | PM15/28.3 (ug/m3) |
| 47) PM2_5 | PM2_5/18.6 (ug/m3) |
| 48) TSP | TSP/55.8 (ug/m3) |
| 49) SO2 | SO2/28.3 (ppb) |
| 50) H | H+/25.8 (nmol/m3) |
| 51) O3 | Daily Mean Ozone (ppb) |
| 52) O3M | Daily max ozone (ppb) |
| 53) NO2 | NO2 (ppb)/15.8 (range) |
| 54) DUSTPM | Dust * PM2_5 |

APPENDIX D. Questionnaires and Codebook Used in the American Cancer Society Study

| AMERICAN CANCER SOCIETY<br>CANCER PREVENTION STUDY II<br>QUESTIONNAIRE FOR MEN  | Division No. | Unit No. | Group No. |
|---|---|---|---|
| | Researcher No. | Family No. | Person No. |

Date: _____

1. Name: _____
2. Date of birth: Month _____ Year _____
3. How old are you now? _____
4. Current weight with indoor clothing: _____ lbs.
5. Weight 1 year ago: _____ lbs.
6. Height (without shoes): _____ ft. _____ in.
7. ☐ White ☐ Black ☐ Hispanic ☐ Oriental ☐ Other _____ (specify)
8. Marital status: ☐ Single ☐ Separated ☐ Widowed ☐ Married ☐ Divorced
9. If ever married, age at first marriage: _____
10. Number of times married: _____
11. Social Security No.: _____ (optional)

## FAMILY HISTORY (IN RELATION TO CANCER):

1. Fill in the following table as completely as possible for parents, brothers and sisters.

| LIST ONE BLOOD RELATIVE PER LINE: (Circle Brother **or** Sister) | IS THIS PERSON? (Circle One) | IF ALIVE, GIVE AGE | IF DEAD, GIVE AGE AT DEATH | DID THIS PERSON **EVER** HAVE CANCER? (Circle One) | IF "YES," SPECIFY TYPE OF CANCER | AT WHAT AGE? |
|---|---|---|---|---|---|---|
| Father | Alive Dead | | | Yes No | | |
| Mother | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |

2. When you were born, a) How old was your mother? _____ b) How old was your father? _____

## HISTORY OF DISEASES:

1. Have you ever had cancer? ☐ Yes ☐ No. If "yes,"
   a) What type? _____
   b) Date of first treatment: _____
2. Place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor:
   - ☐ High Blood Pressure
   - ☐ Heart Disease
   - ☐ Stroke
   - ☐ Diabetes
   - ☐ Gall Stones
   - ☐ Chronic Indigestion
   - ☐ Kidney Disease
   - ☐ Kidney Stones
   - ☐ Bladder Disease
   - ☐ Cirrhosis of the Liver
   - ☐ Tuberculosis
   - ☐ Chronic Bronchitis
   - ☐ Emphysema
   - ☐ Hay Fever
   - ☐ Asthma
   - ☐ Stomach Ulcer
   - ☐ Duodenal Ulcer
   - ☐ Diverticulosis
   - ☐ Rectal Polyps
   - ☐ Colon Polyps
   - ☐ Thyroid Condition
   - ☐ Arthritis
   - ☐ Prostate Trouble
   - ☐ Hepatitis
   - ☐ Any other serious disease (specify) _____
3. Have you ever had an operation? ☐ Yes ☐ No
   If "yes," specify type and date(s) of operation(s):
   _____
   _____
   _____
4. How **many** x-ray or fluoroscopic **examinations** (GI series, barium enema, etc.) have you **ever** had of:

| | 0 | 1-5 | 6 or More | | 0 | 1-5 | 6 or More |
|---|---|---|---|---|---|---|---|
| Stomach | ☐ | ☐ | ☐ | Chest | ☐ | ☐ | ☐ |
| Intestine | ☐ | ☐ | ☐ | Arms/Legs | ☐ | ☐ | ☐ |
| Back | ☐ | ☐ | ☐ | Head/Neck | ☐ | ☐ | ☐ |

5. Have you ever been **treated** with radium, x-rays, or radioactive isotopes? ☐ Yes ☐ No
   If "yes," when? _____
   For what disease? _____
   _____
   What part of your body? _____
   _____
6. How many times have you had colds or flu in the past twelve months? _____

## CURRENT PHYSICAL CONDITION:

1. How much exercise do you get (work or play)?
   ☐ None ☐ Slight ☐ Moderate ☐ Heavy
2. On the average, how many hours do you sleep each night?_____
3. On the average, how many times a month do you have insomnia?_____ ☐ None
4. Within the last month, have you noticed:
   a) Painful or frequent urination? ☐ Yes ☐ No
   b) An unusual discharge from your penis?
   ☐ Yes ☐ No
5. Do you notice pains in your legs when you walk which go away when you rest? ☐ Yes ☐ No
   If "yes," how many years have you had these pains?_____
6. Are you sick at the present time? ☐ Yes ☐ No
   If "yes," with what disease or condition?_____
   _____
   _____
   _____

## HABITS:

1. **Whether or not you smoke,** on the average, how many **hours a day** are you exposed to cigarette smoke of others:
   At home_____, At work_____, In other areas_____.
2. Do you now or have you ever smoked cigarettes, cigars or pipes, at least one a day for one year's time? ☐ Yes ☐ No
   If never smoked, skip to question 8.
3. If you **currently** smoke cigarettes, cigars or pipes, fill in the information below:

| Current Smokers | Cigarettes | Cigars | Pipes |
|---|---|---|---|
| Average number smoked per day | | | |
| Age began smoking | | | |
| **INHALATION:** | | | |
| Do not inhale | | | |
| Inhale slightly | | | |
| Inhale moderately | | | |
| Inhale deeply | | | |
| Total years of smoking | | | |
| Years smoked **filtered** cigarettes | | | |
| Years smoked **non-filtered** cigarettes | | | |

4. Current brand of cigarette:_____
   a) Size: ☐ Regular ☐ King ☐ 100 mm ☐ 120 mm
   b) ☐ Non-filter ☐ Filter ☐ Menthol
   c) Years smoked this brand:_____

5. If you have **quit** smoking cigarettes, cigars or pipes, fill in the information below:

| Ex-Smokers | Cigarettes | Cigars | Pipes |
|---|---|---|---|
| Average number smoked per day | | | |
| Age began smoking | | | |
| Age quit | | | |
| **INHALATION:** | | | |
| Did not inhale | | | |
| Inhaled slightly | | | |
| Inhaled moderately | | | |
| Inhaled deeply | | | |
| Total years smoked | | | |
| Years smoked **filtered** cigarettes | | | |
| Years smoked **non-filtered** cigarettes | | | |

6. Last brand of cigarette smoked:_____
   a) Size: ☐ Regular ☐ King ☐ 100 mm
   ☐ 120 mm
   b) ☐ Non-filter ☐ Filter ☐ Menthol
   c) Years smoked this brand:_____

7. Current **and** ex-cigarette smokers, fill in the following information for:
   1) The **first** brand smoked regularly; and
   2) The brand of cigarette smoked for the **longest** period of time.

| Brand Name | Size | Filter | | Menthol | | Number Per Day | Years |
|---|---|---|---|---|---|---|---|
| | | Yes | No | Yes | No | | |
| 1. | | | | | | | |
| 2. | | | | | | | |

8. Have you ever chewed tobacco at least once a week for at least one year? ☐ Yes ☐ No
   If "no," skip to question 9.
   a) Age began chewing tobacco:_____
   b) How many times a week?_____
   c) For how many years?_____
   d) Do you still chew tobacco? ☐ Yes ☐ No

9. Have you ever used snuff at least once a week for at least one year? ☐ Yes ☐ No
   If "no," skip to "Diet."
   a) Age began using snuff:_____
   b) How many times a week?_____
   c) For how many years?_____
   d) Do you still use snuff? ☐ Yes ☐ No

## DIET:

1. On the average, how many days per week do you eat the following foods? (If less than once a week, but at least twice a month, write 1/2.)

| | |
|---|---|
| Beef | Raw vegetables |
| Pork | Carrots |
| Chicken | Squash/Corn |
| Liver | Citrus fruits/Juices |
| Ham | Spaghetti/Macaroni/ White rice |
| Fish | White bread/Rolls/ Biscuits |
| Smoked meats | Brown rice/Whole wheat/Barley |
| Frankfurters/ Sausage | Bran/Corn muffins |
| Butter | Potatoes |
| Margarine | Oatmeal/Shredded wheat/Bran cereals |
| Cheese | Cold (Dry) cereals |
| Eggs | Ice cream |
| Green leafy vegetables | Chocolate |
| Tomatoes | |
| Cabbage/Broccoli/ Brussels sprouts | |

2. How many days a week do you eat the following **fried** foods?

| | |
|---|---|
| Fried eggs | Fried hamburgers or beef |
| Fried bacon | Other fried foods |
| Fried chicken/fish | |
| French fries | |

DO NOT EAT FRIED FOODS ☐

3. Do you eat a vegetarian diet? ☐ Yes ☐ No
   If "yes," what type and for how many years? _____

4. Has there been a major change in your diet in the last 10 years? ☐ Yes ☐ No
   If "yes," what was the change? _____

5. a) Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?
   ☐ Yes, currently ☐ Formerly ☐ Never
   b) If **ever** used artificial sweeteners, indicate amount per day and for how long.
   Packets: No. per day _____ Years _____
   Drops: No. per day _____ Years _____
   Tablets: No. per day _____ Years _____

6. Do you get your drinking water from: ☐ City supply ☐ Private well ☐ Other (specify) _____

7. Do you add any substances to soften your drinking water? ☐ Yes ☐ No

8. How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years? (If you no longer drink a listed beverage, or your pattern has changed in the last ten years, indicate previous and current amounts. If less than once a day, but at least three times a week, write 1/2.)

| Beverages | Currently | | Previously | |
|---|---|---|---|---|
| | Amount | Years | Amount | Years |
| Whole milk (not skim milk) | | | | |
| Caffeinated coffee | | | | |
| Decaffeinated coffee | | | | |
| Tea | | | | |
| Diet soda or diet iced tea | | | | |
| Non-diet colas | | | | |
| Other non-diet soft drinks | | | | |
| Beer | | | | |
| Wine | | | | |
| Hard liquor | | | | |

## MEDICATIONS AND VITAMINS:

1. How many times in the last month have you used the following and how long have you used them? (If none, write 0; if used only occasionally, write 1/2.)

| Medications and Vitamins | Times | Years |
|---|---|---|
| Aspirin, Bufferin, Anacin | | |
| Tylenol | | |
| Vitamin A | | |
| Vitamin C | | |
| Vitamin E | | |
| Multi-Vitamins | | |
| Blood Pressure pills | | |
| Diuretics (water pills) | | |
| Thyroid medications | | |
| Heart medications | | |
| Anti-Acid medications | | |
| Valium | | |
| Librium | | |
| Prescription sleeping pills | | |
| Tagamet (for ulcers) | | |
| Other: _____ | | |
| _____ | | |

## OCCUPATIONS:

1. What is your current occupation and what are your duties? _____
   _____
   _____ How many years: _____
2. If retired, what was your last occupation? _____
   _____
   _____
   _____ Year retired: _____
3. What other job have you held for the longest period of time? _____
   _____
   _____ How many years: _____
4. What time of day do you start working? _____
   Do you work rotating shifts? ☐ Yes ☐ No
5. How many hours a week do you work on:
   paid jobs _____, volunteer work _____,
   housework _____.
6. In your work or daily life, are (were) you **regularly** exposed to any of the following? If "yes," indicate the number of years exposed.

| Exposure to: | Check One | | Number of Years |
|---|---|---|---|
| | Yes | No | |
| Asbestos | | | |
| Chemicals/Acids/Solvents | | | |
| Coal or Stone Dusts | | | |
| Coal Tar/Pitch/Asphalt | | | |
| Diesel Engine Exhaust | | | |
| Dyes | | | |
| Formaldehyde | | | |
| Gasoline Exhaust | | | |
| Pesticides/Herbicides | | | |
| Textile Fibers/Dusts | | | |
| Wood Dust | | | |
| X-rays/Radioactive Materials | | | |

## REMARKS:

## MISCELLANEOUS:

1. Where were you born? _____ (city) _____ (state/country)
2. Where were your parents born?
   Father: _____
   Mother: _____
3. Religion: ☐ Protestant ☐ Catholic ☐ Jewish
   ☐ LDS ☐ Other _____ ☐ None
   If Protestant, what denomination? _____
4. Education:
   ☐ 8th Grade or Less ☐ Some College
   ☐ Some High School ☐ College Graduate
   ☐ High School Graduate ☐ Graduate School
   ☐ Vocational/Trade School
5. How many years have you lived in your present neighborhood? _____
6. How many friends or relatives do you feel close to? _____
7. How many times a month do you:
   a) Go to church or temple? _____
   b) Attend club meetings? _____
   c) Participate in group activities? _____
8. Were you in the U.S. Armed Services? ☐ Yes ☐ No
   If "yes,"
   a) What branch of the service were you in? _____
      _____
   b) What were your dates of service?
      _____ to _____,
      _____ to _____.
   c) Where did you serve? _____
      _____
9. What is the most upsetting event that happened to you in about the last five years? _____
   _____
   _____ ☐ None
10. Do you now or have you ever used mouthwash? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) How many times a week is it used? _____
    c) For how many years have you used it? _____

| AMERICAN CANCER SOCIETY **CANCER PREVENTION STUDY II** **QUESTIONNAIRE FOR WOMEN**   | Division No. | Unit No. | Group No. |
|---|---|---|---|
| | Researcher No. | Family No. | Person No. |

Date: _____

1. Name: _____
2. Date of birth: Month _____ Year _____
3. How old are you now? _____
4. Current weight with indoor clothing: _____ lbs.
5. Weight 1 year ago: _____ lbs.
6. Height (without shoes): _____ ft. _____ in.
7. ☐ White ☐ Black ☐ Hispanic ☐ Oriental ☐ Other _____ (specify)
8. Marital status: ☐ Single ☐ Separated ☐ Widowed ☐ Married ☐ Divorced
9. If ever married, age at first marriage: _____
10. Number of times married: _____
11. Social Security No.: _____ (optional)

## FAMILY HISTORY (IN RELATION TO CANCER):

1. Fill in the following table as completely as possible for parents, brothers and sisters.

| LIST ONE BLOOD RELATIVE PER LINE: (Circle Brother **or** Sister) | IS THIS PERSON? (Circle One) | IF ALIVE, GIVE AGE | IF DEAD, GIVE AGE AT DEATH | DID THIS PERSON **EVER** HAVE CANCER? (Circle One) | IF "YES," SPECIFY TYPE OF CANCER | AT WHAT AGE? |
|---|---|---|---|---|---|---|
| Father | Alive Dead | | | Yes No | | |
| Mother | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |
| Brother or Sister | Alive Dead | | | Yes No | | |

2. When you were born, a) How old was your mother? _____ b) How old was your father? _____

## HISTORY OF DISEASES:

1. Have you ever had cancer? ☐ Yes ☐ No. If "yes,"
   a) What type? _____
   b) Date of first treatment: _____
2. Place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor:
   - ☐ High Blood Pressure
   - ☐ Heart Disease
   - ☐ Stroke
   - ☐ Diabetes
   - ☐ Gall Stones
   - ☐ Chronic Indigestion
   - ☐ Kidney Disease
   - ☐ Kidney Stones
   - ☐ Bladder Disease
   - ☐ Cirrhosis of the Liver
   - ☐ Tuberculosis
   - ☐ Chronic Bronchitis
   - ☐ Emphysema
   - ☐ Hay Fever
   - ☐ Asthma
   - ☐ Stomach Ulcer
   - ☐ Duodenal Ulcer
   - ☐ Diverticulosis
   - ☐ Rectal Polyps
   - ☐ Colon Polyps
   - ☐ Thyroid Condition
   - ☐ Arthritis
   - ☐ Breast Cysts
   - ☐ Gynecological Problems
   - ☐ Hepatitis
   - ☐ Any other serious disease (specify) _____
3. Have you ever had an operation? ☐ Yes ☐ No
   If "yes," specify type and date(s) of operation(s):
4. How **many** x-ray or fluoroscopic **examinations** (GI series, barium enema, etc.) have you **ever** had of:

| | 0 | 1-5 | 6 or More | | 0 | 1-5 | 6 or More |
|---|---|---|---|---|---|---|---|
| Stomach | ☐ | ☐ | ☐ | Chest | ☐ | ☐ | ☐ |
| Intestine | ☐ | ☐ | ☐ | Breast | ☐ | ☐ | ☐ |
| Back | ☐ | ☐ | ☐ | Head/Neck | ☐ | ☐ | ☐ |

5. Have you ever been **treated** with radium, x-rays, or radioactive isotopes? ☐ Yes ☐ No
   If "yes," when? _____
   For what disease? _____
   What part of your body? _____
6. How many times have you had colds or flu in the past twelve months? _____

## CURRENT PHYSICAL CONDITION:

1. How much exercise do you get (work or play)?
   ☐ None ☐ Slight ☐ Moderate ☐ Heavy
2. On the average, how many hours do you sleep each night?_____
3. On the average, how many times a month do you have insomnia?_____ ☐ None
4. Within the last twelve months, have you noticed:
   a) A lump or thickening in your breast?
   ☐ Yes ☐ No
   b) An unusual discharge from your breast?
   ☐ Yes ☐ No
5. Do you notice pains in your legs when you walk which go away when you rest? ☐ Yes ☐ No
   If "yes," how many years have you had these pains?_____
6. Are you sick at the present time? ☐ Yes ☐ No
   If "yes," with what disease or condition?_____
   _____
   _____

## MENSTRUAL AND REPRODUCTIVE HISTORY:

1. How old were you when menstruation began?____
2. What is your current menopausal status?
   ☐ Still regularly menstruating
   ☐ In menopause ☐ Past menopause
3. During your menstrual history:
   a) Are (were) your periods: ☐ Regular ☐ Irregular
   b) What is (was) the usual number of days of flow?_____
4. **If past menopause:**
   a) Was your menopause: ☐ Natural ☐ Artificial
   b) Age when periods stopped completely?____
   c) Did you have excessive bleeding during menopause? ☐ Yes ☐ No
5. Have you ever had or tried to have children?
   ☐ Yes ☐ No
   If "no," skip to question 9.
6. Have you ever had difficulty becoming pregnant?
   ☐ Yes ☐ No
   If "yes," what was the reason?_____
   _____
   _____
7. How many times have you been pregnant?____
   a) Your age at your first pregnancy?_____
   b) Your age at your first live birth?_____
   c) Number of children born alive?_____
   d) Number of stillbirths (carried 5 months or more)?_____
   e) Number of miscarriages (carried less than 5 months)?_____
8. Were you ever given DES (Diethylstilbestrol) to prevent miscarriage? ☐ Yes ☐ No
   If "yes,"
   a) At what age did you take it?_____
   b) For how many months did you take it?_____
9. Birth control methods: Indicate your age when **first used** and number of years of use.

| Method Used | Age | Years |
|---|---|---|
| Rhythm | | |
| Diaphragm | | |
| Cream/Foam/Jelly | | |
| Tubal Ligation | | |
| Intrauterine Device (IUD) | | |
| Condom (partner) | | |
| Vasectomy (partner) | | |
| NONE OF THE ABOVE ☐ | | |

10. Have you **ever** taken oral contraceptives (birth control pills)? ☐ Yes ☐ No
    If "no," skip to question 11.
    a) Age when you first took them?_____
    b) How many years did you take them?_____
    c) What brand(s) do (did) you take?_____
    _____
    d) If you stopped taking them, what was the reason?_____
    e) Did you have irregular or painful periods when you stopped? ☐ Yes ☐ No
11. Have you **ever** used female hormones (estrogens) other than oral contraceptives? ☐ Yes ☐ No
    a) Why do (did) you take estrogens?
    ☐ Menopausal symptoms ☐ Hysterectomy
    ☐ Bone problems ☐ Cancer
    ☐ Other (specify)_____
    b) Age first took estrogens?_____
    c) For how many years did you take them?_____
    d) How did you take them? ☐ Injection ☐ Cream
    ☐ Pill (brand):_____

## HABITS:

1. **Whether or not you smoke,** on the average, how many **hours a day** are you exposed to cigarette smoke of others:
   At home____, At work____, In other areas____.
2. Do you now or have you ever smoked cigarettes, at least one a day for one year's time? ☐ Yes ☐ No

| Smoking History | Current Smokers | Ex-Smokers |
|---|---|---|
| Number smoked a day | | |
| Age began smoking | | |
| Age quit smoking | | |
| Most recent (last) brand | | |
| Years smoked **this** brand | | |
| Total years smoked **filtered** cigarettes | | |
| Total years smoked **non-filtered** cigarettes | | |
| Total years of smoking (filtered + non-filtered) | | |

3. Current **and** ex-smokers:
   a) Do (did) you inhale? ☐ No, never ☐ Slightly ☐ Moderately ☐ Deeply
   b) Fill in the following information for:
      1) The **first** brand smoked regularly; and
      2) The brand of cigarette smoked for the **longest** period of time.

| Brand Name | Size | Filter | | Menthol | | Number Per Day | Years |
|---|---|---|---|---|---|---|---|
| | | Yes | No | Yes | No | | |
| 1. | | | | | | | |
| 2. | | | | | | | |

## DIET:

1. On the average, how many days per week do you eat the following foods? (If less than once a week, but at least twice a month, write 1/2.)

| | | | |
|---|---|---|---|
| Beef | | Raw vegetables | |
| Pork | | Carrots | |
| Chicken | | Squash/Corn | |
| Liver | | Citrus fruits/Juices | |
| Ham | | Spaghetti/Macaroni/ White rice | |
| Fish | | | |
| Smoked meats | | White bread/Rolls/ Biscuits | |
| Frankfurters/ Sausage | | Brown rice/Whole wheat/Barley | |
| Butter | | Bran/Corn muffins | |
| Margarine | | Potatoes | |
| Cheese | | Oatmeal/Shredded wheat/Bran cereals | |
| Eggs | | | |
| Green leafy vegetables | | Cold (Dry) cereals | |
| Tomatoes | | Ice cream | |
| Cabbage/Broccoli/ Brussels sprouts | | Chocolate | |

2. How many days a week do you eat the following **fried** foods?

| | | | |
|---|---|---|---|
| Fried eggs | | Fried hamburgers or beef | |
| Fried bacon | | | |
| Fried chicken/fish | | Other fried foods | |
| French fries | | | |

   DO NOT EAT FRIED FOODS ☐

3. Do you eat a vegetarian diet? ☐ Yes ☐ No
   If "yes," what type and for how many years? _____

4. Has there been a major change in your diet in the last 10 years? ☐ Yes ☐ No
   If "yes," what was the change? _____

5. a) Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?
   ☐ Yes, currently ☐ Formerly ☐ Never
   b) If **ever** used artificial sweeteners, indicate amount per day and for how long.
   Packets: No. per day _____ Years _____
   Drops: No. per day _____ Years _____
   Tablets: No. per day _____ Years _____

6. Do you get your drinking water from: ☐ City supply ☐ Private well ☐ Other (specify) _____

7. Do you add any substances to soften your drinking water? ☐ Yes ☐ No

8. How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years? (If you no longer drink a listed beverage, or your pattern has changed in the last ten years, indicate previous and current amounts. If less than once a day, but at least three times a week, write 1/2).

| Beverages | Currently | | Previously | |
|---|---|---|---|---|
| | Amount | Years | Amount | Years |
| Whole milk (not skim milk) | | | | |
| Caffeinated coffee | | | | |
| Decaffeinated coffee | | | | |
| Tea | | | | |
| Diet soda or diet iced tea | | | | |
| Non-diet colas | | | | |
| Other non-diet soft drinks | | | | |
| Beer | | | | |
| Wine | | | | |
| Hard liquor | | | | |

## MEDICATIONS AND VITAMINS:

1. How many times in the last month have you used the following and how long have you used them? (If none, write 0; if used only occasionally, write 1/2.)

| Medications and Vitamins | Times | Years |
|---|---|---|
| Aspirin, Bufferin, Anacin | | |
| Tylenol | | |
| Vitamin A | | |
| Vitamin C | | |
| Vitamin E | | |
| Multi-Vitamins | | |
| Blood Pressure pills | | |
| Diuretics (water pills) | | |
| Thyroid medications | | |
| Heart medications | | |
| Anti-Acid medications | | |
| Valium | | |
| Librium | | |
| Prescription sleeping pills | | |
| Tagamet (for ulcers) | | |
| Other: _____ | | |
| _____ | | |

## OCCUPATIONS:

1. What is your current occupation and what are your duties? _____
   _____
   _____ How many years: _____
2. If retired, what was your last occupation? _____
   _____
   _____
   _____ Year retired: _____
3. What other job have you held for the longest period of time? _____
   _____
   _____ How many years: _____
4. What time of day do you start working? _____
   Do you work rotating shifts? ☐ Yes ☐ No
5. How many hours a week do you work on:
   paid jobs _____, volunteer work _____,
   housework _____.
6. In your work or daily life, are (were) you **regularly** exposed to any of the following? If "yes," indicate the number of years exposed.

| Exposure to: | Check One | | Number of Years |
|---|---|---|---|
| | Yes | No | |
| Asbestos | | | |
| Chemicals/Acids/Solvents | | | |
| Coal or Stone Dusts | | | |
| Coal Tar/Pitch/Asphalt | | | |
| Diesel Engine Exhaust | | | |
| Dyes | | | |
| Formaldehyde | | | |
| Gasoline Exhaust | | | |
| Pesticides/Herbicides | | | |
| Textile Fibers/Dusts | | | |
| Wood Dust | | | |
| X-rays/Radioactive Materials | | | |

## REMARKS:

## MISCELLANEOUS:

1. Where were you born? _____ (city) _____ (state/country)
2. Where were your parents born?
   Father: _____
   Mother: _____
3. Religion: ☐ Protestant ☐ Catholic ☐ Jewish
   ☐ LDS ☐ Other _____ ☐ None
   If Protestant, what denomination? _____
4. Education:
   ☐ 8th Grade or Less ☐ Some College
   ☐ Some High School ☐ College Graduate
   ☐ High School Graduate ☐ Graduate School
   ☐ Vocational/Trade School
5. How many years have you lived in your present neighborhood? _____
6. How many friends or relatives do you feel close to? _____
7. How many times a month do you:
   a) Go to church or temple? _____
   b) Attend club meetings? _____
   c) Participate in group activities? _____
8. What is the most upsetting event that happened to you in about the last five years? _____
   _____
   _____ ☐ None
9. How many people do you take care of in your household? (Include yourself) _____
10. Do you now or have you ever used a **permanent** hair dye? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) What color? _____
    c) How often applied? _____
    d) How many years have you used it? _____
11. Do you now or have you ever used mouthwash? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) How many times a week is it used? _____
    c) For how many years have you used it? _____

*ACSS Re-analysis Codebook for RAWDATA*

# ACSS Re-analysis Codebook for RAWDATA

(from CPSII, Poll., Mort. Fail. And Climate)

Observations: 684,296

| Variable Name | Meaning and response codes |
|---|---|
| **Data from CPSII** (Observations: 684,296) | |
| 1) ID | 14-digit, CPS-II ID |
| 2) CANSITE | Site of Cancer (00 - 99, N, U) |
| 3) AGE_INT | Age at Interview |
| 4) RACE | |
| | 1 = White |
| | 2 = White and Hispanic |
| | 3 = Black |
| | 4 = Black and Hispanic |
| | 5 = Hispanic |
| | 6 = Asian |
| | 7 = Other |
| 5) SEX | 1 = Male |
| | 2 = Female |
| 6) EDUCATE | 1 = 8th grade or less |
| | 2 = Some high school |
| | 3 = High school graduate |
| | 4 = Vocational/trade school |
| | 5 = Some college |
| | 6 = College graduate |
| | 7 = Graduate school |
| 7) BMI | Body Mass Index ($Kg/M^2$) |
| 8) ASBESTOS | 1 = Exposed to asbestos |
| | 2 = No. |
| 9) CHEMICAL | 1 = Exposed to chemicals, acids, solvents |
| | 2 = No. |
| 10) COALDUST | 1 = Exposed to coal/stone dust |
| | 2 = No. |
| 11) COALTAR | 1 = Exposed to coal tar, pitch, asphalt |
| | 2 = No. |
| 12) DIESEL | 1 = Exposed to diesel engine exhaust |
| | 2 = No. |
| 13) FORHYDE | 1 = Exposed to formaldehyde |
| | 2 = No. |
| 14) BEERC | Beer, current amount |
| 15) LIQC | Hard liquor, current amount |

*ACSS Re-analysis Codebook for RAWDATA*

| | |
|---|---|
| 16) WINEC | Wine, current amount |
| 17) PSMKHM | Passive smoking at home (hours per day) |
| 18) PSMKWK | Passive smoking at work (hours per day) |
| 19) PSMKOTH | Passive smoking elsewhere (hours per day) |
| 20) SMKSTAT | 1 = Never smoker |
| | 2 = Current cigarette |
| | 3 = Current cig/pipe smoker(Male), Ex-smoker(Female) |
| | 4 = Pipe/cigar smoker only |
| | 5 = Ex-cigarette smoker |
| | 6 = Ex-cig/pipe smoker |
| | 7 = Ex-pipe/cigar smoker only |
| | 8 = Ex-cig smoker, current pipe/cigar smoker |
| 21) SMKCAGE | Age of starting smoking for current cigarette smokers |
| 22) SMKCPD | Number of current cigarette smokers per day |
| 23) SMKCYR | Years of current cigarette smoking |
| 24) SMKCQUIT | Age of quitting smoking for current cigarette smokers |
| 25) XSMKCAGE | Age of starting smoking for former cigarette smokers |
| 26) XSMKCPD | Number of former cigarette smokers per day |
| 27) XSMKCYR | Years of former cigarette smoking |
| 28) FLAGDEL | 0 = No missing data on factors evaluated |
| | 1 = Missing in race |
| | 2 = Missing in smoker or in ex-smoker |
| | 3 = Missing in educate |
| | 4 = Missing in BMI |
| | 5 = Missing in DIV |
| | 6 = Missing in Passive smoking |
| | 7 = Missing in others |
| 29) VS | D = Dead, reported in 1984 |
| | G = Dead, reported in 1986 |
| | K = Dead, reported in 1988 |
| | N = Dead, former lost-to-follow-up 1982 - 1988 |
| | L = Dead, NDI follow-up since 1988 |
| | P = Dead, pending diagnosis |
| | . = Alive, or lost-to follow-up |

***Data from MORT***

| | |
|---|---|
| 30) CODE1 | Code of death (ICD9 - codes) |
| 31) CODETYPE | Death code indicator |
| | 1 = Combined CODE1 with two codes position |
| | 2 = Combined CODE1 with four codes position |
| 32) DEATH_MO | Month of death |
| 33) DEATH_YR | Year of death |

*ACSS Re-analysis Codebook for RAWDATA*

### *Data from FAIL*

| | |
|---|---|
| 34) FAIL | Time on the follow-up in months |

### *Data from POLL*

| | |
|---|---|
| 35) FP | Mean fine particulate |
| 36) FPF | Median fine particulate |
| 37) FPFDEL | 0 = No FPF missing |
| | 1 = FPF missing |
| 38) MEANSULF | Mean sulfates |
| 39) SULFDEL | 0 = No MEANSULF missing |
| | 1 = MEANSULF missing |
| 40) LOGDEN | |
| 41) POVERTY | |
| 42) SO4AST | |
| 43) SO4SA | |
| 44) ST | 2-char, States name |
| 45) NAME | 4-char, Areas name |

***Climate Data*** (observations = 157)

| | |
|---|---|
| 46) TEMPMEAN | Mean temperature |
| 47) TEMPMIN | Minimum temperature |
| 48) TEMPMAX | Maximum temperature |
| 49) DCOLD | Dummy coding for mean temperature |
| | 0 = Greater or equal $50.0^0$ F |
| | 1 = Less than $50.0^0$ F |
| 50) DHOT | Indicator TEMPMEAN |
| | 0 = Equal or less than $60.0^0$ F |
| | 1 = Greater than $60.0^0$ F |

## PART I APPENDICES AVAILABLE ON REQUEST

The following Appendices may be obtained by contacting the Health Effects Institute at 955 Massachusetts Avenue, Cambridge MA 02139, by phone (617-876-6700), fax (617-876-6709), or e-mail (pubs@healtheffects.org). Please give the full title of the Special Report, the Part I title, and the titles of the Appendices you wish to request.

E. Computer Programs and Output Used in the Replication of the Original Analyses of the Harvard Six Cities Study

F. Computer Programs and Output Used in the Replication of the Original Analyses of the American Cancer Society Study

HEALTH EFFECTS INSTITUTE

# Part II: Sensitivity Analyses

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



*Continued*

# ∞ *Errata* ∞

Created 11/01/01

---

## 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

Final version, July 2000
Posted to the HEI Website 10/27/00

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."

# Part II: Sensitivity Analyses

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

## THE HARVARD SIX CITIES STUDY

### QUALITY ASSURANCE AUDIT OF THE DATA FOR THE HARVARD SIX CITIES STUDY

An independent Audit Team (led by Ms Kristin Hoover; see Appendix A to Part I) conducted a detailed audit of all data used in the analyses reported by the Original Investigators (Dockery et al 1993*; referred to as the Part I data quality audit), in addition to auditing the new variables used in the Reanalysis Team's sensitivity analyses. We designed the Part I data quality audit to provide an overview of the databases and an assessment of the data management procedures used by the Original Investigators. The Part I audit also assessed the accuracy of data in the analytic files used in the original analyses relative to the original data from which they had been derived. Our objective in the Part II data quality audit was to evaluate the accuracy of the new variables selected by the Reanalysis Team for inclusion in its sensitivity analyses. For both Parts I and II, we randomly selected 250 subjects whose questionnaires became the basis of the data quality audit. Part I included an additional random sample of 250 death certificates; these were used to audit the nosologic coding of each underlying cause and date of death. We selected a sample size of 250 in order to provide reasonable statistical accuracy for achieving the goals of the data quality audit. Specifically, we selected this sample size to provide almost complete certainty of finding an error as small as 1% (Y Wang et al, unpublished data, 1995), to distinguish between error rates of 1% and 5% with reasonable confidence, and to estimate error rates within about two percentage points of the true value. (Further details are provided in Appendix A of Part I.)

For the Part II data quality audit, we included 17 variables from the initial questionnaires, 5 variables from follow-up questionnaires completed at 3, 6, and 12 years after enrollment into the study (these were not used in the original paper), and 2 variables derived from measurements of pulmonary function conducted at the time of enrollment. In addition, for the 60 subjects selected for the questionnaire audit and who had died during the follow-up period, we audited the underlying cause of death from death certificates obtained by the Original Investigators. The audit also examined the time of subjects' first move outside the original city of residence, on the basis of residence histories that the Reanalysis Team coded; we used these data in our assessment of population mobility in the Six Cities Study.

#### Part II Audit

We audited variables for the Part II analysis by comparing selected variables from the initial questionnaire that had been completed at the time of enrollment, as well as some other selected variables from the follow-up questionnaires, to the data in the electronic analysis file provided to the Reanalysis Team. We evaluated underlying causes of death using death certificates obtained by the Original Investigators for 60 subjects known to have died out of the 250 subjects in the random sample of audited questionnaires. We found no errors in variables for bronchial asthma, city of residence, date of birth, amount of wine/liquor consumed, marital status, race, or underlying cause of death. Variables in which we detected errors include occupation code from census, industry code, number of years living in same town, chest illness, alcohol consumption (multiple variables), age started smoking, number of packs of cigarettes smoked per week, number of years of smoking cigarettes, and heart trouble or high blood pressure.

Table 1 summarizes the variables in error (in alphabetical order by SAS variable name [SAS Institute, Cary NC] from the analysis file), and includes comments about these errors. (A more detailed presentation is in Appendix A,

* The original article appears in its 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 (Introduction, Summary, Part I, and Part II), a Commentary by the Institute's Health Review Committee, and the Original Publications and Comments on the Reanalysis by the Original Investigators. Correspondence concerning *Part II: Sensitivity Analyses* 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.

Although this document was produced with partial funding by the United States Environmental Protection 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.

**Table 1.** Findings from the Phase II Audit of the Initial Study Questionnaires[a] from the Six Cities Study

| SAS Variable Name from the Analysis File | Description of Variable | Number (and %) of Errors Found in 249 Questionnaires | Number (and %) of Errors Found in 89 Questionnaires by Original Investigators' Internal Audit (1981) | Type of Error Noted in Phase II Audit |
|---|---|---|---|---|
| AGECIG | Age started smoking: 0 = nonsmokers; ages 1–75 allowed by coding | 1 (0.4) | 0 (0.0) | Apparent coding error |
| BEER | Beer: 0 = none; 1 = < 200 oz/wk; 2 = > 200 oz/wk | 2 (0.8) | 1 (1.1) | Apparent coding errors |
| CHSTIL1 | Chest illness diagnosed by doctor: 0 = no for bronchitis, emphysema, or pneumonia; 1 = yes for bronchitis; 2 = yes for emphysema; 4 = yes for pneumonia; higher numbers for subjects diagnosed with two or more diseases | 4 (1.6) | 3 (3.4) HSPH's audit concluded that error rate for this variable had not resulted from any systematic problem, so no recoding had been done. | Apparent coding errors |
| CIGWK | Number of packs of cigarettes smoked per week (20 cigarettes/pack) | 3 (1.2) | 3 (3.4) | Apparent coding errors |
| DRINK | Present use of alcoholic beverages: 0 = no; 1 = yes; part B asks if use is as often as 1 day/wk, for which 0 = no, 1 = yes, 2 = sum of both yes scores | 1 (0.4) | 0 (0.0) | Apparent coding error |
| HBP | Heart/blood pressure trouble: Has doctor ever diagnosed high blood pressure or heart problems? If yes, has this been treated in the last ten years? Scores could total as high as 8 | 4 (1.6) | 0 (0.0) | Apparent coding errors |
| IND | Industry code | 5 (2.0) | 11 (12.4) HSPH's audit stated that retired, disabled, and unemployed subjects could not be distinguished, which resulted in many errors in interpretation. Other common errors: Working wives were often coded as housewives without reference to outside employment; unjustified assumptions were made about jobs when no information was available as to specific duties. Documents show efforts to correct errors. | Discussed in detail in Appendix A[b] |
| OCC | Occupation code (documents show that this variable was later superceded by another code) | 5 (2.0) | 21 (23.6) Documents show efforts to correct errors. | Discussed in detail in Appendix A |
| YRSCIG | Total years smoked cigarettes | 2 (0.8) | 0 (0.0) | Apparent coding errors |
| YRSHERE1 | Number of years resident in this town | 5 (2.0) | 7 (7.9) Audit noted that consistent coding rules had not been carefully followed, and that years in military service should have been subtracted. Years in same city were counted even if not continuous. | Discussed in detail in Appendix A |

[a] A total of 249 baseline questionnaires were available to audit the variables listed in this table. In addition, the Audit Team was able to extract information from follow-up questionnaires to confirm variables for marital status, race, city of residence, and date of birth.

[b] Appendix A is available on request from the Health Effects Institute.

which is available on request from the Health Effects Institute.) We audited five variables not included in the Original Investigators' published paper from follow-up questionnaires that had been completed 3 and 6 years after enrollment. These variables included height, weight, smoking history, number of years of cigarette smoking, and number of packs of cigarettes smoked per week. Audit of the analysis file for the height (HT) variable from the 3-year follow-up questionnaire revealed three errors in 249 questionnaires examined (1.2% error rate). For two subjects the height data for years 3 and 6 had been switched, which also caused an error in year 6 (0.8% error rate). The third had an incorrect entry for the year 3 questionnaire. One rounding error was noted in year 6 data when we audited the weight (WT) variable for the 3- and 6-year follow-up intervals, producing an error rate for year 6 of 0.4% (1/250). We observed no errors at the 3-year follow-up interval for any of the smoking variables (smoking status [SMOK], number of packs of cigarettes smoked per week [CIGWK], and number of years of cigarette smoking [YRSCIG]). There were no errors in SMOK at the 6-year follow up. We noted one rounding error in year 6 for YRSCIG, which resulted in an error rate of 0.4% (1/250), and there was one incorrect entry (0.4%; 1/250) in CIGWK at the 6-year follow up.

We audited three variables (HT, WT, CIGWK) from the last follow-up questionnaire, which had been completed 12 years after subjects had been enrolled in the study. A total of 247 questionnaires were available for year 12 (3 missing); we observed no errors in any of the variables with the possible exception of one case in which the entries for height and weight appeared to have been reversed on the questionnaire.

### Summary of Audit Findings

The Audit Team found no errors in these data that would induce important effects in the statistical analyses (ie, errors in excess of 5%; the highest error rate was 2.4%). Coding of residential histories was done by subcontractors to the Reanalysis Team; the error rate in the coded variables for the date subjects first moved outside the original city of residence was 3.6%. Five of the nine observed discrepancies involved an error of 1 calendar year in the date of the first move. Although this error rate was somewhat higher than those for the original studies, it was still less than 5%. We thus concluded that the data were of sufficient quality for the purposes of the Part II sensitivity analyses.

## ALTERNATIVE RISK MODELS

### The Six Cities Study Original Investigators' Analytic Approach

Using Cox proportional-hazards regression models of survival, the Original Investigators (Dockery et al 1993) had examined the association between mortality in the Six Cities Study cohort and ambient air quality, as indexed by fine particles ($PM_{2.5}$)*, sulfate ($SO_4^{2-}$), total suspended particles (TSP), nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), ozone ($O_3$), and aerosol acidity ($H^+$). Positive associations were observed with all measures of air pollution except ozone, and fine particles displayed the strongest association with mortality of all the measures examined; consequently, the Original Investigators had focused their analysis on this pollutant. In our reanalysis, we also focused on this pollutant in order to examine the robustness of this association when specifying models with different determinants of mortality and when applying different statistical approaches.

An assumption of the Six Cities Study Original Investigators' survival model had been that the relative increase in the underlying hazard function, or instantaneous rate of death, was constant over the entire follow-up period and was modulated by a number of risk factors for mortality such as smoking habits, education, and air pollution. The time axis for this survival analysis had been calendar year (1974 through 1989).

Effects of gender and age at enrollment in the study had been accounted for in the analysis by stratifying the baseline hazard function according to different categories of the covariates; age had been stratified on the basis of 5-year age groups. Because over 95% of the cohort was white, only whites had been included in the original analysis. The mortality risk factors that had been considered in the Original Model used by the Original Investigators of the Six Cities Study are listed in Table 2.

In addition to overall mortality, the mortality rate ratios had also been examined by the Original Investigators for the following underlying causes as defined in the *International Classification of Diseases, Ninth Edition* (ICD-9; World Health Organization 1975): cardiopulmonary diseases (ICD-9 codes 400–440, 485–496), lung cancer (ICD-9 code 162), and all other causes excluding cardiopulmonary disease and lung cancer. The Original Investigators used "mortality rate ratios" (Dockery et al 1993) and "mortality risk ratios" (Pope et al 1995) to describe the association between air pollution and mortality. Both

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

**Table 2.** Covariates Included in the Original, Full, and Extended Models for the Reanalysis of the Six Cities Study[a]

| Covariate | Alternative Risk Model | | |
|---|---|---|---|
| | Original | Full | Extended |
| Tobacco consumption | | | |
| Current-smoker[b] | ✓ | ✓ | ✓ |
| Current-smoker years of smoking | | ✓ | ✓ |
| (Current-smoker years of smoking)$^2$ | | ✓ | |
| Current-smoker cigarettes per day | | ✓ | ✓ |
| (Current-smoker cigarettes per day)$^2$ | | ✓ | |
| Current-smoker pack-years | ✓ | | |
| Former-smoker[b] | ✓ | ✓ | ✓ |
| Former-smoker pack-years | ✓ | ✓ | ✓ |
| (Former-smoker pack-years)$^2$ | | ✓ | |
| Age started smoking (current-smokers) ≤ 18 years[b] | | ✓ | ✓ |
| Age started smoking (current-smokers) > 18 years[b] | | ✓ | ✓ |
| Education level | | | |
| High school versus less than high school[b] | | ✓ | ✓ |
| More than high school versus less than high school[b] | | ✓ | ✓ |
| Less than high school versus high school or more than high school[b] | ✓ | | |
| Exposure to dust or fumes[b] | ✓ | ✓ | ✓ |
| Body mass index | ✓ | ✓ | ✓ |
| (Body mass index)$^2$ | | ✓ | ✓ |
| Marital status | | | |
| Married versus single[b] | | ✓ | ✓ |
| Separated versus single[b] | | ✓ | ✓ |
| Widowed versus single[b] | | ✓ | ✓ |
| Alcohol consumption | | | |
| Beer consumption [b] | | ✓ | ✓ |
| Wine consumption[b] | | ✓ | ✓ |
| Liquor consumption[b] | | ✓ | ✓ |
| Interaction with gender | | | |
| Current-smoker[b] | | ✓ | |
| Current-smoker years of smoking | | ✓ | |
| (Current-smoker years of smoking)$^2$ | | ✓ | |
| Current-smoker cigarettes per day | | ✓ | |
| (Current-smoker cigarettes per day)$^2$ | | ✓ | |
| Current-smoker pack-years | ✓ | | |
| Former-smoker[b] | | ✓ | |
| Former-smoker pack-years | | ✓ | |
| (Former-smoker pack-years)$^2$ | | ✓ | |
| Age started smoking (current-smokers) ≤ 18 years[b] | | ✓ | |
| Age started smoking (current-smokers) > 18 years[b] | | ✓ | |
| High school versus less than high school[b] | | ✓ | |
| More than high school versus less than high school[b] | | ✓ | |

*(Table continues next page)*

[a] All three of these models were analyzed with standard Cox proportional-hazards regressions.

[b] Dichotomous (yes/no) variable.

**Table 2 *(continued)*.** Covariates Included in the Original, Full, and Extended Models for the Reanalysis of the Six Cities Study[a]

| Covariate | Alternative Risk Model | | |
|---|---|---|---|
| | Original | Full | Extended |
| Interaction with gender (*continued*) | | | |
| Occupational exposure to dust or fumes[b] | | | |
| Body mass index | | ✓ | |
| (Body mass index)$^2$ | | ✓ | |
| Married versus single[b] | | ✓ | ✓ |
| Separated versus single[b] | | ✓ | ✓ |
| Widowed versus single[b] | | ✓ | ✓ |
| Beer consumption[b] | | ✓ | ✓ |
| Wine consumption[b] | | ✓ | ✓ |
| Liquor consumption[b] | | ✓ | ✓ |

[a] All three of these models were analyzed with standard Cox proportional-hazards regressions.

[b] Dichotomous (yes/no) variable.

terms refer to the ratio of the mortality rate at a higher level of air pollution relative to the mortality rate at some lower level. (Under the proportional hazards assumption made by the Original Investigators, this ratio is constant over time.) The Original Investigators found it convenient to use the pollution levels in the cities with the highest and lowest ambient air pollution levels as the basis for calculating the ratio of mortality rates. Unless otherwise specified, we follow this practice and use the term relative risk to denote the mortality risk ratio.

Note the relative risk can be calculated using the data from only two cities with the highest and lowest pollution levels, or by fitting an exposure-response model to the data for all cities together, and then evaluating the relative risk at the average pollution levels observed in the most-polluted and least-polluted cities. In most cases, relative risks reported by the Reanalysis Team are based on fitted exposure-response models.

Estimates of the log–relative risks had been obtained by maximizing the partial likelihood function of the Cox proportional-hazards model. Confidence intervals (95%) for the log–relative risks had been calculated under the assumption that they were normally distributed; that is, by adding and subtracting 1.96 times the standard error of the estimated regression coefficient.

### The Reanalysis Team's Analytic Approach

The Reanalysis Team considered a number of alternative risk models that included additional covariates not examined in the original analysis; we also considered different functional forms or categorizations of original covariates, and 1-year age groups to stratify the baseline hazard function.

In our reanalysis, the Team also used age as the time axis, with age at enrollment into the study and age at event (death or censoring) modeled with respect to air pollution and other determinants of mortality. This approach has been shown to more fully capture the effects of age on survival than does using calendar year as the time axis (Breslow and Day 1987).

The Reanalysis Team initially considered a Base Model (with stratification by age and gender) that included air pollution with no additional determinants of mortality. We also included several additional covariates in a new regression model (the Full Model, Table 2). The Team included quadratic terms of a number of continuous variables that might have nonlinear effects, such as number of packs of cigarettes smoked, years of smoking, and body mass index (BMI); we also included other variables, not considered by the Original Investigators, that accounted for age at which smoking started and marital status. Because we wished to examine the effects of educational attainment in more detail, we considered three levels of attained education (less than high school, high school, and more than high school). The Team took into account the possibility that the effects of these risk factors could vary by gender by including an interaction term for each of these factors.

We then developed a more parsimonious model by removing those variables that did not significantly improve the goodness of fit. In particular, we dropped any

covariate from the Full Model if the *P* value derived from an increase in the log-likelihood function when we removed the covariate was greater than 0.05 (ie, likelihood ratio test). We continued this procedure until there was no further statistical justification for removing any other covariate. Regardless of the results of the likelihood ratio test, we retained a covariate when the corresponding gender interaction was statistically significant (Wald test $P < 0.05$). The parsimonious model derived in this way for all-cause mortality is referred to as the Extended Model. The Team also used this set of covariates to model mortality for cardiovascular disease (ICD-9 codes 400–459), respiratory disease (ICD-9 codes 460–519), lung cancer (ICD-9 code 162), other types of cancer excluding lung (ICD-9 codes 140–161, 163–239), and all remaining causes.

We also examined indicators of pulmonary function, forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$), that the Original Investigators had obtained but had not included in their original analysis. We considered only pulmonary function data obtained at the time of enrollment because follow-up tests that had been conducted during the course of the study were judged to be a new analysis and thus outside the terms of reference of the reanalysis. We incorporated these variables by first carrying out a regression of the natural logarithm against the logarithms of height and age, thereby obtaining predicted pulmonary function values specific to the height and age of each individual in the study. We then included the residuals (observed minus predicted logarithmic pulmonary function volumes) from these models as determinants of mortality in the Cox proportional-hazards regression models.

**Testing the Cox Proportional-Hazards Assumption**

The validity of the Cox proportional-hazards assumption was evaluated in all models using test statistics provided in the statistical computing software S-PLUS (Grambsch and Therneau 1994). This test examines departures from the Cox proportional-hazards assumption in a linear manner. (Nonlinear departures from proportionality are examined in the Flexible Modeling section.) Although we found no statistical evidence of departures from the Cox proportional-hazards assumption in any model we examined ($P > 0.2$) using either calendar year or age as the time axis, the relative risk of mortality for fine particles varied slightly from a linear association that is consistent with the assumption of proportional hazards with both calendar year and age (Figure 1).

Relative risks of mortality associated with an increase in ambient fine particles are shown in Table 3 according to model specification (Base, Original, Full, and Extended), time axis used in the Cox model (calendar year or age), and cause of death (all causes, cardiopulmonary disease, cardiovascular disease, respiratory disease, lung cancer, other cancers, and other causes). The relative risks provided in Table 3 were scaled to estimate relative risks across the range of distribution levels of $PM_{2.5}$ (18.6 $\mu g/m^3$), the benchmark used by the Original Investigators.

Adjusting covariates using either time axis (age or calendar year) reduced the relative risk for each underlying cause of death, except for other cancers, for which a small increase was observed using the Full and Extended Models. We found that the relative risks in all three alternative risk models (Original, Full, and Extended) were similar.

The Reanalysis Team found that relative risk of mortality associated with an increase in fine particles had the following ranking among the underlying causes of death: lung cancer > cardiovascular disease > cardiopulmonary disease > all causes > other causes > other cancers > respiratory disease. Formal statistical significance ($P < 0.05$) was achieved for all causes and for cardiovascular and cardiopulmonary disease, in part because of the greater number of deaths in these categories than in other disease groupings. [The relative risk associated with fine particles was slightly higher if the underlying cause of death was restricted to ischemic heart disease (ICD-9 codes 410–414), with relative risk of 1.43 (95% CI: 1.06–1.92), based on the Extended Model and calendar year as the time axis (data not shown).] This result suggests that particulate air pollution may be affecting people with heart diseases more than it affects those with vascular problems.

The Reanalysis Team examined the effect of health status at enrollment on the association between mortality and fine particle air pollution by including adjusted FVC or $FEV_1$ as a covariate in the Extended Model using calendar year as the time axis for all causes of death. Both FVC and $FEV_1$ were strong predictors of mortality. A reduction in FVC corresponding to a change in the ratio of FVC to its adjusted value from 1 to 0.85 (representing a clinically significant reduction) resulted in a relative risk of death of 1.33 (95% CI: 1.28–1.39). The corresponding relative risk of a similar decrease in $FEV_1$ was 1.22 (95% CI: 1.18–1.25). However, the effect of fine particles on mortality was not appreciably altered by adjustment for $FEV_1$; RR = 1.27 (95% CI: 1.09–1.49) as compared with RR = 1.26 (95% CI: 1.08–1.47) prior to adjustment. Adjustment for FVC also did not influence the effect of fine particles on mortality (RR = 1.19, 95% CI: 1.11–1.52).

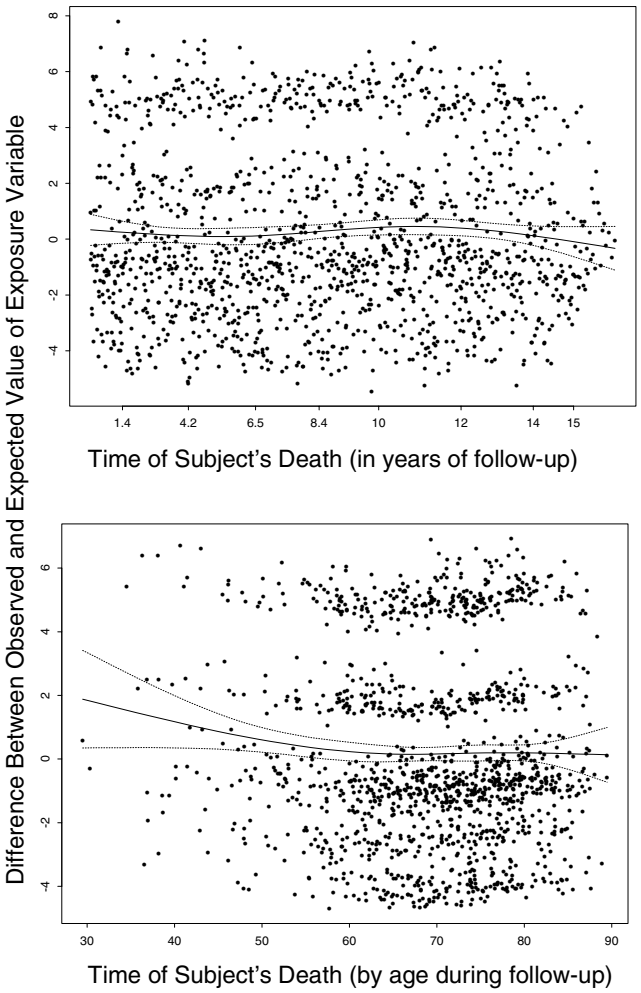



**Figure 1. Proportional-hazards model assumptions for two time axes in the Six Cities Study.** Log–relative risks due to each failure time (or time of death) [$\beta(t)$] for fine particles are plotted; relative risk estimates are based on the Extended Model. The y axis in both panels represents the difference between the observed value of the exposure variable for the person who died and the value expected on the basis of the fitted model. Panel A: Time of subject's death on the basis of years of follow-up. Panel B: Time of subject's death on the basis of age. Spline function smoothing of the association between log–relative risk and the time axis is shown by the solid line; the 95% confidence interval is shown by the dashed lines.

## IDENTIFICATION OF SENSITIVE SUBGROUPS

Ambient air pollution, as indexed by fine particles, was associated positively with mortality from all underlying causes of death. To explore this finding in greater depth, the Reanalysis Team examined the association between particles and mortality within a number of cohort subgroups in order to identify those that may be more or less susceptible to the effects of ambient air pollution.

The relative risks for all-cause mortality associated with an increase in $PM_{2.5}$ of 18.6 $\mu g/m^3$ are shown in Table 4 for selected personal characteristics. We derived these estimates using the Extended Model with calendar year as the time axis and stratifying the baseline hazard function by 1-year age groups and gender. The relative risk of death associated with exposure to fine particles decreased with educational attainment and age; and it was higher in those people who reported workplace exposure to dust or fumes, less for married persons, greater for males than for females, greater for those subjects with self-reported heart or lung disease at time of enrollment, and greater for those individuals with compromised lung function. However, none of these interactions with air pollution achieved statistical significance ($P > 0.2$, likelihood ratio test). Fine particle association with mortality was insensitive to smoking status.

The Reanalysis Team also examined the influence of each of the six cities on the relative risk from fine particles by individually excluding each city from the analysis (see Table 4). The relative risks varied little after exclusion of any single community, with a range of 1.26 (excluding Portage) to 1.31 (excluding Steubenville). We note, however, that the 95% confidence interval (CI) in the relative risk included unity when Steubenville was omitted from the analysis. The associated relative risk of 1.31 was the highest among all cities in this influence analysis, indicating that the residents of Steubenville were dying at a lower rate than would be predicted by their air pollution exposure. However, exclusion of Steubenville also reduced the range in city-specific average $PM_{2.5}$ levels from 18.6 $\mu g/m^3$ to 9.8 $\mu g/m^3$, thereby increasing the standard error of the log–relative risk estimate and in turn widening the confidence interval.

Because the attained level of education appeared to have the strongest effect on the fine particle–mortality association, we examined the modifying effect of education in relation to the effect of other personal characteristics. Specifically, Table 5 shows the relative risk of all-cause mortality associated with increases in $PM_{2.5}$ of 18.6 $\mu g/m^3$, stratified on selected personal characteristics and educational attainment (high school or less, more than high school). These estimates are adjusted for all covariates included in the Extended Model.

The relative risk of mortality associated with fine particles was greater among individuals with high school education or less, compared to those with more than high school education in all subgroups examined except the "Other" marital status group; the relatively few subjects (517) in this group led to unstable estimates of risk (95% CI: 0.63–5.61). In the case of subjects under 40 years of age with more than high school education, the relative risk was higher (3.80) th9an for subjects with less education (1.54); however, there was considerable uncertainty in

**Table 3**. 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 for a description of models and Table 2 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.

**Table 4.** Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles for Selected Personal Characteristics in the Six Cities Study[a]

| Characteristic | Percentage of Cohort | All-Cause Mortality |
|---|---|---|
| **Age at Enrollment** | | |
| ≤ 40 | 27.4 | 2.11 (0.88–5.07) |
| 41–55 | 35.0 | 1.66 (1.17–2.35) |
| > 55 | 37.6 | 1.17 (0.98–1.40) |
| **Gender** | | |
| Male | 45 | 1.33 (1.08–1.63) |
| Female | 55 | 1.20 (0.94–1.53) |
| **Smoking Status** | | |
| Never-smoker | 40 | 1.36 (1.02–1.82) |
| Former-smoker | 24 | 1.29 (0.97–1.72) |
| Current-smoker | 36 | 1.35 (1.04–1.74) |
| **Education Level** | | |
| Less than high school | 28 | 1.45 (1.13–1.85) |
| High school | 38 | 1.30 (0.98–1.73) |
| More than high school | 34 | 0.98 (0.72–1.36) |
| **Occupational Exposure to Dust or Fumes[b]** | | |
| Yes | 45 | 1.39 (1.13–1.72) |
| No | 55 | 1.17 (0.92–1.50) |
| **Marital Status** | | |
| Married | 81 | 1.29 (1.08–1.54) |
| Other | 19 | 1.42 (1.02–1.98) |
| **Heart or Lung Disease[c]** | | |
| Yes | 34 | 1.32 (1.06–1.63) |
| No | 66 | 1.24 (0.99–1.57) |
| **$FEV_1$[d]** | | |
| High | 83 | 1.24 (1.03–1.49) |
| Low | 17 | 1.35 (1.00–1.84) |
| **FVC[d]** | | |
| High | 85 | 1.28 (1.07–1.54) |
| Low | 15 | 1.44 (1.02–2.02) |
| **Community Influence[e]** | | |
| Not Harriman | 85 | 1.28 (1.10–1.50) |
| Not Portage | 80 | 1.26 (1.05–1.52) |
| Not Steubenville | 83 | 1.31 (0.96–1.79) |
| Not St Louis | 84 | 1.28 (1.10–1.50) |
| Not Topeka | 85 | 1.28 (1.09–1.51) |
| Not Watertown | 84 | 1.30 (1.11–1.53) |

[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 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups and gender. See Table 2 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[b] Self-reported.

[c] Defined as doctor-diagnosed high blood pressure, heart disease, chronic bronchitis, emphysema, or asthma.

[d] High pulmonary function measure > 85% of predicted value based on subject's height and age. Low pulmonary function measure ≤ 85% of predicted value based on subject's height and age.

[e] Analysis dataset did not specify city.

**Table 5.** Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles for Selected Personal Characteristics and Education Level in the Six Cities Study[a]

| | High School or Less | | More Than High School | |
|---|---|---|---|---|
| Characteristic | *n* | All-Cause Mortality | *n* | All-Cause Mortality |
| **Age at Enrollment** | | | | |
| ≤ 40 | 1,189 | 2.42 (0.88–6.61) | 1,035 | 0.87 (0.07–11.54) |
| 41–55 | 1,895 | 1.70 (1.10–2.62) | 942 | 1.30 (0.70–2.41) |
| > 55 | 2,273 | 1.32 (1.08–1.62) | 777 | 0.86 (0.58–1.27) |
| **Gender** | | | | |
| Male | 2,330 | 1.48 (1.16–1.87) | 1,341 | 1.07 (0.70–1.63) |
| Female | 3,027 | 1.29 (0.97–1.70) | 1,413 | 0.81 (0.49–1.36) |
| **Smoking Status** | | | | |
| Never-smoker | 2,099 | 1.65 (1.17–2.33) | 1,174 | 0.88 (0.49–1.60) |
| Former-smoker | 1,250 | 1.38 (0.99–1.94) | 687 | 1.06 (0.54–2.09) |
| Current-smoker | 2,008 | 1.38 (1.03–1.85) | 893 | 1.02 (0.55–1.90) |
| **Occupational Exposure to Dust or Fumes[b]** | | | | |
| Yes | 2,722 | 1.49 (1.18–1.88) | 923 | 1.11 (0.64–1.93) |
| No | 2,635 | 1.31 (0.97–1.77) | 1,831 | 0.88 (0.56–1.39) |
| **Marital Status** | | | | |
| Married | 4,336 | 1.42 (1.15–1.75) | 2,237 | 0.96 (0.67–1.37) |
| Other | 1,021 | 1.30 (0.89–1.90) | 517 | 1.88 (0.63–5.61) |
| **Heart or Lung Disease[c]** | | | | |
| Yes | 1,940 | 1.48 (1.16–1.89) | 828 | 0.95 (0.58–1.55) |
| No | 3,417 | 1.28 (0.97–1.69) | 1,926 | 1.17 (0.74–1.87) |
| **$FEV_1$[d]** | | | | |
| High | 4,361 | 1.34 (1.08–1.68) | 2,398 | 0.95 (0.65–1.40) |
| Low | 996 | 1.37 (0.97–1.94) | 356 | 0.68 (0.25–1.86) |
| **FVC[d]** | | | | |
| High | 4,491 | 1.42 (1.15–1.76) | 2,414 | 0.89 (0.61–1.31) |
| Low | 866 | 1.45 (0.98–2.15) | 340 | 1.21 (0.49–3.04) |

[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 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups and gender. See Table 2 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[b] Self-reported.

[c] Defined as doctor-diagnosed high blood pressure, heart disease, chronic bronchitis, emphysema, or asthma.

[d] High pulmonary function measure > 85% of predicted value based on subject's height and age. Low pulmonary function measure ≤ 85% of predicted value based on subject's height and age.

the estimate of relative risk of the more educated group (95% CI: 0.94–15.35). None of the relative risks in the group with more than high school was statistically significantly different from unity ($P > 0.05$).

## OCCUPATIONAL EXPOSURES

Occupational exposure to dusts, fumes, carcinogens, and other toxic substances is an important potential confounder in both of the studies under review because it is plausible that individuals who live in areas of high pollution tend, on average, to work in more polluted workplaces than subjects who live in clean areas. It is also plausible that subjects who work in polluted workplaces suffer higher risks of disease than subjects who work in clean workplaces. Indeed, there is extensive evidence that several workplace exposures (eg, asbestos, chromium) can cause lung cancer in workers (Siemiatycki et al 1991). (Credible estimates of the general population's attributable risk of lung cancer due to occupational exposures in industrialized countries are on the order of 10%.) There is also evidence that some workplace exposures can lead to nonmalignant respiratory disease (Christiani and Wegman 1995). For cardiovascular disease, however, although there are hints that a few workplace exposures may be risk factors, the evidence is weak and the attributable risk would be small. If there is an effect due to air pollution on any of these diseases, it is plausible that the effect differs depending on whether the subject has had significant occupational exposure to harmful substances in the workplace.

In both the Six Cities Study and the American Cancer Society (ACS) Study, some information was collected on the subjects' occupations and on their opinion as to whether they had been exposed to dusts and fumes in the workplace. This information had been used by the Original Investigators in their analyses to control for possible confounding by occupation. However, it is known that self-reported exposure to workplace substances is an inadequate indicator of exposure. Consequently, it is not clear that the self-reports of dusts and fumes and the simple white collar/blue collar variable created by the Original Investigators provided effective control for occupational confounders. The Reanalysis Team decided a more detailed assessment of the potential for confounding of the relation between particulate air pollution and mortality would be informative. The occupational data that were available in coded form were very limited. For the Six Cities Study, only the occupation and industry as recorded at the baseline interview were available.

Considering the type of data available and the nature of the diseases at issue, we developed a strategy to create two new variables that could be used to improve the control for possible confounding by workplace exposures. The first is a variable that we refer to as a "dirtiness index"; it describes, on a semiquantitative scale, the degree of dusts, gases, and fumes present in a subject's occupational environment. Conceptually, this is somewhat the same as assigning subjects to either white- or blue-collar worker categories. The dirtiness index plays a role similar to the "self-reported exposure to dusts, gases, and fumes" that had been used by the Original Investigators. We believe that the dirtiness index affords better control for general occupational exposures than either the self-reports by study subjects of exposure to dusts and fumes, or the Original Investigators' translation of job codes into a blue-collar/white-collar index. The lung carcinogen index was designed to indicate whether the subject's particular occupation would be considered to constitute an excess risk of lung cancer.

### Occupational Exposure Indices

A research group within the Reanalysis Team that has had extensive and long-standing experience in assessing occupational exposure in the context of community-based studies (Gérin et al 1985; Siemiatycki et al 1991) oversaw the creation of new exposure indices. The development of these new indices of occupational exposure is described in detail in Appendix B (which is available from the Health Effects Institute upon request).

Briefly, the two new variables were based on the occupational/industrial coding systems that the Original Investigators had used, supplemented by additional information. In the case of the dirtiness index, the additional information came from work conducted in Montréal in the context of a large community-based cancer case-control study (Siemiatycki et al 1991). A dirtiness index had been developed and used in the Montréal study, and we adapted it to both the ACS Study and the Six Cities Study. For each of the 442 occupation codes in the 1970 US Census Classification system used to classify jobs in the Six Cities Study, we used the same criteria that had been used earlier in Montréal. With the resulting correspondences between job codes and dirtiness scores, the Reanalysis Team was able to attribute a measure of occupational dirtiness to each individual in the two studies. This index ranged from 0 (a very clean occupational environment) to 6 (a very dirty workplace environment).

In the case of the lung carcinogen indicator, the additional information came from lists of carcinogens evaluated by the International Agency for Research on Cancer (IARC), summarized by Boffetta and colleagues (1995), and by Ahrens and Merletti (1998).

### Adjustment for Occupational Exposures

After calculating a dirtiness index score for job codes and assigning a binary variable for occupations with exposure to lung carcinogens (new occupational exposure indices; see Appendix B), we fit Cox proportional-hazards models identical to those that had been used by the Original Investigators, but with one or both of the new occupational covariates included in the models. We also carried out some analyses using the dirtiness index as a stratification variable to assess effect modification. We conducted all the analyses using calendar year as the time axis, as the Original Investigators had done, and we repeated them using age as the time axis. Because the resulting two sets of relative risks were virtually identical, we will present only the results using calendar time here.

### Results

As shown in Appendix B, nearly 40% of all subjects were in the lowest (ie, cleanest) of the seven occupational dirtiness categories. The following population subgroups had much higher dirtiness levels than their respective complementary subgroups (see Table 6): males, subjects with less than high school education, and subjects who self-reported that they had exposure to dusts and fumes. Ever-smokers had slightly higher occupational dirtiness scores than never-smokers. Most importantly, subjects in Topeka and Watertown (among the least-polluted towns) had somewhat lower occupational dirtiness scores than subjects from other towns, and subjects in Steubenville were most likely to have jobs with high dirtiness scores. The percentage of subjects who worked in an occupation that has been shown or suspected to constitute an elevated risk of lung cancer was 7.5%. The patterns by gender, education, and smoking status for the indicator of occupational exposure to lung carcinogens were similar to those patterns observed for the dirtiness index. There was some variability by town of residence, but it was not clearly associated with the town's respective pollution level. There was some indication that cardiopulmonary disease and lung cancer were elevated in subjects who had higher dirtiness indices. Subjects who had ever been occupationally exposed to known lung carcinogens did not exhibit an elevated risk of lung cancer.

Table 7 shows estimates of the overall fine particle–mortality associations when different sets of covariates are included as confounders. In our reanalysis, neither the dirtiness index, in two different parameterizations, nor the lung carcinogen variable had any impact on the estimates of interest for all-cause mortality and cardiopulmonary disease mortality. For lung cancer mortality, the magnitude of the relative risk estimates was considerably reduced once the occupational confounders were included. Table 8 shows the relative risks of all-cause mortality, cardiopulmonary disease mortality, and lung cancer mortality due to air pollution among different subsets of the population. In contrast to the original analyses, in our statistical models we included the dirtiness index (as a categorical variable) for all three causes of death; in addition, for lung cancer mortality, we included the binary lung carcinogen variable. Cardiopulmonary mortality relative risks were distributed equally among males and females when all subjects were considered, and more heavily among never-smokers than ever-smokers. The lung cancer results were very unstable; there was an indication of greater effect of air pollution among males, especially among never-smokers, although deaths from lung cancer among the latter constituted a very small number of events.

**Table 6.** Occupational Dirtiness Scores and Prevalence of Occupational Exposure to Known Lung Carcinogens in the Harvard Six Cities Study

| Characteristic | Mean Dirtiness Score[a] | Prevalence of Exposure to Lung Carcinogens (%) |
|---|---|---|
| All subjects | 2.10 | 7.53 |
| Air pollution by city | | |
| Harriman | 2.40 | 7.04 |
| Portage | 2.31 | 8.94 |
| Steubenville | 2.24 | 6.77 |
| St Louis | 2.31 | 9.27 |
| Topeka | 1.40 | 6.55 |
| Watertown | 1.85 | 6.13 |
| Education level | | |
| Less than high school | 1.25 | 3.09 |
| High school | 2.10 | 8.46 |
| More than high school | 3.17 | 11.87 |
| Occupational exposure to dust or fumes[b] | | |
| Yes | 2.85 | 10.17 |
| No | 1.46 | 5.31 |
| Gender | | |
| Female | 1.72 | 5.49 |
| Male | 2.53 | 9.86 |
| Smoker | | |
| Never-smoker | 1.90 | 7.96 |
| Ever-smoker | 2.23 | 6.87 |

[a] Occupational dirtiness score ranges from 0 (very clean) to 6 (very dirty) (SEs were all within the range 0.02–0.06).

[b] Self-reported.

**Table 7.** Relative Risks of Mortality from All Causes, Cardiopulmonary Disease, and Lung Cancer Associated with an Increase in Fine Particles Using the Original and Extended Models and Adjusting for Alternative Indices of Occupational Exposure in the Reanalysis of the Six Cities Study[a]

| Model | All Causes | Cardiopulmonary Disease | Lung Cancer |
|---|---|---|---|
| Original[b] | 1.26 (1.08–1.46) | 1.31 (1.07–1.61) | 1.40 (0.82–2.38) |
| Original + dirtiness A[c] (+ lung carcinogens[d]) | 1.24 (1.07–1.45) | 1.28 (1.04–1.58) | 1.32 (0.76–2.31) |
| Original + dirtiness B[e] (+ lung carcinogens) | 1.27 (1.08–1.48) | 1.34 (1.09–1.66) | 1.30 (0.75–2.27) |
| Extended[f] | 1.28 (1.09–1.49) | 1.32 (1.07–1.63) | 1.13 (0.65–1.97) |
| Extended + dirtiness A (+ lung carcinogens) | 1.26 (1.07–1.47) | 1.29 (1.04–1.60) | 1.06 (0.59–1.91) |
| Extended + dirtiness B (+ lung carcinogens) | 1.28 (1.09–1.50) | 1.35 (1.09–1.68) | 1.05 (0.59–1.89) |

[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 $\mu g/m^3$. Data are RRs with 95% CIs.

[b] The Original Model included $PM_{2.5}$, indicators of current and former smoking, a two-level indicator of education, occupational exposure to dust or fumes, and body mass index; baseline hazard function was stratified by 1-year age groups. See Table 2 for a complete list of covariates included in the Original Model. For consistency with our Extended Model, occupational analyses using the Original Model are based on 1-year age stratification, rather than the 5-year age stratification used by the Original Investigators.

[c] Dirtiness A is a categorical dirtiness variable.

[d] A binary variable for occupations with exposure to lung carcinogens; used only in the analyses for lung cancer.

[e] Dirtiness B is a continuous dirtiness variable.

[f] The Extended Model included the following covariates: (1) the Original Model covariates except for current-smoker pack-years and the two-level indicator of education level; (2) current-smoker, years of smoking, cigarettes per day, indicators of age started smoking, a three-level indicator of education level, marital status, alcohol consumption; and (3) interactions between gender and each of three covariates: current-smoker, marital status, and alcohol consumption; baseline hazard function was stratified by 1-year age groups. See Table 2 for a complete list of covariates included in the Extended Model.

**Table 8.** Relative Risks of Mortality from All Causes, Cardiopulmonary Disease, and Lung Cancer Associated with an Increase in Fine Particles in Various Subsets of the Population Using the Original Model + Dirtiness + Lung Carcinogens in the Reanalysis of the Six Cities Study[a]

| Group | All Causes | Cardiopulmonary Disease | Lung Cancer |
|---|---|---|---|
| All subjects | 1.26 (1.08–1.48) | 1.34 (1.08–1.65) | 1.30 (0.75–2.27) |
| Females | 1.19 (0.92–1.53) | 1.33 (0.92–1.90) | 0.67 (0.22–2.08) |
| Males | 1.31 (1.07–1.61) | 1.34 (1.03–1.75) | 1.64 (0.85–3.16) |
| Never-smokers | 1.24 (0.92–1.66) | 1.39 (0.93–2.10) | 3.88 (0.44–34.18) |
| Females | 1.16 (0.80–1.67) | 1.21 (0.70–2.08) | 4.06 (0.46–36.12) |
| Males | 1.25 (0.77–2.04) | 1.61 (0.85–3.06) | NA[c] |
| Ever-smokers | 1.33 (1.10–1.61) | 1.37 (1.07–1.76) | 1.40 (0.80–2.46) |
| Females | 1.29 (0.90–1.84) | 1.56 (0.96–2.54) | 0.52 (0.13–2.10) |
| Males | 1.38 (1.11–1.73) | 1.33 (0.99–1.78) | 1.82 (0.97–3.43) |

[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 fine particles was 18.6 $\mu g/m^3$. The Original Model included the following covariates: $PM_{2.5}$, indicators of current- and former-smokers, current-smoker pack-years, former-smoker pack-years, a two-level indicator of education level, occupational exposure to dust or fumes, and body mass index. See Table 2 for a complete list of covariates included in the Original Model. "Dirtiness" is a continuous occupational variable; "lung carcinogens" is a binary variable for occupations with exposure to lung carcinogens and was used only in the analyses for lung cancer. Data are RRs with 95% CIs.

[b] The large upper confidence limit is due to the small number of deaths (8) in this group.

[c] NA = no deaths in that group.

**Table 9.** Relative Risks of Mortality from All Causes and Cardiopulmonary Disease Associated with an Increase in Fine Particles Using the Original Model Stratified by Occupational Dirtiness in the Reanalysis of the Six Cities Study[a]

| Dirtiness | All Causes | Cardiopulmonary Disease |
|---|---|---|
| Low | 1.28 (0.96–1.70) | 1.49 (1.00–2.22) |
| Medium | 1.08 (0.81–1.43) | 1.19 (0.81–1.74) |
| High | 1.47 (1.13–1.90) | 1.45 (1.04–2.04) |

[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 $\mu g/m^3$. See Table 2 for a complete list of covariates incorporated into the Original Model; baseline hazard function was stratified by 1-year age groups. For occupational dirtiness, low = 0, medium = 1–3, and high = 4–6. Data are RRs with 95% CIs.

Table 9 shows that the relative risks of mortality from air pollution differ by dirtiness stratum for all-cause mortality and cardiopulmonary disease mortality, but with no coherent trend; the lowest relative risk is in the middle dirtiness stratum. Table 10 shows the results of an analysis of the relative risks of air pollution for all-cause mortality stratified by dirtiness score and education level. There is no clear indication as to whether the air pollution effect is more dependent on occupational dirtiness or on education.

## POPULATION MOBILITY

The Original Investigators in the Six Cities Study had examined the association between fine particle air pollution and mortality using a cross-sectional personal interview of subjects selected in six cities, with interviews conducted between 1974 and 1977. Although subjects had been reinterviewed 3, 6, and 12 years after the initial interview, and their residences were recorded during follow up, this information had not been used in the original analyses. Information on the number of years the subject had lived in the city of enrollment prior to recruitment also was recorded, but not used. Air pollution concentrations averaged over the follow-up period had been assigned to each individual by city regardless of the amount of time that individual had lived in the city of enrollment.

The Reanalysis Team attempted to evaluate the impact of population mobility, which would affect exposure to ambient air pollution, on mortality. Mobility both before and after enrollment in the study was considered.

### Preenrollment Mobility

Only limited information was available on mobility within the cohort prior to enrollment. Partial residence histories, tied to job history, had been recorded on the initial questionnaire but not in computer files. However, the number of years in which subjects lived in the city of enrollment had been noted during the initial interview, and was available for analysis.

The distribution of the numbers of years subjects had resided in their community of enrollment before the study began is shown in Table 11 both by city and for all cities combined. Subjects had lived in the original city of enrollment for 30 years on average, ranging from an average of 23 years in Watertown to 44 years in St Louis. We note that the two of the most highly polluted cities (Steubenville and St Louis) also had the longest average residency of subjects prior to enrollment. When we included residency duration as a predictor of all-cause mortality, it did not change the association between fine particles and relative risk of mortality (RR = 1.28, 95% CI: 1.09–1.50); residency duration was a weak predictor of mortality (RR = 0.99 on the basis of the observed range of 74 years, 95% CI: 0.79–1.24). We obtained these results using the Extended Model with calendar year as the time axis.

We examined the potential for residency duration to modify the association between fine particles and mortality by relating fine particles to mortality within three levels of residency duration (< 20 years [34% of sample],

**Table 10.** Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles Using the Original Model Stratified by Occupational Dirtiness and Educational Level in the Reanalysis of the Six Cities Study[a]

| Dirtiness | Less Than High School | High School | More Than High School |
|---|---|---|---|
| Low | 1.72 (0.87–3.40) | 1.40 (0.85–2.30) | 0.94 (0.60–1.47) |
| Medium | 0.97 (0.61–1.52) | 1.13 (0.67–1.89) | 1.26 (0.74–2.16) |
| High | 1.67 (1.19–2.34) | 1.65 (0.99–2.75) | 0.93 (0.37–2.36) |

[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 $\mu g/m^3$. See Table 2 for a complete list of covariates incorporated into the Original Model; baseline hazard function was stratified by 1-year age groups. For occupational dirtiness, low = 0, medium = 1–3, and high = 4–6. Data are RRs with 95% CIs.

**Table 11.** Distribution of Residence Duration Before Enrollment (in Years) by City of Enrollment in the Reanalysis of the Six Cities Study

| | | | Percentiles | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| City | Mean | SD | 0 | 5 | 25 | 50 | 75 | 95 | 100 |
| Harriman | 24.9 | 16.2 | 0 | 3 | 13 | 22 | 33 | 58 | 74 |
| Portage | 25.9 | 18.1 | 0 | 3 | 9 | 24 | 38 | 60 | 74 |
| Steubenville | 36.0 | 16.4 | 0 | 8 | 24 | 37 | 48 | 62 | 73 |
| St Louis | 43.7 | 16.1 | 0 | 17 | 31 | 45 | 56 | 69 | 74 |
| Topeka | 25.7 | 15.6 | 2 | 5 | 13 | 24 | 35 | 55 | 74 |
| Watertown | 22.9 | 17.4 | 0 | 1 | 7 | 20 | 34 | 55 | 73 |
| All cities | 29.8 | 18.3 | 0 | 3 | 15 | 28 | 44 | 63 | 74 |

20–40 years [36%], and > 40 years [30%]). The relative risk of fine particles and all-cause mortality was 1.41 (95% CI: 0.94–2.12), 1.21 (95% CI: 0.91–1.62), and 1.32 (95% CI: 1.05–1.65), respectively, within these three groups. Consequently, the length of time spent in the community before enrollment does not appear to affect the association between fine particle air pollution and mortality.

### Mobility After Enrollment

Subject mobility after enrollment had been ascertained through the use of annual letters, postcards, or phone calls to study participants. Follow-up interviews also had been conducted at 3, 6, and 12 years, which further extended the mobility database. The Reanalysis Team computerized this information for the purposes of assessing the influence of post-enrollment subject mobility on the association between air pollution and mortality.

A minority (18.5%) of the cohort had moved outside the city of enrollment before follow up was completed. Mobility increased with educational attainment; 12.8% of subjects with less than a high school education had moved, 16.9% of high school graduates had moved, and 25.0% of those subjects with more than high school education had moved. Mobility did not vary with occupational exposure to dust or fumes. Of those subjects not occupationally exposed, 19.2% had moved; 17.6% of those in the exposed group had moved. The frequency of moving was similar for all smoking status groups (19.7% for current-smokers, 16.8% for former-smokers, and 18.4% for never-smokers). Moving was less frequent among married persons (17.8%) than nonmarried persons (22.1%). Mobility was similar in males (18.2%) and females (18.7%). However, movers tended to be younger (average age at enrollment, 44.6 years) than nonmovers (50.8 years). Mobility was similar in all cities (12.7% to 19.0%) except Watertown (31.8%). The crude death rate (the number of deaths/number of subjects) was much lower for the movers (12.1%) compared with nonmovers (18.9%), likely due to the younger average age of subjects that moved.

Reanalysis showed that relative risk of fine particle exposure and all-cause mortality for the nonmover group was 1.30 (95% CI: 1.10–1.54), notably comparable to that for the entire sample (RR = 1.28, 95% CI: 1.09–1.49). We based this analysis on the Extended Model with calendar year as the time axis. The relative risk of movers was 1.08 (95% CI: 0.67–1.76), a value clearly lower than that observed for the nonmoving cohort. Subjects in the mover group tended to have higher educational attainment than did nonmovers. Fine particle pollution was not related to mortality in the group with higher education. We determined the relative risk within the three educational groups for movers and nonmovers separately. Among the nonmovers, the relative risk associated with fine particles was lower for the subjects with the highest level of education (RR = 1.41, 95% CI: 1.10–1.82 for subjects without high school education; RR = 1.42, 95% CI: 1.06–1.91 for subjects with high school education; and RR = 0.96, 95% CI: 0.68–1.35 for subjects with more than high school education). Our analysis showed a similar risk for subjects without high school education among the movers (RR = 1.56, 95% CI: 0.67–3.64) as for the nonmovers without high school education. However, we obtained relative risks less than 1 among the high school–educated movers (RR = 0.71, 95% CI: 0.26–1.99) and movers with more than high school education (RR = 0.96, 95% CI: 0.40–2.30). The weakness of the association between fine particles and mortality in the

mover group thus was due largely to those subjects with at least high school education.

The Reanalysis Team also conducted an analysis of population mobility in which subjects were treated as being lost to follow up once they moved out of the original city of residence. The advantage of this analysis is that subjects who moved are not assigned an inappropriate exposure level. The relative risk of fine particle exposure on mortality for this new analysis was 1.23 (95% CI: 1.05–1.45), a value only slightly lower than that observed for the entire cohort.

Finally, we conducted an analysis of the mover group using long-term average exposures to fine particles but ignoring follow-up data on this group before the time the subjects first moved from the city of enrollment. This analysis produced a relative risk of all-cause mortality of 1.25 (95% CI: 0.75–2.10), similar to that in the entire sample (RR = 1.28), but greater than that in our first analysis of the mover group (RR = 1.08) based on full follow-up information starting at the time of enrollment into the study. The confidence interval on estimates of the relative 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 biased low because some individuals who otherwise might have moved from the original city of residence may have died before they had the opportunity to do so. However, because members of the mover group were notably younger than members of the nonmover group, this bias is expected to be small.

**TIME-DEPENDENT COVARIATES**

The Reanalysis Team undertook Poisson regression analyses of data from the Six Cities Study to estimate the relative risk of mortality from fine particles while taking into account changes in the values of both the air pollution exposures and risk factors that occurred during follow up. The Cox proportional-hazards model used by the Original Investigators had provided an estimate of the relative risk under the assumption that exposure to fine particles remained fixed during follow up. Specifically, exposure to fine particles had been assigned by the Original Investigators using the mean exposure determined on the basis of samples taken between 1979 and 1985. In this section, we have used Poisson regression to provide a separate series of risk estimates that can be compared with those generated by the Original Investigators. More importantly, by using the Poisson model, we can evaluate the impact of temporal changes in the values of both fine particles and other risk factors.

Using fixed-in-time covariates, a positive association had been demonstrated between mortality and fine particle air pollution by the Original Investigators in the Six Cities Study, with the age-adjusted hazard ratio estimated from the Cox proportional-hazards model for the most-polluted city compared to that for the least-polluted being 1.26 (95% CI: 1.08–1.46). We also considered the potential confounding influence of several other variables measured at baseline: smoking status, number of pack-years of smoking, educational level achieved, and BMI.

During follow up of the Six Cities cohort, attempts had been made to reinterview subjects to ascertain changes in these covariates. Longitudinal data were available for up to four interview dates: date of enrollment, and 3, 6, and 12 years later. We evaluated the effects of changes in the values of these covariates over time using the Poisson regression model:

$$\log RR\,(z,w) = \log r\,(x,z,w) - \log r_0\,(x)$$

in which $RR$ denotes the relative risk of mortality, $z$ represents a set of covariates (BMI, education, smoking, and occupational exposure) that can modify the mortality rate $r$ in addition to the effect of the air pollution exposure $w$, and $x$ represents a set of covariates (here, age and gender) that describe the background mortality rate $r_0$. We fit this model to the Six Cities Study data using EPICURE (Preston et al 1993).

In order to compare results from the Poisson regression to previously derived relative risk estimates using the Cox proportional-hazards model, we first modeled exposure to fine particles by using a city-specific mean concentration of fine particles over the follow-up period. We assessed the effect of changes in exposure over time in later models that incorporated city-specific concentration levels calculated for the following periods: before 1981, 1981–1982, 1983–1984, 1985–1986, and 1987 or after. We calculated these values separately for each city by smoothing available mean annual levels of fine particles using log-linear regression.

We adjusted all models for gender and the following age groups: < 45, 45 through 49, 50 through 54, ... 75 through 79, and 80 or older; and also evaluated the effects of BMI, education, occupational exposures, and smoking. We categorized BMI into quartiles on the basis of frequency distribution in the study population at time of enrollment; specifically, we placed subjects into one of the following quartiles: < 22.70, 25.26, 28.21, and ≥ 28.21 kg/m$^2$. Using these same cutpoints, we also evaluated changes in BMI over time on the basis of data collected during follow-up interviews.

We created an indicator variable to denote whether or not an individual had completed high school education. Although a more detailed categorization of this variable was available, education was dichotomized to ensure

consistency with the approach that had been taken by the Original Investigators. Similarly, we assigned occupational exposure to dust and fumes using a binary variable.

The Reanalysis Team modeled the effect of smoking behavior on mortality three ways. First, we conducted an analysis by using the same variables as in the original study. These models included terms for current-smokers, former-smokers, cigarette pack-years for current-smokers, and cigarette pack-years for former-smokers. Thus we were able to examine whether Poisson regression (which we were using) produced results similar to Cox regression (which the Original Investigators had used). Second, we included in our model terms that represented the number of years of cigarette smoking (at baseline, or time of enrollment), and the number of packs of cigarettes smoked weekly. Finally, because of information obtained in follow-up interviews, we were able to model changes over time in the number of packs of cigarettes smoked weekly. (There were inconsistencies in the smoking status and number of smoking years reported during follow-up interviews, which precluded the use of these indicators of tobacco consumption as time-dependent covariates.)

The adjusted mortality rate ratios based on the Cox regression (Original Model) used by the Original Investigators (Table 12) provided a benchmark against which we compared similar estimates of risk generated by Poisson regression (Table 13). Both regression analyses are based on the same variables from the baseline questionnaire; however, unlike the Cox regression model, Poisson regression requires categorization of all variables, including BMI and cigarette consumption, prior to analysis. Nonetheless, there were no appreciable differences in the city-specific risk estimates obtained using the Cox and Poisson regression models. For example, the Poisson regression–based risk of mortality in Steubenville relative to that in Portage is 1.32 (95% CI: 1.11–1.57), comparable to the Cox regression–based relative risk of 1.26 (95% CI: 1.06–1.50).

Table 14 presents the relative risk estimates of mortality we obtained using the Cox and Poisson regression models with exposure to fine particles defined as a continuous covariate. Model 1 in Table 14 corresponds to the Original Model used by the Original Investigators. Model 2, which is based on Poisson regression with tobacco consumption as described in Model 1, gives slightly higher risk estimates than Model 1. Model 3, also based on Poisson regression but using duration and intensity of cigarette smoking at time of enrollment to characterize tobacco consumption, leads to risk estimates very close to those of Model 2. The agreement between Models 2 and 3 indicates that the two methods of controlling for tobacco consumption are equally effective.

Model 4 is the same as Model 3, except that the number of packs of cigarettes smoked per week is updated on the basis of information collected at the follow-up interviews 3, 6, and 12 years post-enrollment. Comparison of the relative risk estimates from these two models (RR = 1.31 and 1.32 for Models 3 and 4, respectively) indicates that the incorporation of time-dependent information on cigarette smoking did not have an appreciable impact on the association between particulate air pollution and mortality. Similarly, when we accounted for temporal changes in BMI (Model 5), it did not materially affect the relative risks for fine particles.

Table 15 shows the annual mean concentrations of fine particles between 1979 and 1988 within each of the six cities. Concentrations of fine particles decreased during the study period in Steubenville, Harriman, and St Louis; downward trends were less consistent in Portage, Topeka, and Watertown. The city-specific mean fine particle levels exhibited sizeable year-to-year variations.

Model 6 in Table 14 takes into account the generally declining levels of fine particles over time on the basis of the city-specific annual average fine particle concentrations shown in Table 15. The estimated relative risk of mortality associated with fine particles of 1.16 for Model 6 is lower than the comparable estimate of 1.31 for Model 5, although the confidence intervals for these two estimates demonstrate a degree of overlap.

There are several possible explanations for the attenuated relative risk estimates that were generated when fine particle exposures were modeled as calendar time-dependent variables (Model 6). First, it is possible that the smoothing of data using the log-linear regression did not yield exposures that were representative of those received by the residents in each city. Second, the use of time-dependent exposures resulted in less between-city variability in exposure to fine particles in the latter part of the follow-up period, during which most of the deaths had occurred; this lowered the relative risk of mortality per 18.6 $\mu g/m^3$ change in fine particle concentration. Finally, it is possible that for all-cause mortality, chronic exposure to fine particles is more important than acute exposure as a predictor of death. Unfortunately, we were unable to discriminate between risks of mortality estimated by using various exposure-time windows because of the high correlations between selected city-specific exposure indices based on various lag intervals.

## AIR QUALITY DATA

A major strength of the Six Cities Study is that the Original Investigators had prospectively monitored a number of ambient air pollutants, using monitors specifically

**Table 12.** Adjusted Mortality Rate Ratios Estimated from Cox Proportional-Hazards Models: Original Results[a] from the Six Cities Study

| Variable | All Subjects | Men | Women |
|---|---|---|---|
| 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) |
| 20 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[b] | | | |
| Portage | 1.0 | 1.0 | 1.0 |
| Topeka | 1.01 (0.82–1.24) | 1.04 (0.79–1.36) | 0.97 (0.71–1.34) |
| Harriman | 1.17 (0.97–1.41) | 1.21 (0.96–1.54) | 1.07 (0.79–1.45) |
| Watertown | 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 | 1.26 (1.06–1.50) | 1.29 (1.03–1.62) | 1.23 (0.93–1.61) |

[a] Referred to as the Original Model by the Reanalysis Team; see Table 2 for a complete list of covariates incorporated into the Original Model. From Dockery et al 1993; corresponds to Table 2 in the original publication (Copyright © 1993, Massachusetts Medical Society, all rights reserved). Values are rate ratios (95% CIs). 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). (Neither the text nor table in the original publication identify which pollutant is associated with these data.)

[b] City-specific rate ratios are all expressed in relation to Portage.

**Table 13.** Relative Risks of All-Cause Mortality in the Six Cities Study from Poisson Regression of Time-Varying Covariates[a]

| Variable | All Subjects | Men | Women |
|---|---|---|---|
| Current-smoker | 1.37 (0.98–1.87) | 1.79 (1.05–2.86) | 1.16 (0.73–1.74) |
| < 10 Pack-years[b] | 1.0 | 1.0 | 1.0 |
| 10–30 Pack-years | 1.57 (1.13–2.24) | 1.35 (0.83–2.31) | 1.74 (1.12–2.82) |
| > 30 Pack-years | 1.87 (1.36–2.64) | 1.56 (0.99–2.63) | 1.93 (1.24–3.15) |
| Former-smoker | 1.23 (0.99–1.52) | 1.21 (0.88–1.63) | 1.30 (0.95–1.75) |
| < 10 Pack-years[b] | 1.0 | 1.0 | 1.0 |
| 10–25 Pack-years | 0.96 (0.73–1.27) | 0.96 (0.67–1.36) | 1.12 (0.70–1.78) |
| > 25 Pack-years | 1.47 (1.17–1.86) | 1.54 (1.15–2.07) | 1.73 (1.09–2.76) |
| Less than high school education | 1.26 (1.13–1.41) | 1.29 (1.12–1.49) | 1.22 (1.03–1.45) |
| Body mass index[c] | | | |
| 4th Quartile[b] | 1.0 | 1.0 | 1.0 |
| 3rd Quartile | 0.85 (0.74–0.98) | 0.91 (0.77–1.09) | 0.74 (0.59–0.93) |
| 2nd Quartile | 0.78 (0.67–0.90) | 0.80 (0.66–0.97) | 0.75 (0.59–0.93) |
| 1st Quartile | 0.82 (0.70–0.96) | 0.98 (0.79–1.22) | 0.69 (0.56–0.87) |
| City[d] | | | |
| Portage | 1.0 | 1.0 | 1.0 |
| Topeka | 1.01 (0.82–1.24) | 1.04 (0.79–1.36) | 0.96 (0.69–1.31) |
| Harriman | 1.16 (0.96–1.39) | 1.20 (0.94–1.51) | 1.06 (0.78–1.43) |
| Watertown | 1.06 (0.89–1.27) | 0.98 (0.77–1.24) | 1.13 (0.86–1.49) |
| St Louis | 1.13 (0.95–1.35) | 1.16 (0.92–1.45) | 1.07 (0.81–1.41) |
| Steubenville | 1.32 (1.11–1.57) | 1.39 (1.11–1.74) | 1.22 (0.93–1.61) |

[a] Risks have been adjusted for age, sex, and all other variables listed in this table.

[b] Other relative risks in this category are expressed in relation to this variable.

[c] Body mass index was categorized into quartiles based on the 8,111 subjects at baseline. Cutpoints in $kg/m^2$ were: ≤ 22.7, 25.26, 28.21, and > 28.21.

[d] City-specific relative risks are all expressed in relation to Portage.

**Table 14.** Relative Risks of Mortality from All Causes Associated with Selected Indices of Fine Particle Air Pollution[a] Based on Cox Proportional-Hazards Regression or Poisson Regression Models with Time-Dependent Covariates in the Reanalysis of the Six Cities Study

| Model | Type | Covariates | Relative Risk (95% CI) |
|---|---|---|---|
| 1 | Cox | Age (5-year groupings), sex, current-smokers, pack-years for current-smokers, former-smokers, pack-years for former-smokers, high school education, body mass index, and occupational exposure to dust or fumes; values are based on data collected at baseline | 1.26 (1.08–1.46) |
| 2 | Poisson | Same as Model 1[b] | 1.32 (1.13–1.53) |
| 3 | Poisson | Age (5-year groupings), sex, number of years smoked, number of packs smoked per week, high school education, body mass index, and occupational exposure to dust or fumes; values are based on data collected at baseline | 1.31 (1.13–1.53) |
| 4 | Poisson | Same as model 3 except deaths and person-years for category of "number of packs smoked per week" were calculated using changes indicated by follow-up interviews | 1.32 (1.13–1.53) |
| 5 | Poisson | Same as model 4 except deaths and person-years for category of "body mass index" were calculated using changes indicated by follow-up interviews | 1.31 (1.13–1.52) |
| 6 | Poisson | Same as model 5 except changes in exposure to particulate matter over time were incorporated into the model[c] | 1.16 (1.02–1.32) |

[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 $\mu g/m^3$. The exposure for each city was based on the mean of sampled measures taken between 1979 and 1985.

[b] The use of the Poisson regression model required the categorization of body mass index as well as duration, intensity, and cumulative tobacco consumption that had been modeled as continuous variables in the Cox model.

[c] Exposures were defined according to 13 calendar periods: earlier than 1979, 1979, 1980, 1981, ... , 1989, and 1990 or later.

**Table 15.** Annual Average Concentration of Fine Particles by Calendar Year in Each of the Six Cities[a]

| Year | Harriman | Portage | Steubenville | St Louis | Topeka | Watertown |
|---|---|---|---|---|---|---|
| 1979 | — | 11.4 | 40.3 | 24.0 | 12.6 | 16.7 |
| 1980 | 26.3 | 12.8 | 30.0 | 22.7 | 15.6 | 17.3 |
| 1981 | 20.7 | 11.4 | 33.5 | 19.9 | 15.1 | 16.3 |
| 1982 | 18.7 | 10.1 | 27.9 | 17.7 | 11.9 | 13.4 |
| 1983 | 19.5 | 11.4 | 25.4 | 17.3 | 11.8 | 12.3 |
| 1984 | 19.7 | 11.1 | 26.1 | 18.4 | 12.9 | 17.4 |
| 1985 | 20.1 | 9.3 | 24.7 | 18.0 | 10.5 | 14.5 |
| 1986 | 20.5 | 10.8 | 21.7 | 17.9 | 9.2 | — |
| 1987 | 18.6 | 10.7 | 28.6 | — | 10.7 | — |
| 1988 | — | — | — | — | 13.7 | — |
| Mean (available years 1979–1985) | 20.9 | 11.0 | 29.6 | 19.0 | 12.5 | 14.9 |
| Mean (all available years) | 20.7 | 10.9 | 28.7 | 18.7 | 12.1 | 14.9 |

[a] A dash (—) indicates that no fine particle data were collected for that year.

**Table 16.** Relative Risks of Mortality from All Causes, Cardiopulmonary Disease, and Lung Cancer Associated with Various Measures of Air Pollution from the Reanalysis of the Six Cities Study[a]

| | | Cause of Death | | |
|---|---|---|---|---|
| Pollutant | Range[b] | All Causes | Cardiopulmonary Disease | Lung Cancer |
| $PM_{2.5}$ | 18.6 μg/m$^3$ | 1.28 (1.09–1.49) | 1.32 (1.07–1.63) | 1.17 (0.67–2.04) |
| $SO_4^{2-}$ | 8.0 μg/m$^3$ | 1.28 (1.09–1.50) | 1.32 (1.06–1.63) | 1.15 (0.66–2.01) |
| $SO_4^{2-}$ adjusted[c] | 9.1 μg/m$^3$ | 1.27 (1.09–1.48) | 1.30 (1.05–1.59) | 1.14 (0.66–1.96) |
| TSP | 55.8 μg/m$^3$ | 1.26 (1.07–1.47) | 1.21 (0.98–1.50) | 1.25 (0.71–2.20) |
| $PM_{15}$ | 28.3 μg/m$^3$ | 1.28 (1.09–1.51) | 1.30 (1.04–1.62) | 1.21 (0.67–2.18) |
| $H^+$ | 25.8 nmol/m$^3$ | 1.12 (0.97–1.30) | 1.25 (1.03–1.53) | 0.97 (0.57,1.64) |
| $SO_2$ | 22.4 ppb | 1.26 (1.08–1.47) | 1.25 (1.01–1.54) | 1.13 (0.66–1.95) |
| $SO_2$ reconstructed[d] | 22.1 ppb | 1.26 (1.08–1.48) | 1.24 (1.00–1.54) | 1.08 (0.63–1.88) |
| $NO_2$ | 15.8 ppb | 1.25 (1.07–1.46) | 1.28 (1.04–1.59) | 1.15 (0.65–2.04) |
| $O_3$ | 8.3 ppb | 0.87 (0.76–1.00) | 0.78 (0.64–0.95) | 0.94 (0.56–1.59) |

[a] Data are RRs with 95% CIs.

[b] Unless otherwise noted, all ranges were calculated from the values in Table 17a in Part I of this report, which corresponds to Table 1 in Dockery et al 1993.

[c] This range was calculated by the Reanalysis Team to adjust for artifactual sulfate.

[d] This range was reconstructed by the Original Investigators during the reanalysis.

developed for this purpose. For the same study population used by the Original Investigators, the Reanalysis Team calculated relative risks for ambient air pollutants that had been measured in the Six Cities Study ($PM_{2.5}$, $SO_4^{2-}$, TSP, inhalable particles, $H^+$, $SO_2$, $NO_2$, and $O_3$). As indicated in Table 16, associations with all-cause mortality were demonstrated by a number of pollutants, including fine particles, sulfate particles, total suspended particles, inhalable particles, aerosol acidity, sulfur dioxide, and nitrogen dioxide. Of the pollutants they had measured, only ozone did not appear to be associated with all-cause mortality. With the exception of aerosol acidity, all pollutants that demonstrated an association with mortality yielded a relative risk comparable to that for fine particles (RR = 1.28, 95% CI: 1.09–1.49). However, as can be seen in Table 17, a high degree of multicollinearity is evident between the different pollutants measured in the Six Cities Study.

A higher relative risk of cardiopulmonary mortality (RR = 1.32, 95% CI: 1.07–1.63) than for all-cause mortality had been demonstrated by fine particles. As was the case with all-cause mortality, increased cardiopulmonary mortality was associated with all other pollutants except ozone. No significant association with lung cancer mortality was demonstrated by any of the pollutants measured in the Six Cities Study, although the relative risks for lung cancer mortality were greater than unity for all pollutants except aerosol acidity and ozone.

With only six cities and a single fixed-site monitor within each city, the Reanalysis Team did not attempt to fit multiple-pollutant models to these data to identify which of these pollutants were most strongly associated with mortality. Multiple-pollutant models were used, however, in the ACS Study, which included 151 cities in the sulfate cohort and 50 cities in the fine particle cohort (see the Spatial Analyses section).

During the course of the Part I audit, it became apparent that sulfate data collected between 1979 and 1984 had been obtained using high-volume samplers that were subject to a known artifact. As detailed in Part I, the Reanalysis Team constructed city-specific calibration equations to correct for this known artifact, and developed adjusted estimates of the city-specific sulfate levels in the Six Cities Study. (The original/corrected sulfate concentrations [μg/m$^3$] in the six cities were 8.1/7.9 in Harriman, 5.3/4.7 in Portage, 12.8/13.5 in Steubenville, 8.0/7.6 in St Louis, 4.8/4.4 in Topeka, and 6.5/5.9 in Watertown; see Table 14 in Part I.) The relative risk of mortality from all causes was, however, virtually unchanged (RR = 1.27, 95% CI: 1.09–1.48), when compared with the estimate calculated using the Extended

**Table 17.** Correlation Between Pollutants in the Six Cities Study

| | $PM_{2.5}$ | $SO_4^{2-}$ | TSP | $PM_{15}$ | $H^+$ | $SO_2$ | $NO_2$ | $O_3$ |
|---|---|---|---|---|---|---|---|---|
| $PM_{2.5}$ | 100 | 98 | 84 | 97 | 59 | 85 | 78 | −53 |
| $SO_4^{2-}$ | | 100 | 83 | 94 | 50 | 85 | 78 | −50 |
| TSP | | | 100 | 90 | 12 | 86 | 82 | −36 |
| $PM_{15}$ | | | | 100 | 50 | 81 | 77 | −43 |
| $H^+$ | | | | | 100 | 17 | 32 | −56 |
| $SO_2$ | | | | | | 100 | 84 | −47 |
| $NO_2$ | | | | | | | 100 | −80 |
| $O_3$ | | | | | | | | 100 |

Model (RR = 1.28, 95% CI: 1.09–1.50; see Table 16), after adjustment for this artifact.

Although the Audit Team, during the Part I audit, was able to confirm the city-specific annual average air pollutant levels for most pollutants measured by the Original Investigators, the reconstructed results for sulfur dioxide were somewhat different from those originally reported. The largest difference occurred in the St Louis data, for which the reconstructed sulfur dioxide concentration of 9.2 ppb was notably lower than the original value of 14.1 ppb. Nevertheless, the Reanalysis Team, using the reconstructed sulfur dioxide concentrations, obtained a relative risk of all-cause mortality (RR = 1.26, 95% CI: 1.08–1.48) that was virtually identical to the relative risk calculated for the same study population used by the Original Investigators (RR = 1.26, 95% CI: 1.08–1.47; see Table 16).

## FLEXIBLE MODELING

Two important assumptions lie behind the Six Cities Study's original analysis, which had been based on the Cox proportional-hazards model. First, the Cox proportional-hazards assumption requires that, for each variable in the model, the hazard ratio remains constant over the entire follow-up period. Second, as in all parametric general linear models, the effect of each continuous predictor on the log hazard is assumed to be linear. The Original Investigators had not reported on the validity of these assumptions in the context of the Six Cities Study data. The Reanalysis Team needed to verify these assumptions to ensure that the estimates of the effects of particulate air pollution, and other covariates, would be unbiased.

Evidence that these assumptions may not hold could offer new insights into the impact of particulate air pollution on mortality. The extent to which the hazard ratio for long-term exposure to particles remains constant over time is of particular interest in light of the changes in ambient fine particle concentration during the follow-up period. Verification of both assumptions for major potential confounders is important, because misspecification of the effects assumptions may result in residual confounding of the estimated association between exposure and mortality. For these reasons, we examined the proportional-hazards and linearity assumptions underlying the original analysis using a flexible spline regression model.

As described in Appendix C (available upon request from the Health Effects Institute), the regression spline modeling approach allows for the simultaneous flexible estimation of (1) changes over time in the log hazard ratios of interest, and (2) nonlinear effects of continuous independent variables. Simultaneous estimation and testing of both effects is essential because failure to account for nonlinearity may result in spurious evidence of time dependence, and vice versa. We modeled time-dependent effects using a quadratic spline with 5 degrees of freedom (*df*) and 4 *df* used to represent nonlinear effects.

To reduce the size of the dataset to tractable levels, we relied on separate analyses of four disjoint and complementary subsets of the entire cohort. Each subset included about 2,000 participants, selected by simple random sampling without replacement. To test the hypotheses of interest, we then combined the four subset-specific likelihood ratio test statistics and adjusted the degrees of freedom appropriately (see Appendix C for details). We stratified the analyses by sex and 5-year age groups, as in the original study, and adjusted the effect of particulates for current and former smoking and for BMI. We conducted sensitivity analyses by varying the degrees of freedom for the covariates, and by varying the set of covariates included in the model.

Our tests of the proportional-hazards assumption using the default 5 *df* regression spline model yielded marginally significant time-dependent effects for both fine particles ($P = 0.0320$) and sulfate ($P = 0.0316$). Sensitivity analyses indicated that the statistical significance of these effects was robust with respect to choice of the covariates in the model, and did not depend on whether the effect of particulate air pollution, at a given point in time, was constrained to be linear or not. In contrast, we found that the significance of the time-dependent effects depended strongly on the number of degrees of freedom used to model these effects. Whereas more flexible 4 *df* and 5 *df* models provided evidence of significant departures from the Cox proportional-hazards assumption, such departures were not significant with 3 *df* or less. (The latter, less flexible models fitted the data considerably less well.) This indicates that considerable flexibility is essential to detect time dependence of the adjusted effects of both types of particles.

Figures 2 and 3 show the 5 *df* quadratic spline estimates of the time-dependent log–hazard ratio for fine particles and sulfate, respectively. Both estimates suggest that the respective hazard ratio is a nonmonotone function of the follow-up time. Specifically, the impact of fine particles on the mortality hazard decreases to near zero after five years of follow up, but later increases to reach a peak at about 10 to 12 years of follow up. One possible explanation for this could be that the pattern of temporal changes in the fine particle effect may reflect concurrent changes in between-city variations of the yearly particle concentration levels. (Indeed, the middle graph in Figure 2 of the original publication by Dockery and colleagues [1993] shows a sharp increase in fine particle levels in Steubenville at about 11 years of follow up, which coincides with the peak in our Figure 2.)

Although yearly fine particle levels are not available for the first 5 years of the follow up in the Six Cities Study, it can be seen from the upper graph in Figure 1 of the original publication that TSP had decreased substantially during this period in the two cities with the highest air pollution levels. This suggests that fine particle levels also may have decreased during this period, which corresponds to the initial decrease in the Reanalysis Team's estimate of the time-dependent effect of fine particles (our Figure 2). Thus, both the initial decrease and later increase in the estimated impact of fine particles on mortality seem to coincide with concurrent changes in between-city differences in yearly fine particle levels. This suggests that estimation of the impact of air pollution on mortality may be refined by taking into account the yearly variation in particulate levels, as represented by time-dependent covariates. (In the Time-Dependent Covariates section, we present the results of an analysis of the relation between mortality and fine

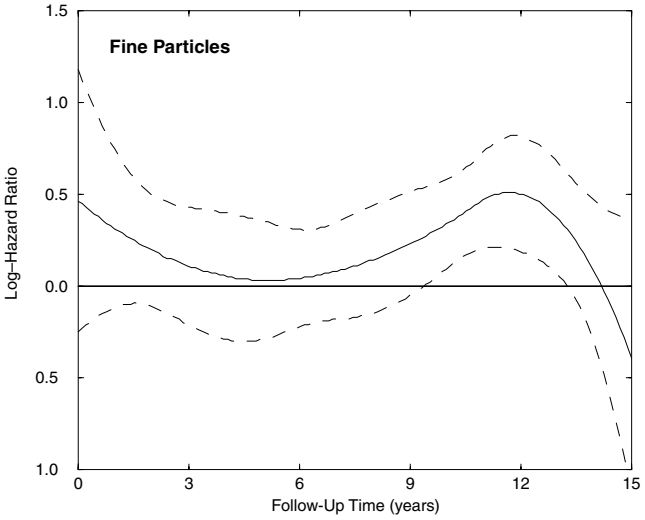



**Figure 2. Change in the impact of fine particles over time in the Six Cities Study.** Flexible quadratic spline estimate (5 *df*) of the time-dependent effect of fine particles on the log–hazard ratio of mortality in a subset of the Six Cities Study ($n$ = 2,856 of which 1,430 were deaths). The log–hazard ratio was associated with a change in fine particles (18.6 μg/m$^3$) equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. The solid curve represents the point estimate of the log–hazard ratio and the dashed curves represent the point-wise 95% confidence interval.

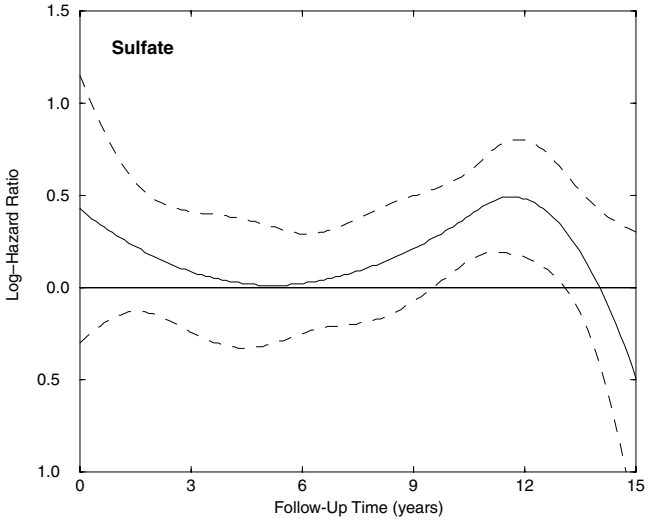



**Figure 3. Change in the impact of sulfate over time in the Six Cities Study.** Flexible quadratic spline estimate (5 *df*) of the time-dependent effect of sulfate on the log–hazard ratio of mortality in a subset of the Six Cities Study ($n$ = 2,856 of which 1,430 were deaths). The log–hazard ratio was associated with a change in sulfate (8.0 μg/m$^3$) equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. The solid curve represents the point estimate of the log–hazard ratio and the dashed curves represent the point-wise 95% confidence interval.

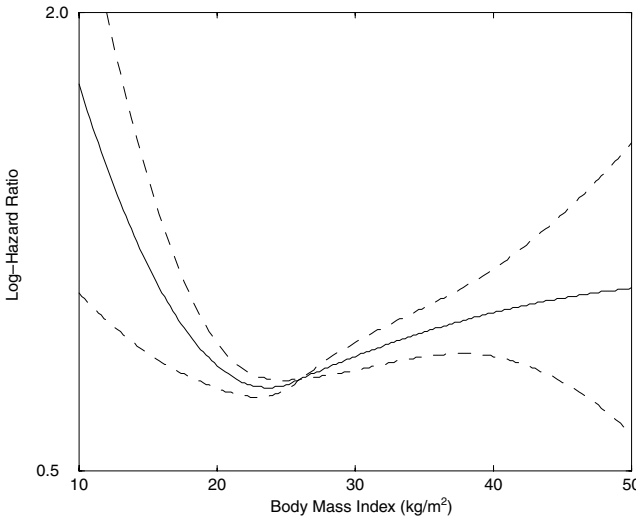



**Figure 4. Flexible nonlinear estimate of the effect of BMI in the Six Cities Study.** Flexible quadratic spline (4 *df*) estimate of the nonlinear effect of increasing BMI on the log–hazard ratio of mortality in a subset of the Six Cities Study ($n$ = 2,856 of which 1,430 were deaths). The log–hazard ratio is plotted with respect to the mean BMI as the reference value. The solid curve represents the point estimate of the log–hazard ratio and the dashed curves represent the point-wise 95% confidence interval.

particle levels, using Poisson regression to take into account changes in fine particle levels over time.)

We found no evidence against the proportional-hazards assumption for BMI and the smoking variables considered ($P > 0.20$). However, we noted a significant departure from the linearity assumption for BMI. Figure 4 depicts the increases in the mortality hazard for both low and high values of BMI. This relation appears to be well approximated by the quadratic function used in the Full and Extended Models to characterize the effects of BMI.

## AMERICAN CANCER SOCIETY STUDY

### QUALITY ASSURANCE AUDIT OF THE DATA FOR THE AMERICAN CANCER SOCIETY STUDY

The Audit Team conducted a similar data audit of the ACS study, using data from the reduced ACS Cancer Prevention Study II (CPS-II) cohort described by Pope and colleagues (1995)*. There were three main differences between our audits of this and the Six Cities Study. First, the SAS data files that had been used in the original analysis were not available. Thus it was necessary for the ACS to reconstruct these datasets to correspond to the analytic files that had been used by the Original Investigators. Second, personnel who had been involved in the original formulation and conduct of CPS-II were no longer available to answer detailed questions about the procedures for data collection and management. Third, significant amounts of documentation for the ACS study were lost when ACS moved their main office from New York City to Atlanta. Thus, in comparison with the Six Cities Study, we had less documentation available to audit each variable; the auditable information and data were limited to microfilmed death certificates, microfilmed questionnaires, and some computer programming information. As was reported in Part I of this report, documentation of the ascertainment of vital status during the follow up no longer exists, nor does detailed information on the coding of each variable. Thus, the Audit Team often determined the coding rules by inference instead of documentation.

As we did for the Six Cities Study, we randomly selected 250 questionnaires and 250 death certificates for audit. We were able to trace microfilm copies of questionnaires and death certificates with the exception of three questionnaires (1.2%) and eight death certificates (3.2%). We were not able to decipher the causes of death on two additional death certificates.

#### Part II Audit

We audited variables for the Part II analysis by conducting a comparison of the data from baseline questionnaires to data in the electronic analysis file provided to the Reanalysis Team. Variables (in alphabetical order by SAS variable name from the analysis file) obtained from the baseline questionnaire and audited in Part II appear in Table 18.

We found no errors in 34 of the 55 audited variables. The error-free variables (by SAS name) were arthritis, asbestos, bladder disease, beer consumption (previous amount and years), chronic indigestion, cirrhosis of the liver, coal/stone dust and coal tar/pitch/asphalt exposure, colon polyps, breast cysts, diabetes, diverticulosis, diesel engine exhaust, duodenal ulcer, emphysema, exercise, formaldehyde exposure, gall stones, gynecologic problems, heart disease, heart medicine (two variables), prostate problems, rectal polyps, stroke, stomach ulcer, tuberculosis, thyroid medication, Tylenol (two variables), water additives, wine (previous years), and years resident in present neighborhood. Table 18 summarizes the errors we found in the remaining audited Part II variables.

#### Summary of Audit Findings

In this part of the audit, for the nonoccupational variables, we found no errors that would induce important effects (over 5%) in the statistical analyses; the highest error

* The original article appears in its entirety at the end of this Special Report.

**Table 18.** Findings from the Phase II Audit of the Original Study Questionnaires from the ACS Study

| SAS Variable Name from the Analysis Files | Description of Variable | Number (and %) of Errors Found in 247 Questionnaires[a] | Comments from the Phase II Audit Team |
|---|---|---|---|
| ASTHMA | Asthma diagnosed by physician | 1 (0.4) | Apparent coding error |
| COLDS | Colds/flu (number of times subject had colds or flu in the past year) | 1 (0.4) | Apparent coding error |
| EVERSMK | Ever smoked cigarettes at least one per day for one year's time | 5 (2.0 | Apparent coding errors |
| HBP | High blood pressure diagnosed by physician | 1 (0.4) | Apparent coding error |
| HEPTS | Hepatitis diagnosed by physician | 1 (0.4) | Apparent coding error |
| HF | Hay fever diagnosed by physician | 2 (0.8) | Apparent coding errors |
| KD | Kidney disease diagnosed by physician | 2 (0.8) | Apparent coding errors |
| KS | Kidney stones diagnosed by physician | 3 (1.2) | Apparent coding errors |
| LIQPR | Liquor (amount consumed in previous years) | 2 (0.8) | Apparent coding errors |
| LIQPRYR | Liquor (years of previous consumption) | 1 (0.4) | Apparent coding error |
| L_OCCUP | Last occupation/retired | 18 (7.3) | Discussed in detail in Appendix A[b] |
| | | 103 (41.7)[c] | |
| MARITAL | Marital status | 1 (0.4) | Apparent coding error |
| OCCUP | Occupation (current) | 39 (15.8) | Discussed in detail in Appendix A |
| OCCUPYR | Occupation (total years in current occupation) | 2 (0.8) | Apparent coding errors |
| OTH_JOB | Occupation (longest occupation) | 20 (8.1) | Discussed in detail in Appendix A |
| OTH_YRS | Occupation (total years for longest occupation) | 8 (3.2) | Discussed in detail in Appendix A |
| OTHER | Other medical conditions | 2 (0.8) | Apparent coding errors |
| THYROID | Thyroid condition diagnosed by physician | 1 (0.4) | Apparent coding error |
| THYRX | Thyroid medication (monthly consumption) | 1 (0.4) | Apparent coding error |
| WATER | Water (source of drinking water) | 3 (1.2) | Apparent coding errors |
| WINEPR | Wine (previous amount of consumption) | 1 (0.4) | Apparent coding error |

[a] Note that two questionnaires were missing and one copy of a questionnaire did not match the requested identification number.

[b] Appendix A is available on request from the Health Effects Institute.

[c] The analysis file contained entries for this variable that matched an adjacent, related column. If one interprets this variable without regard to the adjacent column, the error rate is 103/247 (41.7%); if one allows for this variation, the error rate is 18/247 (7.3%).

rate was 3.2%. However, we found very large discrepancies in the coding of occupation and industry, namely, last occupation/retired (error rate 7.3%), current occupation (15.8%), occupation of longest employment (8.1%), and total years of employment in longest occupation (3.2%). With the possible exception of the occupational data, our data quality audit results indicate that the information used in the ACS Study is of sufficient quality for use in the sensitivity analyses.

## ALTERNATIVE RISK MODELS

### The ACS Study Original Investigators' Analytic Approach

The association between ambient air quality and longevity had been examined by the Original Investigators in the ACS cohort using the Cox proportional-hazards model of survival. With this approach, the relative increase in the underlying hazard function, or instantaneous rate of death, was assumed to be modulated by a number of risk

factors for mortality, such as smoking habits, education, and air pollution, by a constant amount over the follow-up period. The time axis for this survival analysis was calendar year (1982 through 1989). Effects of age at enrollment into the study, gender, and race had been accounted for in the analysis by stratifying the baseline hazard function according to different categories of these covariates, with 5-year age groups used for age stratification. Other determinants of mortality that had been used by the Original Investigators in the Original Model are listed in Table 19.

In addition to overall mortality, cardiopulmonary disease, lung cancer, and all other causes excluding cardiopulmonary disease and lung cancer had been examined by the Original Investigators. Estimates of the log–relative risks had been obtained by maximizing the partial likelihood function for the Cox proportional-hazards model; and 95% confidence intervals for the log–relative risks had been obtained by adding and subtracting 1.96 times the standard error for the point estimate.

**The Reanalysis Team's Analytic Approach**

The Reanalysis Team considered a number of alternative risk models that included additional covariates not included in the Original Model, as well as different functional forms or categorizations of the original covariates. Also in our reanalyses, we used either calendar year or age as the time axis; when using age, we modeled age at enrollment into the study and age at event (death or censoring) in relation to air pollution and other determinants of mortality. This approach has been shown to more fully represent the effects of age on survival than does using calendar year as the time axis (Breslow and Day 1987).

We initially considered a Base Model that included air pollution with no additional determinants of mortality, with the baseline hazard function stratified by 1-year age groups, race, and gender. We then incorporated additional covariates into the Full Model used in the reanalysis (see Table 19). Specifically, we included square terms of continuous variables such as number of cigarettes smoked, years of smoking, and BMI in order to account for nonlinear effects on mortality. We also included variables to account for the age at which a subject started smoking and marital status, which had not been considered by the Original Investigators. To describe the effects of educational attainment in more detail, we considered three levels of education: less than high school, high school, and more than high school. We also included indicator variables for missing data on alcohol consumption due to the large fraction (nearly 70%) of missing observations; that is, 70% of the questionnaires did not have this information, which likely reflects a reluctance on the part of study participants to respond to this question. (A value of "no consumption" had been assigned to these missing data points by the Original Investigators.) We took into account the possibility that the effects of these risk factors could vary by gender by including an interaction term between gender and each of these factors.

We then developed a more parsimonious model by removing those variables that proved to be of least significance on the basis of Wald tests. We dropped a covariate from the Full Model if, when the covariate was removed, the $P$ value based on the increase in the log-likelihood function was greater than 0.05. We continued this procedure until there was no statistical justification for removal of additional covariates. We did, however, keep a covariate in the model if the corresponding gender interaction was statistically significant ($P < 0.05$). We have referred to the parsimonious model derived in this way as the Extended Model (see Table 19).

The Reanalysis Team examined the potential effect of physical exercise on the relation between air pollution and mortality by including self-reported amounts of physical exercise (none or some, moderate, or heavy) as a covariate in the Extended Model. The level of physical exercise could be dependent on health status, with healthier people able to perform more intense exercise. Exposure to ambient air pollution also may increase the risk of developing disease; disease, in turn, may lead to less exercise. Thus, exercise level may be in the path of causation between exposure and death. We examined this possibility by including exercise level in the Extended Model for all causes of death for those people who reported ever having a selected number of diseases, and for those individuals who did not report having any of these diseases at the time of enrollment. These were defined as diseases or conditions for which a subject had ever been diagnosed by a doctor, and included high blood pressure, heart disease, stroke, diabetes, gall stones, chronic indigestion, kidney disease, kidney stones, bladder disease, cirrhosis of the liver, tuberculosis, chronic bronchitis, emphysema, asthma, stomach ulcer, duodenal ulcer, diverticulosis, rectal polyps, colon polyps, thyroid condition, arthritis, prostate trouble, and hepatitis.

**Table 19.** Covariates Included in the Original, Full, and Extended Models for the Reanalysis of the ACS Study[a]

| Covariate | Alternative Risk Model | | |
|---|---|---|---|
| | Original | Full | Extended |
| Tobacco consumption | | | |
| Current-smoker[b] | ✓ | ✓ | ✓ |
| Current-smoker years of smoking | ✓ | ✓ | ✓ |
| (Current-smoker years of smoking)$^2$ | | ✓ | ✓ |
| Current-smoker cigarettes per day | ✓ | ✓ | ✓ |
| (Current-smoker cigarettes per day)$^2$ | | ✓ | |
| Former-smoker years of smoking | ✓ | ✓ | ✓ |
| (Former-smoker years of smoking)$^2$ | | ✓ | ✓ |
| Former-smoker cigarettes per day | ✓ | ✓ | ✓ |
| (Former-smoker cigarettes per day)$^2$ | | ✓ | ✓ |
| Age started smoking (current-smoker) ≤18 years[b] | | ✓ | ✓ |
| Age started smoking (current-smoker) > 18 years[b] | | ✓ | ✓ |
| Age started smoking (former-smoker) ≤18 years[b] | | ✓ | ✓ |
| Age started smoking (former-smoker) > 18 years[b] | | ✓ | ✓ |
| Pipe and/or cigar smoker only[b] | ✓ | ✓ | ✓ |
| Passive cigarette exposure (hours/day) | ✓ | ✓ | ✓ |
| Education Level | | | |
| High school versus other[b] | | ✓ | ✓ |
| More than high school versus other[b] | | ✓ | ✓ |
| Less than high school versus other[b] | ✓ | | |
| Occupational exposure[b,c] | ✓ | ✓ | ✓ |
| Body mass index | ✓ | ✓ | ✓ |
| (Body mass index)$^2$ | | ✓ | ✓ |
| Marital status | | | |
| Married versus single[b] | | ✓ | ✓ |
| Other marital status versus married[b] | | ✓ | ✓ |
| Alcohol consumption | | | |
| Drinks of alcohol per day | ✓ | | |
| Beer consumption[b] | | ✓ | ✓ |
| Missing beer consumption[b] | | ✓ | ✓ |
| Wine consumption[b] | | ✓ | ✓ |
| Missing wine consumption[b] | | ✓ | ✓ |
| Liquor consumption[b] | | ✓ | |
| Missing liquor consumption[b] | | ✓ | |

*(Table continues next page)*

[a] All three of these models were analyzed with standard Cox proportional-haards regressions.

[b] Dichotomous (yes/no) variable.

[c] Regular occupational exposure to any of the following: asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel engine exhaust, formaldehyde.

**Table 19 *(continued)*.** Covariates Included in the Original, Full, and Extended Models for the Reanalysis of the ACS Study[a]

| Covariate | Alternative Risk Model | | |
|---|---|---|---|
| | Original | Full | Extended |
| Interaction with gender | | | |
| Current-smoker[b] | | ✓ | |
| Current-smoker years of smoking | | ✓ | ✓ |
| (Current-smoker years of smoking)$^2$ | | ✓ | ✓ |
| Current-smoker cigarettes per day | | ✓ | ✓ |
| (Current-smoker cigarettes per day)$^2$ | | ✓ | |
| Former-smoker years of smoking | | ✓ | ✓ |
| (Former-smoker years of smoking)$^2$ | | ✓ | ✓ |
| Former-smoker cigarettes per day | | ✓ | ✓ |
| (Former-smoker cigarettes per day)$^2$ | | ✓ | ✓ |
| Age started smoking (current-smoker) ≤ 18 years[b] | | ✓ | |
| Age started smoking (current-smoker) > 18 years[b] | | ✓ | |
| Age started smoking (former-smoker) ≤ 18 years[b] | | ✓ | ✓ |
| Age started smoking (former-smoker) > 18 years[b] | | ✓ | ✓ |
| Pipe and/or cigar smoker only[b] | | ✓ | |
| Passive cigarette exposure (hours/day) | | ✓ | |
| High school versus other[b] | | ✓ | |
| More than high school versus other[b] | | ✓ | |
| Less than high school versus other[b] | | ✓ | |
| Occupational exposure to air toxics[b] | | ✓ | ✓ |
| Body mass index | | ✓ | ✓ |
| (Body mass index)$^2$ | | ✓ | ✓ |
| Married versus single[b] | | ✓ | |
| Other marital status versus married[b] | | ✓ | |
| Drinks of alcohol per day | | ✓ | |
| Beer consumption[b] | | ✓ | |
| Missing beer consumption[b] | | ✓ | |
| Wine consumption[b] | | ✓ | |
| Missing wine consumption[b] | | ✓ | |
| Liquor consumption[b] | | ✓ | |
| Missing liquor consumption[b] | | ✓ | |

[a] All three of these models were analyzed with standard Cox proportional-hazards regressions.

[b] Dichotomous (yes/no) variable.

[c] Regular occupational exposure to any of the following: asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel engine exhaust, formaldehyde.

**Table 20.** 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 (1.08–1.20) |
| **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 for a description of models and Table 19 for a list of covariates included in each model.

### Alternative Risk Estimates

The relative risks of mortality associated with increases in fine particles or sulfate evaluated at the ranges in exposure that had been considered by the Original Investigators are shown in Table 20 by covariate model specification (Base, Original, Full, and Extended), time axis used in the survival model (calendar year or age), and cause of death (all causes, cardiopulmonary diseases, cardiovascular diseases, respiratory diseases, lung cancer, other cancers, and all other causes). Compared with the Base Model with only air pollution, adjustment for selected risk factors for mortality reduced the relative risk associated with either fine particles or sulfate for all underlying causes of death for both time axes. We observed similar air pollution mortality risks in the three risk models with different groups of covariates: Original, Full, and Extended. The Full and Extended Models included terms for all gender interactions, age started smoking, and nonlinear (squared) terms for cigarettes smoked and BMI that had not been included in the Original Model. Although these additional covariates contributed to the overall characterization of the factors influencing mortality, their inclusion in the Full and Extended Models did not appreciably alter the asso-ciation between air pollution and mortality that had been observed in the Original Model.

Air pollution does not appear to be associated with either deaths from respiratory causes or the "other" causes of death, which include death from all causes except cardiopulmonary disease or cancer. However, both fine particles and sulfate are clearly associated with all-cause mortality and cardiovascular mortality. We found slightly higher air pollution risks if the underlying causes of death were restricted to ischemic heart disease (ICD-9 codes 410–414), with risks associated with sulfate of 1.32 (95% CI: 1.20–1.44) and risks associated with fine particle exposures of 1.37 (95% CI: 1.22–1.53), using the Extended Model with calendar year as the time axis. These results suggest that particulate air pollution may be affecting people with heart diseases more than it affects those with vascular problems.

Although the relative risk of death from lung cancer in relation to exposure to sulfate was significantly greater than unity, fine particles were not associated with an increased risk of lung cancer mortality. A weaker association was observed between deaths from other types of cancer and air pollution. Relative risks of mortality were similar in magnitude for fine particles and sulfate except in the case of lung cancer, for which the relative risk for fine particles (0.99) was less than that for sulfate (1.32). Reanalysis also showed that the association between air pollution and mortality was not sensitive to the specification of the time axis, suggesting that stratification of the hazard function by 1-year age groups was adequate to control for effects of age on survival.

Finally, to test the hypothesis that air pollution was not associated with a cause of death thought not to be affected by air pollution, we conducted an analysis of accidental mortality (ICD-9 codes > 800). Using the Extended Model with calendar year as the time axis, we estimated the risk of accidental deaths associated with particulate air pollution to be 1.07 (95% CI: 0.82–1.39) in the fine particle cohort and 1.01 (95% CI: 0.82–1.23) in the sulfate cohort, which confirmed our hypothesis.

### Effect of Physical Activity and Disease History

We examined the effect of exercise on the association between ambient air pollution and mortality by including exercise level in the Extended Model for all causes of death. Of the full cohort, 28% reported no or a slight amount of exercise, 64% reported moderate exercise, and 8% reported heavy exercise. Exercise level was a determinant of mortality. For the sulfate cohort of 151 cities, for example, the relative risk of mortality associated with exposure to sulfate for subjects at the none/slight exercise level compared with those at the moderate exercise level was 0.63 (95% CI: 0.62–0.65); those engaged in heavy exercise had an even lower risk of mortality, with a relative risk of 0.54 (95% CI: 0.52–0.57). The inclusion of exercise in the Extended Model reduced the relative risk of sulfate from 1.15 (95% CI: 1.09–1.21) to 1.11 (95% CI: 1.05–1.18), using calendar year as the time axis, as it did for fine particles as well; the relative risk of mortality associated with fine particles was reduced from 1.18 to 1.13.

When we controlled for exercise level, the attenuation in risk associated with ambient air pollution was much less in the group without any reported diseases at time of enrollment (a reduction from 1.33 to 1.32 for sulfate and 1.30 to 1.29 for fine particles) than in the group with some reported disease (reduction from 1.14 to 1.10 for sulfate and 1.17 to 1.11 for fine particles). Although it was reduced somewhat, the air pollution effect persisted after we controlled for exercise. We found that the beneficial health effects of exercise were less obvious in the group without disease (RR = 0.88 for moderate versus none/slight, and 0.84 for heavy versus none/slight) than in the group with disease (0.63 for moderate and 0.53 for heavy exercisers).

We note that the effect of air pollution on mortality was more pronounced in people with no reported diseases than in the cohort with some reported disease. The group with no disease was younger overall than the group with a history of disease, with an average age at enrollment of

62.5 years compared to 66.9 years for the group with disease. Members of the disease-free group tended to die at an earlier age (66.8 years on average), compared with the group with disease (70.9 years), but experienced a lower percentage of deaths (3.4%) than the the group with disease (9.0%). Air pollution was associated with a relative risk of 1.30 in the disease-free group, with a corresponding increase of 1.0% in the number of deaths in this group. Air pollution also was associated with a relative risk of 1.14 for the group with disease, corresponding to a 1.3% increase in the number of deaths. The impact of air pollution on the number of deaths as a percentage of cohort members is thus seen to be greater in the group with a history of disease than in the disease-free group.

### Shape of the Concentration-Response Function

The shape of the concentration-response function was examined by plotting city-specific estimates of the logarithm of the relative risk for each city compared with an index city against either fine particles or sulfate for three causes of death (all causes, cardiopulmonary disease, and lung cancer; Figure 5). We determined city-specific relative risk by including all individual risk factors in the Extended Model and the indicator functions for city (using one city as an index) from the Cox regression model, but excluding air pollution. For the sulfate cohort, we chose Greenville SC as the index city because it had sulfate levels near the overall mean concentration observed in the ACS Study. For the same reason, we selected Raleigh NC as the index city for the fine particle cohort of subjects. (Note, however, that we could have selected any index city with identical results.)

We didn't include data for Beaumont TX in these graphs for the sulfate cohort because the log–relative risk of this city was very low for all three causes of death. Boise City ID, with a fine particle concentration of 12.1 $\mu g/m^3$, also had a very low relative risk of all three causes of death compared with the index city. When we removed these two outlying data points, it enhanced the resolution of these graphs for assessing the shape of the concentration-response functions for fine particles and sulfate.

A nonparametric smoothed representation of the relation between air pollution and the city-specific logarithms of the adjusted relative risks is represented on each panel in Figure 6 using a locally weighted smoothing function (LOESS) with a 40% span (Cleveland and Devlin 1988), along with corresponding 95% confidence intervals.

The concentration-response function for sulfate demonstrates an increasing trend across the range of sulfate concentrations in the sulfate cohort, although the curve is relatively flat for concentrations of 10–15 $\mu g/m^3$. The concentration-response curves for fine particles and both all-cause and cardiopulmonary mortality demonstrate near-linear increasing trends through the range of particle levels observed in the fine particle cohort. The apparent absence of an association between lung cancer mortality and exposure to fine particles is consistent with our previous finding that the relative risk of lung cancer mortality was not elevated in this cohort. The relation between mortality and both fine particles and sulfate is explored further in the Flexible Modeling section using flexible spline regression models.

## IDENTIFICATION OF SENSITIVE SUBGROUPS

In addition to examining the sensitivity of the association between air pollution and mortality to specifications of the risk model, the Reanalysis Team sought to identify population subgroups that may be especially susceptible to the health effects of exposure to air pollution. Unless otherwise specified, we have based all analyses of population subgroups on the Extended Model using calendar year as the time axis.

We examined effect modification by stratifying the cohort into categorical levels of the following covariates: educational attainment, reported heart or lung disease, exposure to air toxics, marital status, gender, smoking status (never-, former-, or current-smoker), exercise level, and age at enrollment. These stratified analyses, summarized in Table 21, permitted the Reanalysis Team to identify subgroups of the cohort that were more or less susceptible to sulfate or fine particle air pollution.

For both fine particles and sulfate, air pollution mortality risks decreased significantly ($P < 0.05$) with increasing educational attainment. We observed a similar pattern for cardiopulmonary disease and lung cancer causes of death (Figure 7). There was some evidence ($0.05 < P < 0.1$) that married persons demonstrated a reduced risk related to air pollution (RR = 1.14 for $PM_{2.5}$ and RR = 1.12 for $SO_4^{2-}$) compared with subjects who were not married at the time of the interview (RR = 1.31 for $PM_{2.5}$ and RR = 1.26 for $SO_4^{2-}$).

Although education appeared to be an effect modifier, it was not a strong confounder. The relative risk of mortality from all causes of death associated with exposure to sulfate was 1.16 (95% CI: 1.10–1.23), based on the Extended Model with no adjustment for education and calendar time as the time axis; we obtained a similar value after adjusting for education (RR = 1.15, 95% CI: 1.09–1.21). Exposure to fine particles yielded similar results (RR = 1.19 with no educational adjustment compared to 1.18 with adjustment for education) on the same basis. Education also was not a strong confounder of the air pollution effect for any of the

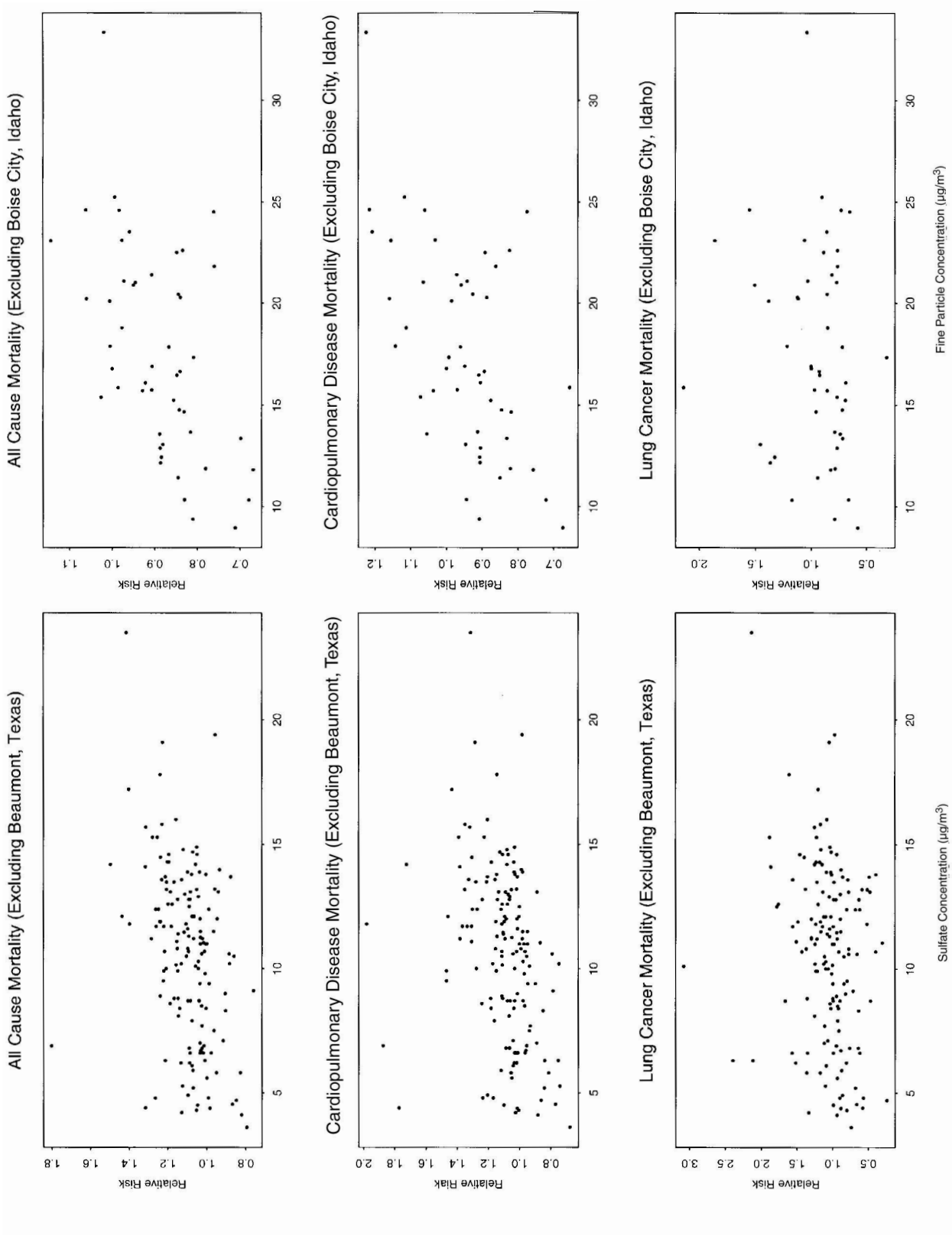



**Figure 5. Shape of concentration-response function (relative risks) in the ACS Study.** Relative risks of mortality from all causes, cardiopulmonary disease, and lung cancer by ambient concentrations of sulfate (linear-quadratic model) or fine particles (linear-quadratic-cubic model) for the reanalysis of the ACS Study. Based on the Extended Model and calendar year as the time axis. Relative risk scaled to unity at minimum concentration. Baseline hazard function stratified by 1-year age groups, gender, and race.

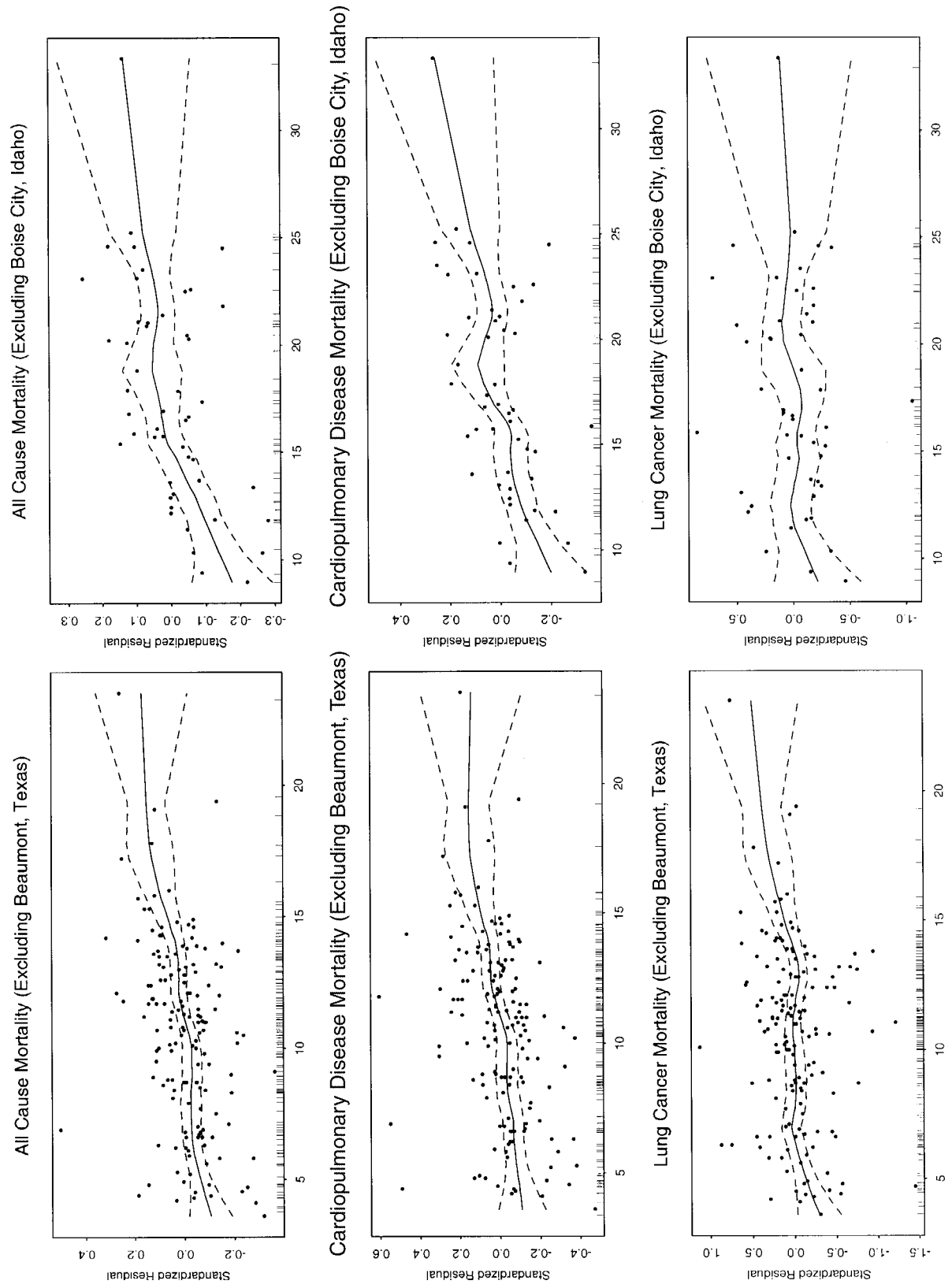



**Figure 6. Shape of concentration-response function (standardized residuals) in the ACS Study.** Standardized residuals of mortality from all causes, cardiopulmonary disease, and lung cancer by ambient concentrations of sulfate (linear-quadratic model) or fine particles (linear-quadratic-cubic model) for the reanalysis of the ACS Study. Based on the Extended Model and calendar year as the time axis. Standardized residual scaled to unity at minimum concentration. Baseline hazard function stratified by 1-year age groups, gender, and race.

**Table 21.** Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles or Sulfate for Selected Personal Characteristics in the ACS Study[a]

| | Fine Particles | | Sulfate | |
|---|---|---|---|---|
| Characteristic | Percent of Cohort | All-Cause Mortality | Percent of Cohort | All-Cause Mortality |
| **Age at Enrollment** | | | | |
| < 50 | 29.3 | 1.19 (0.91–1.56) | 29.3 | 1.14 (0.91–1.42) |
| 50–60 | 36.4 | 1.13 (0.97–1.30) | 36.5 | 1.12 (0.99–1.26) |
| > 60 | 34.3 | 1.19 (1.09–1.29) | 34.2 | 1.16 (1.09–1.24) |
| **Gender** | | | | |
| Male | 43.6 | 1.17 (1.07–1.29) | 43.4 | 1.12 (1.04–1.21) |
| Female | 56.4 | 1.18 (1.06–1.32) | 56.6 | 1.18 (1.09–1.29) |
| **Smoking Status** | | | | |
| Never-smoker | 48.4 | 1.25 (1.11–1.40) | 48.3 | 1.18 (1.08–1.29) |
| Former-smoker | 30.2 | 1.21 (1.07–1.37) | 30.0 | 1.14 (1.03–1.25) |
| Current-smoker | 21.4 | 1.14 (0.99–1.31) | 21.7 | 1.21 (1.08–1.35) |
| **Education Level** | | | | |
| Less than high school | 11.3 | 1.35 (1.17–1.56) | 12.3 | 1.27 (1.13–1.42) |
| High school | 29.8 | 1.23 (1.07–1.40) | 31.3 | 1.20 (1.08–1.33) |
| More than high school | 58.9 | 1.06 (0.95–1.17) | 56.3 | 1.05 (0.96–1.14) |
| **Occupational Exposure to Dust or Fumes[b]** | | | | |
| Yes | 19.4 | 1.08 (0.93–1.27) | 19.8 | 1.14 (1.01–1.28) |
| No | 80.6 | 1.20 (1.11–1.30) | 80.2 | 1.15 (1.08–1.23) |
| **Marital Status** | | | | |
| Married | 84.0 | 1.14 (1.05–1.23) | 84.0 | 1.12 (1.05–1.19) |
| Other | 16.0 | 1.31 (1.13–1.52) | 16.0 | 1.26 (1.12–1.41) |
| **Disease Status[c]** | | | | |
| Heart or lung | 37.1 | 1.15 (1.05–1.26) | 37.2 | 1.15 (1.07–1.23) |
| Cancer | 10.1 | 1.34 (1.15–1.57) | 9.9 | 1.19 (1.05–1.34) |
| Other | 63.7 | 1.19 (1.09–1.29) | 63.2 | 1.12 (1.05–1.20) |
| **Exercise** | | | | |
| No or slight | 28.1 | 1.02 (0.90–1.15) | 27.4 | 1.04 (0.95–1.15) |
| Moderate | 64.4 | 1.19 (1.08–1.31) | 64.7 | 1.16 (1.08–1.25) |
| Heavy | 7.5 | 1.00 (0.73–1.37) | 7.9 | 0.97 (0.76–1.23) |

[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 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender, and race. See Table 19 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[b] Self-reported exposure to asbestos, chemicals/acids/solvents, coal or stone dust, coal tar/pitch/asphalt, diesel engine exhaust, or formaldehyde.

[c] Defined as doctor-diagnosed high blood pressure, heart disease, stroke, chronic bronchitis, emphysema, or asthma. Cancer defined as any type. Other diseases defined as diabetes, gall stones, chronic indigestion, kidney disease, kidney stones, bladder disease, cirrhosis of the liver, tuberculosis, stomach ulcer, duodenal ulcer, diverticulosis, rectal polyps, colon polyps, thyroid condition, arthritis, prostate trouble, or hepatitis.

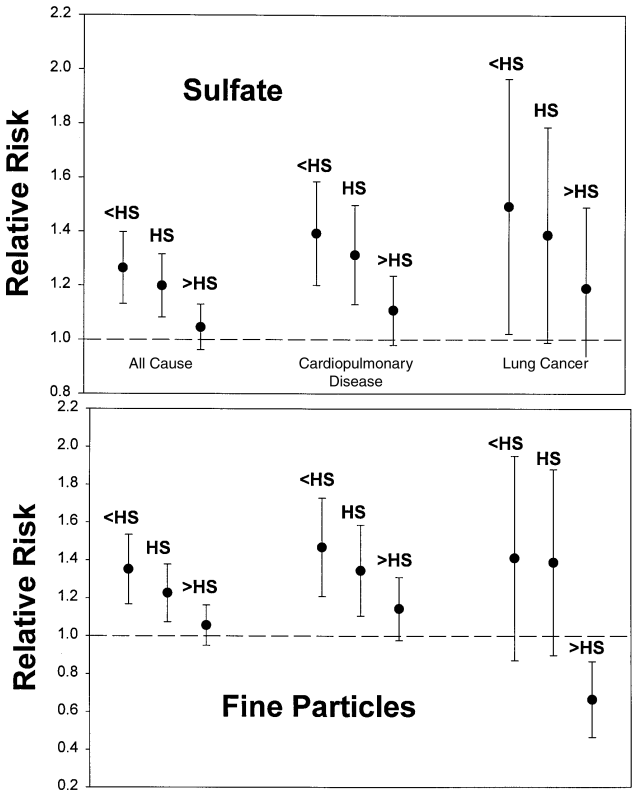



**Figure 7. Relative risks of mortality by cause of death and educational attainment associated with sulfate or fine particles in the reanalysis of the ACS Study.** HS = high school. Error bars represent ±2 SE.

specific underlying causes of death considered (results not shown).

The relative risk of lung cancer mortality for sulfate (RR = 1.33, 95% CI: 1.10–1.61) was greater than that for fine particles (RR = 1.00, 95% CI: 0.79–1.28). As shown in Figure 7, this difference in effect of air pollution largely can be explained by educational attainment. The relative risk of death from lung cancer associated with exposure to fine particles was 1.41 (95% CI: 0.87–2.29) for those individuals who had not completed high school, 1.39 (95% CI: 0.90–2.15) for those who had graduated from high school, and 0.66 (95% CI: 0.46–0.95) for those who had more than high school school education. The corresponding relative risks for exposure to sulfate were 1.49 (95% CI: 1.02–2.18), 1.39 (95% CI: 0.99–1.95), and 1.19 (95% CI: 0.89–1.59), respectively. The inverse relation between mortality and exposure to fine particles among individuals with more than high school education reduced the overall effect of fine particles on mortality; the relation between education and sulfate was attenuated by comparison. For subjects with high school education or less, the effects of fine particles and sulfate on lung cancer mortality were similar.

Although the general pattern of decreasing relative risk with increasing educational attainment shown in Figure 7 for all-cause and cardiopulmonary mortality is similar for fine particles and sulfate, the relative risk of lung cancer mortality is greater than unity (RR = 1.19) for sulfate and less than unity (RR = 0.66) for fine particles. In order to investigate the possibility that this difference might be due to the larger number of cities in the sulfate cohort ($n$ = 151) than in the fine particle cohort ($n$ = 50), we conducted a similar analysis restricted to the 47 cities for which both sulfate and fine particle measurements were available. This restricted analysis produced results similar to those obtained with the full sulfate and fine particle cohorts. Specifically, the relative risks of lung cancer mortality associated with sulfate based on the 47 cities were RR = 2.02 (95% CI: 1.25–3.25) for those with less than high school, 1.42 (95% CI: 0.91–2.21) for those with high school, and 1.14 (95% CI: 0.79–1.67) for those with more than high school education. The relative risks of lung cancer mortality associated with fine particles were 1.45 (95% CI: 0.89–2.36), 1.39 (95% CI: 0.89–2.16), and 0.72 (95% CI: 0.50–1.04), respectively, for the same three educational attainment groups.

To further characterize the effects of air pollution on mortality in relation to educational level or cohort, we classified members into two subgroups corresponding to high school education or less and more than high school education. For each of these two groups, we conducted analyses within categories of the following personal characteristics: exposure to air toxics, marital status, gender, smoking status, presence of heart or lung disease, exercise level, and age at enrollment. Table 22 illustrates that the relative risk for air pollution was greater in the lower education group than in the more educated cohort for all characteristics examined. On the basis of this analysis, it is not clear if there exists a subgroup of the cohort with more than high school education whose longevity is adversely affected by air pollution.

## OCCUPATIONAL EXPOSURES

Occupational exposure is an important potential confounder in air pollution studies because it is plausible that individuals who live in highly polluted areas also work in more polluted environments. Extensive evidence indicates that several types of workplace exposure can cause lung cancer in exposed workers and can lead to nonmalignant respiratory disease. As described in the Occupational Exposures section of the Six Cities Study section, the Reanalysis Team attempted to control for occupational

**Table 22.** Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles or Sulfate for Selected Personal Characteristics by Educational Level and Sample Size[a] in the Reanalysis of the ACS Study[b]

| | Fine Particles | | | | Sulfate | | | |
|---|---|---|---|---|---|---|---|---|
| | High School or Less | | More Than High School | | High School or Less | | More Than High School | |
| Characteristic | *n* | Relative Risk | *n* | Relative Risk | *n* | Relative Risk | *n* | Relative Risk |
| **Age at Enrollment** | | | | | | | | |
| < 50 | 29,130 | 1.51 (1.00–2.27) | 58,421 | 1.00 (0.70–1.43) | 59,411 | 1.29 (0.92–1.81) | 104,587 | 1.05 (0.78–1.41) |
| 50–60 | 42,705 | 1.27 (1.02–1.60) | 66,025 | 1.03 (0.84–1.26) | 85,811 | 1.28 (1.08–1.52) | 118,295 | 0.99 (0.83–1.17) |
| > 60 | 51,105 | 1.28 (1.14–1.43) | 51,432 | 1.08 (0.95–1.23) | 98,818 | 1.23 (1.13–1.34) | 92,127 | 1.08 (0.97–1.19) |
| **Gender** | | | | | | | | |
| Male | 45,708 | 1.34 (1.17–1.52) | 84,602 | 1.02 (0.89–1.17) | 92,078 | 1.24 (1.12–1.37) | 150,620 | 1.00 (0.90–1.12) |
| Female | 77,231 | 1.24 (1.07–1.44) | 91,276 | 1.12 (0.94–1.32) | 151,962 | 1.24 (1.11–1.39) | 164,389 | 1.12 (0.98–1.28) |
| **Smoking Status** | | | | | | | | |
| Never-smoker | 61,540 | 1.35 (1.15–1.57) | 83,127 | 1.13 (0.95–1.35) | 121,612 | 1.22 (1.09–1.37) | 148,329 | 1.12 (0.98–1.28) |
| Former-smoker | 29,191 | 1.40 (1.17–1.66) | 34,680 | 1.06 (0.89–1.26) | 63,596 | 1.25 (1.09–1.44) | 104,016 | 1.03 (0.89–1.18) |
| Current-smoker | 32,208 | 1.30 (1.08–1.57) | 58,071 | 0.98 (0.80–1.21) | 58,832 | 1.38 (1.19–1.59) | 62,664 | 1.01 (0.85–1.20) |
| **Occupational Exposure to Dust or Fumes[c]** | | | | | | | | |
| Yes | 25,385 | 1.14 (0.93–1.39) | 32,440 | 1.04 (0.81–1.32) | 51,862 | 1.20 (1.03–1.39) | 51,017 | 1.07 (0.88–1.30) |
| No | 97,554 | 1.34 (1.20–1.50) | 143,438 | 1.06 (0.94–1.19) | 192,178 | 1.26 (1.15–1.37) | 255,992 | 1.04 (0.95–1.14) |
| **Marital Status** | | | | | | | | |
| Married | 100,712 | 1.29 (1.15–1.44) | 150,203 | 1.00 (0.89–1.13) | 200,713 | 1.23 (1.12–1.34) | 268,686 | 1.01 (0.92–1.11) |
| Other | 22,227 | 1.32 (1.09–1.60) | 25,675 | 1.29 (1.02–1.64) | 43,327 | 1.30 (1.12–1.50) | 46,323 | 1.19 (0.99–1.43) |
| **Heart or Lung Disease[d]** | | | | | | | | |
| Yes | 52,028 | 1.26 (1.11–1.42) | 61,751 | 1.00 (0.87–1.15) | 102,663 | 1.26 (1.15–1.38) | 110,761 | 1.00 (0.90–1.29) |
| No | 70,911 | 1.29 (1.09–1.53) | 114,127 | 1.14 (0.97–1.35) | 141,377 | 1.17 (1.03–1.32) | 204,248 | 1.13 (0.99–1.29) |
| **Exercise** | | | | | | | | |
| No or slight | 30,840 | 1.08 (0.92–1.27) | 51,984 | 0.94 (0.79–1.13) | 59,538 | 1.12 (0.99–1.28) | 91,533 | 0.94 (0.81–1.08) |
| Moderate | 79,494 | 1.31 (1.15–1.49) | 110,483 | 1.09 (0.95–1.25) | 158,238 | 1.24 (1.12–1.37) | 199,022 | 1.08 (0.97–1.20) |
| Heavy | 10,642 | 1.40 (0.92–2.14) | 11,711 | 0.69 (0.42–1.12) | 22,317 | 1.05 (0.77–1.43) | 21,417 | 0.80 (0.55–1.17) |

[a] All *n* values include the two subcohorts of women who had been excluded from the original ACS analyses; however, they do not include subjects with missing data in a particular stratification variable.

[b] 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 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender, and race. See Table 19 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[c] Self-reported exposure to asbestos, chemicals/acids/solvents, coal or stone dust, coal tar/pitch/asphalt, diesel engine exhaust, or formaldehyde.

[d] Defined as doctor-diagnosed high blood pressure, heart disease, stroke, chronic bronchitis, emphysema, or asthma.

confounding by supplementing the original datasets with two new variables: a dirtiness indicator and an indicator of exposure to occupational carcinogens.

The new exposure indices were created by a research team that has had extensive and long-standing experience in assessing occupational exposure in the context of community-based studies (Gérin et al 1985; Siemiatycki et al 1991). One index, the dirtiness indicator, was developed and used in Montréal in a large community-based cancer case-control study (Siemiatycki et al 1991). The other index, a lung carcinogen indicator, was developed with additional information provided by the International Agency for Research on Cancer (Boffetta et al 1995; Ahrens and Merletti 1998). During the baseline interview in the ACS Study, questions had been asked about current or last occupation and the occupation of longest duration. These had been coded by means of an ad hoc system developed by the ACS investigators. Whereas the Six Cities Study coding system had used 442 occupational and industrial categories, the ACS Study coding system had used only 68 occupational categories. Employing these codes, we allocated two new variables to each study subject.

Because the ACS Study used only occupation codes in a relatively small number of categories, it was often impossible

**Table 23.** Occupational Dirtiness Scores and Prevalence of Occupational Exposure to Known Lung Carcinogens in the ACS Study Sulfate Cohort

| Characteristic | Mean Dirtiness Score[a] | Prevalence of Exposure to Known Lung Carcinogens (%) |
|---|---|---|
| All subjects | 1.14 | 2.74 |
| Air pollution[b] | | |
| Low | 1.17 | 2.92 |
| Medium | 1.12 | 2.6 |
| High | 1.13 | 2.74 |
| Education level | | |
| Less than high school | 1.01 | 1.61 |
| High school | 1.13 | 3.68 |
| More than high school | 1.78 | 5.52 |
| Occupational exposure to dust or fumes[c] | | |
| No | 0.91 | 1.55 |
| Yes | 0.08 | 7.57 |
| Gender | | |
| Female | 0.69 | 0.25 |
| Male | 1.76 | 5.99 |
| Smoker | | |
| Never-smoker | 1.03 | 1.87 |
| Ever-smoker | 1.24 | 3.55 |

[a] Occupational dirtiness score ranges from 0 (very clean) to 6 (very dirty) (SEs were less than 0.01).

[b] Based on tertiles of the distribution of sulfate across the 151 cities in the sulfate cohort.

[c] Self-reported in response to checklist of six occupational dusts and fumes.

to find a good fit between our occupation-industry combination and the ACS coding system. The occupation and industry codes used in the Six Cities Study allowed for a much better specification of at-risk jobs.

Appendix B shows that over half of all subjects were in the lowest (cleanest) of the seven occupational dirtiness categories. The following population subgroups had much higher dirtiness levels than their respective complementary subgroups (Table 23): males, subjects with less than high school education, and subjects who self-reported exposure to dusts and fumes. Smokers had slightly higher dirtiness scores than never-smokers or former-smokers. Most important, we found no clear relation between the occupational dirtiness scores and the pollution levels of the towns of residence.

The percentage of subjects who worked in an occupation that has been shown, or that is suspected, to be associated with an elevated risk of lung cancer was 2.7%. The patterns by subgroup were similar to those of the dirtiness index; again, we found no evidence of increasing exposure to occupational carcinogens with increasing environmental pollution.

As detailed in Appendix B, we found little evidence of any independent effect of the occupational dirtiness score on mortality from any of the causes examined. However, we found a relative risk of mortality from lung cancer associated with occupational exposure to lung carcinogens, as determined by our lung carcinogens variable, of 1.23 (95% CI: 1.00–1.51) in the fine particle cohort and 1.19 (95% CI: 1.02–1.39) in the sulfate cohort. Taken together, the lack of association between both new covariates and air pollution, and the equivocal findings on the associations between the new covariates and mortality, would suggest that the air pollution–mortality associations are unlikely to be confounded by either the occupational dirtiness score or the lung carcinogen variable.

Tables 24 and 25 show estimates of the overall air pollution–mortality associations when we included different sets of covariates as confounders. Neither the dirtiness index, in two different parameterizations, nor the lung carcinogen variable had a noticeable impact on the estimates of interest.

Table 26 shows the relative risks of mortality from all causes, cardiopulmonary disease, and lung cancer associated with sulfate and fine particle indices of air pollution among different population subgroups. In contrast with the original analysis, we included in the statistical models the dirtiness index for all three causes of death and, in addition, the lung carcinogen index for lung cancer mortality. We obtained results very similar to those that had been published by the Original Investigators.

We examined whether occupational dirtiness is an effect modifier for the air pollution effects. As indicated in Table 27, we found an apparently much greater effect of air pollution among subjects with the highest dirtiness score compared with those with low or medium levels of occupational dirtiness; however, there was no logical trend from the low to the medium category. We previously showed that educational attainment was also an important effect modifier, so we further explored the way the risk due to air pollution is mediated by education and occupational dirtiness. Table 28 shows the results of an analysis of the air pollution effect on all-cause mortality stratified by education level and dirtiness score. We see some indication in the fine particle cohort that the two effect modifiers have independent effects; this is less clear in the sulfate cohort, however, where the dirtiness variable appears to have a stronger impact than the education variable.

**Table 24.** Relative Risks of Mortality Associated with an Increase in Fine Particles Using the Original and Extended Models and Adjusting for Alternative Indices of Occupational Exposure in the Reanalysis of the ACS Study[a]

| Model | All Causes | Cardiopulmonary Disease | Lung Cancer |
|---|---|---|---|
| Original[b] | 1.19 (1.10–1.27) | 1.30 (1.18–1.45) | 1.03 (0.81–1.31) |
| Original + dirtiness A[c] (+ lung carcinogens[d]) | 1.18 (1.10–1.27) | 1.30 (1.17–1.44) | 1.03 (0.81–1.31) |
| Original[e] | 1.16 (1.08–1.26) | 1.29 (1.15–1.44) | 1.02 (0.79–1.32) |
| Original + dirtiness B[f] (+ lung carcinogens) | 1.16 (1.08–1.26) | 1.29 (1.15–1.44) | 1.02 (0.79–1.32) |
| Extended[g] | 1.18 (1.09–1.26) | 1.30 (1.17–1.44) | 1.00 (0.79–1.28) |
| Extended[g] + dirtiness A (+ lung carcinogens) | 1.17 (1.09–1.26) | 1.29 (1.16–1.43) | 1.00 (0.79–1.28) |
| Extended[e] | 1.15 (1.07–1.24) | 1.28 (1.15–1.43) | 0.99 (0.77–1.28) |
| Extended[e] + dirtiness B (+ lung carcinogens) | 1.15 (1.07–1.24) | 1.28 (1.14–1.43) | 0.99 (0.77–1.28) |

[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$^3$. Data are RRs with 95% CIs.

[b] The Original Model included indicators of current and former smoking, a two-level indicator of education, occupational exposure to dust or fumes, body mass index, and an indicator of alcohol consumption; baseline hazard function was stratified by 5-year age groups. See Table 19 for a complete list of covariates included in the Original Model. This analysis used a cohort of 298,817 subjects. For consistancy with our Extended Model, occupational analyses using the Original Model are based on 1-year age stratificaton, rather than the 5-year age stratification used by the Original Investigators.

[c] Dirtiness A is a categorical dirtiness variable.

[d] A binary variable for occupations with exposure to lung carcinogens; used only in the analyses for lung cancer.

[e] This analysis used only the 274,022 observations for which occupational codes were available.

[f] Dirtiness B is a continuous dirtiness variable.

[g] The Extended Model included the Original Model covariates plus other indicators of smoking status, a different two-level indicator of education, marital status, other indicators of alcohol consumption, and interactions between gender and various other covariates; baseline hazard function was stratified by 1-year age groups. See Table 19 for a complete list of covariates included in the Extended Model. This analysis used a cohort of 298,817 subjects.

**Table 25.** Relative Risks of Mortality Associated with an Increase in Sulfate Using the Original and Extended Models and Adjusting for Alternative Indices of Occupational Exposure in the Reanalysis of the ACS Study[a]

| Model | All Causes | Cardiopulmonary Disease | Lung Cancer |
|---|---|---|---|
| Original[b] | 1.17 (1.10–1.23) | 1.27 (1.17–1.38) | 1.36 (1.13–1.65) |
| Original + dirtiness A[c] (+ lung carcinogens[d]) | 1.16 (1.10–1.23) | 1.26 (1.17–1.40) | 1.36 (1.12–1.64) |
| Original[e] | 1.14 (1.08–1.21) | 1.25 (1.15–1.36) | 1.34 (1.09–1.64) |
| Original + dirtiness B[f] (+ lung carcinogens) | 1.14 (1.07–1.21) | 1.25 (1.15–1.36) | 1.34 (1.09–1.64) |
| Extended[g] | 1.15 (1.09–1.21) | 1.25 (1.16–1.36) | 1.33 (1.10–1.61) |
| Extended[g] + dirtiness A (+ lung carcinogens) | 1.14 (1.08–1.21) | 1.25 (1.15–1.35) | 1.32 (1.09–1.60) |
| Extended[e] | 1.12 (1.06–1.19) | 1.24 (1.13–1.35) | 1.31 (1.07–1.60) |
| Extended[e] + dirtiness B (+ lung carcinogens) | 1.12 (1.06–1.19) | 1.23 (1.13–1.34) | 1.31 (1.07–1.61) |

[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$^3$. Data are RRs with 95% CIs.

[b] The Original Model included indicators of current and former smoking, a two-level indicator of education, occupational exposure to dust or fumes, body mass index, and an indicator of alcohol consumption; baseline hazard function was stratified by 1-year age groups. See Table 19 for a complete list of covariates included in the Original Model. This analysis used a cohort of 559,049 subjects.

[c] Dirtiness A is a categorical dirtiness variable.

[d] A binary variable for occupations with exposure to lung carcinogens; used only in the analyses for lung cancer.

[e] This analysis used only the 511,031 observations for which occupational codes were available.

[f] Dirtiness B is a continuous dirtiness variable.

[g] The Extended Model included the Original Model covariates plus other indicators of smoking status, a different two-level indicator of education, marital status, other indicators of alcohol consumption, and interactions between gender and various other covariates; baseline hazard function was stratified by 1-year age groups. See Table 19 for a complete list of covariates included in the Extended Model. This analysis used a cohort of 559,049 subjects.

**Table 26.** Relative Risks of Mortality from All Causes, Cardiopulmonary Disease, and Lung Cancer Associated with an Increase in Fine Particles or Sulfate in Various Subsets of the Population Using the Original Model + Dirtiness + Lung Carcinogens in the Reanalysis of the ACS Study[a]

| Model | All Causes | Cardiopulmonary Disease | Lung Cancer |
|---|---|---|---|
| **Fine Particles** | | | |
| All subjects | 1.16 (1.08–1.26) | 1.29 (1.15–1.44) | 1.02 (0.79–1.32) |
| Females | 1.14 (1.02–1.29) | 1.40 (1.17–1.67) | 0.83 (0.53–1.28) |
| Males | 1.18 (1.06–1.30) | 1.22 (1.06–1.40) | 1.14 (0.83–1.56) |
| Never-smokers | 1.23 (1.08–1.40) | 1.36 (1.13–1.64) | 0.75 (0.29–1.90) |
| Females | 1.21 (1.03–1.42) | 1.44 (1.14–1.83) | 0.74 (0.25–2.21) |
| Males | 1.29 (1.02–1.62) | 1.21 (0.88–1.65) | 0.85 (0.14–5.10) |
| Ever-smokers | 1.13 (1.03–1.24) | 1.24 (1.08–1.42) | 1.03 (0.79–1.35) |
| Females | 1.07 (0.90–1.28) | 1.33 (1.01–1.76) | 0.83 (0.51–1.33) |
| Males | 1.15 (1.03–1.29) | 1.21 (1.04–1.42) | 1.14 (0.83–1.58) |
| **Sulfate** | | | |
| All subjects | 1.14 (1.07–1.21) | 1.25 (1.15–1.36) | 1.34 (1.09–1.64) |
| Females | 1.18 (1.07–1.29) | 1.36 (1.18–1.56) | 1.23 (0.86–1.75) |
| Males | 1.11 (1.03–1.20) | 1.19 (1.06–1.32) | 1.39 (1.09–1.79) |
| Never-smokers | 1.19 (1.08–1.31) | 1.33 (1.15–1.53) | 2.08 (1.03–4.23) |
| Females | 1.20 (1.06–1.35) | 1.34 (1.12–1.60) | 2.15 (0.92–5.03) |
| Males | 1.17 (0.99–1.39) | 1.29 (1.03–1.62) | 2.03 (0.56–7.33) |
| Ever-smokers | 1.12 (1.04–1.21) | 1.21 (1.09–1.35) | 1.28 (1.04–1.58) |
| Females | 1.15 (1.00–1.32) | 1.38 (1.11–1.72) | 1.08 (0.74–1.59) |
| Males | 1.11 (1.01–1.21) | 1.16 (1.03–1.31) | 1.38 (1.07–1.78) |

[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 $\mu g/m^3$. The Original Model included the following covariates: $PM_{2.5}$, indicators of current- and former-smokers, current-smoker pack-years, former-smoker pack-years, a two-level indicator of education level, occupational exposure to dust or fumes, and body mass index; baseline hazard function was stratified by 1-year age groups. See Table 19 for a complete list of covariates included in the Original Model. "Dirtiness" is a continuous occupational variable; "lung carcinogens" is a binary variable for occupations with exposure to lung carcinogens and was used only in the analyses for lung cancer. Data are RRs with 95% CIs.

**Table 27.** Relative Risks of Mortality from All Causes and Cardiopulmonary Disease Associated with an Increase in Fine Particles or Sulfate Using the Original Model Stratified by Occupational Dirtiness in the Reanalysis of the ACS Study[a]

| | Fine Particles | | Sulfate | |
|---|---|---|---|---|
| Dirtiness | All Causes | Cardiopulmonary Disease | All Causes | Cardiopulmonary Disease |
| Low | 1.13 (1.02–1.25) | 1.28 (1.10–1.48) | 1.12 (1.03–1.21) | 1.25 (1.11–1.40) |
| Medium | 1.10 (0.96–1.27) | 1.13 (0.92–1.40) | 1.10 (0.98–1.22) | 1.12 (0.95–1.31) |
| High | 1.39 (1.16–1.67) | 1.52 (1.18–1.96) | 1.30 (1.14–1.49) | 1.46 (1.21–1.76) |

[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 $\mu g/m^3$. Analyses based on the Original Model; baseline hazard function was stratified by 1-year age groups. See Table 19 for a complete list of covariates incorporated into the Original Model. For occupational dirtiness, low = 0, medium = 1–3, and high = 4–6. Data are RRs with 95% CIs.

**Table 28.** Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles or Sulfate Using the Original Model[a] Stratified by Occupational Dirtiness and Educational Level in the Reanalysis of the ACS Study[b]

| Dirtiness | Less Than High School | High School | More Than High School |
|---|---|---|---|
| **Fine Particles** | | | |
| Low | 1.26 (1.01–1.57) | 1.13 (0.94–1.36) | 1.08 (0.93–1.25) |
| Medium | 1.48 (1.03–2.13) | 1.12 (0.81–1.54) | 1.02 (0.85–1.23) |
| High | 1.46 (1.09–1.95) | 1.42 (1.03–1.95) | 1.41 (0.98–2.03) |
| **Sulfate** | | | |
| Low | 1.41 (1.18–1.67) | 1.09 (0.95–1.26) | 1.01 (0.89–1.14) |
| Medium | 1.11 (0.85–1.46) | 1.16 (0.91–1.48) | 1.07 (0.93–1.23) |
| High | 1.20 (0.97–1.48) | 1.50 (1.19–1.90) | 1.32 (1.00–1.74) |

[a] Analyses based on the Original Model without the two-level indicator of education; baseline hazard function was stratified by 1-year age groups. See Table 19 for a complete list of covariates incorporated into the Original Model.

[b] 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 $\mu g/m^3$. For occupational dirtiness, low = 0, medium = 1–3, and high = 4–6. Data are RRs with 95% CIs.

## ALTERNATIVE AIR QUALITY DATA

### The Original Investigators' Approach

A database had been developed by the Original Investigators on sulfate particle concentrations [$SO_4^{2-}$(OI)] from high-volume samplers for total suspended particles, starting with sulfate data for 98 cities assembled by Özkaynak and Thurston (1987), who had previously developed city-specific ambient sulfate levels using monitoring data from the National Aerometric Database (NAD). Specifically, annual average sulfate concentrations had been calculated by Özkaynak and Thurston for 1980 using monitoring stations that met selection criteria established by the US EPA. This database then was augmented by the addition of average annual sulfate concentrations for 27 cities not meeting EPA's criteria for annual coverage, bringing the total number of cities to 127.

In order to further increase the number of cities available for analyses, sulfate data obtained from the Inhalable Particle Monitoring Network (IPMN) had also been included by the Original Investigators. Sulfate data from the IPMN were used for an additional 29 cities. Sites were required to have reported at least ten samples in each quarter of the year, and the annual mean had been computed as the mean of the four quarterly means. Sulfate means thus were available for a total of 154 metropolitan statistical areas (MSAs). Of these, three MSAs were not represented in the ACS cohort, which left 151 cities for analysis by the Original Investigators.

Data on fine particles from the IPMN had been obtained by the Original Investigators for 50 cities as reported in Lipfert and colleagues (1988). Because only median values by city were displayed in this report, median rather than mean values were used to characterize annual fine particle concentrations in the analysis conducted by the Original Investigators.

### The Reanalysis Team's Approach

In order to evaluate the sensitivity of the original findings to the indicators of exposure to fine particle air pollution used by the Original Investigators, the Reanalysis Team constructed a number of alternative indicators of ambient particle levels using data from the US EPA's Aerometric Information Retrieval System (AIRS). We also obtained 1980 to 1989 daily 24-hour cumulative concentrations of TSP, and sulfate from TSP, for all monitoring stations in as many of the cities used in the original ACS analysis as possible. This latter information was extracted from the AIRS database by the Center for Air Pollution Impact and Trend Analysis (CAPITA) at Washington University in St Louis.

Sulfate data derived from TSP were available from AIRS for 132 cities in 1980, 124 in 1981, and no more than 60 cities in 1982 to 1989. Because of the marked reduction in sulfate monitoring in the latter period, we restricted our attention to the two years 1980 and 1981 for which data were available for at least 124 cities. In addition to ambient sulfate concentrations, we also retrieved supplementary data on land use surrounding the monitor (mobile, commercial, residential, agricultural, or industrial). In further sensitivity analyses, we restricted our attention to sulfate data for which there were at least 20 observations per year among all monitoring stations within a given city. Imposition of this selection criterion resulted in 107 eligible cities

for 1980, and 111 cities for 1981. There were a total of 126 cities for which sulfate concentrations were available for either 1980 or 1981. There were a total of 156 cities for which TSP data were available for either 1980 or 1981.

The high-volume samplers employed in the National Aerometric Database used glass-fiber filters, which were subject to artifacts because sulfur dioxide was present in the atmosphere. The sulfate measurements obtained from the IPMN were not subject to such artifacts because Teflon filters were used. In 41 cities both monitoring systems were employed. We adjusted the sulfate values obtained using glass-fiber filters to those obtained using Teflon filters by applying a linear regression equation in which city-specific averages were compared. We present details of the methods used and equations formed in Appendix D (which is available on request from the Health Effects Institute). We also developed separate calibration equations for three regions of the United States (West; Ohio Valley and Northeast; and East) and two seasons (April to September and October to March), because both sulfate and sulfur dioxide levels vary by region and season. We then augmented the city-specific average adjusted sulfate values, for those cities without sulfate observations from AIRS, by average sulfate values from the IPMN. This resulted in estimates for 144 of the 151 cities that had been examined by the Original Investigators. We were unable to find sulfate data for seven cities in either the AIRS or IPMN databases.

Recognizing that artifactual sulfate is associated with the use of glass-fiber filters in air quality samplers, the Reanalysis Team conducted an analysis of the association between mortality and ambient sulfate after correcting for the artifactual sulfate using a calibration equation we developed empirically. To compare our results with those obtained by the Original Investigators, however, we conducted other sensitivity analyses using the uncorrected sulfate data. (The results presented below permit one to assess the impact of the artifactual sulfate on the sulfate-mortality associations.)

The Reanalysis Team also obtained data from the IPMN directly from the EPA (this network is maintained by EPA for research rather than monitoring purposes). For the data pertinent to the ACS Study, the network consisted of dichotomous (DC) samplers with 15-μm and 2.5-μm cutpoints that measured $PM_{15}$(DC) (the mean inhalable fraction from dichotomous samplers), $PM_{15-2.5}$(DC) (mean coarse fraction from dichotomous samplers), and $PM_{2.5}$(DC) (mean fine fraction from dichotomous samplers). The IPMN also maintained high-volume samplers measuring mass, or total suspended particles [TSP(IPMN)], in addition to high-volume samplers using size-selective inlet (SSI) technology to record $PM_{15}$(SSI). Each method and instrument that measured mass also recorded data on sulfate concentrations.

Table 29 presents the definitions of pollutant variables and the sources of pollutant data. The city-specific mean or median levels of each of the indices of fine particle air pollution developed by the Reanalysis Team are presented in Appendix D. These values formed the basis for the following sensitivity analyses.

**Risk Estimates Based on Alternative Air Quality Data**

The means or medians of various indices of air pollution are summarized in Table 30. The median fine particle concentrations that had been used by the Original Investigators are denoted by $PM_{2.5}$(OI MD). These values are in good agreement with $PM_{2.5}$(DC MD), the median fine particle concentrations based on data from the dichotomous samplers, used by the Reanalysis Team, and are slightly less than the mean values $PM_{2.5}$(DC) used by the Team. Note that the sulfate levels $SO_4^{2-}$(OI) that had been used by the Original Investigators on the basis of 1980 monitoring data are comparable to the unadjusted sulfate data for the years 1980–1981 inclusive [$SO_4^{2-}{}_{(cb\text{-}unadj)}$] used by the Reanalysis Team. Adjustment by region and season for the artifactual sulfate resulted in notably reduced mean sulfate levels for $SO_4^{2-}{}_{(cb\text{-}adj\ US)}$, $SO_4^{2-}{}_{(cb\text{-}adj\ region)}$, and $SO_4^{2-}{}_{(cb\text{-}adj\ season)}$.

Figure 8 shows a comparison of the city-specific median concentrations of fine particles used by the Original Investigators and by the Reanalysis Team. With the exception of results for Denver CO, these two datasets had very good agreement. We calculated a median value of 7.20 μg/$m^3$ for fine particles in Denver, whereas the Original Investigators had used a median value of 16.09 μg/$m^3$. The IPMN database used by the Reanalysis Team included two stations operating in Denver from July 1980 to June 1983, which yielded median values of 5.67 μg/$m^3$ and 15.39 μg/$m^3$, respectively. A third station, which operated from July 1980 to March 1983, recorded a median value of 8.75 μg/$m^3$. A fourth station operated as a duplicate colocated station from July 1981 to June 1982, yielding a median value of 9.31 μg/$m^3$. In the absence of more detailed information on the source of the values reported by Lipfert and colleagues (1988), it is not possible to resolve this discrepancy between the values that had been used by the Original Investigators and those calculated by the Reanalysis Team.

We evaluated the influence of this discrepancy on the association between mortality and fine particle air pollution by removing the data for Denver from the analysis. We determined that Denver had not been an influential

**Table 29.** Summary of Pollutant Variables and the Sources of Data Used in the Reanalysis of the ACS Study

| Pollutant | Definition | Source of Data | Number of Cities in Original ACS Dataset[a] | Number of Cities in Alternative Dataset | Used by |
|---|---|---|---|---|---|
| $PM_{2.5}$(DC) | **Mean** fine particle fraction | Dichotomous samplers; based on IPMN 1979–1983 | | 63 | Reanalysis Team |
| $PM_{2.5}$(DC MD) | **Median** fine particle mass concentration | Dichotomous samplers; based on IPMN 1979–1983 | | 50 | Reanalysis Team |
| $PM_{2.5}$(OI MD) | **Median** fine particle mass concentration | Based on IPMN 1979–1983 | 50 | | Original Investigators |
| $PM_{15-2.5}$(DC) | **Mean** coarse particle fraction (15-μm particles minus 2.5-μm particles) | Dichotomous samplers; based on IPMN 1979–1983 | | 63 | Reanalysis Team |
| $PM_{15}$(DC) | **Mean** inhalable particle fraction | Dichotomous samplers; based on IPMN 1979–1983 | | 63 | Reanalysis Team |
| $PM_{15}$(SSI) | **Mean** inhalable particle fraction | High-volume SSI samplers; based on IPMN 1979–1983. | | 59 | Reanalysis Team |
| $SO_4^{2-}$(OI) | Sulfate data | Based on NAD 1980–1981 | 151 | | Original Investigators |
| $SO_4^{2-}$(DC) | Sulfate data from $PM_{15}$(DC) | Based on IPMN 1979–1983 | | 51 | Reanalysis Team |
| $SO_4^{2-}{}_{(cb\text{-}unadj)}$ | Sulfate data for 1980–1981 inclusive, unadjusted for artifactual sulfate | Based on IPMN and NAD 1980–1981 | | 144 | Reanalysis Team |
| $SO_4^{2-}{}_{(cb\text{-}adj\ season)}$ | Sulfate data for 1980–1981 inclusive, with season-specific adjustment for artifactual sulfate | Based on IPMN and NAD 1980–1981 | | 144 | Reanalysis Team |
| $SO_4^{2-}{}_{(cb\text{-}adj\ region)}$ | Sulfate data for 1980–1981 inclusive, with region-specific adjustment for artifactual sulfate | Based on IPMN and NAD 1980–1981 | | 144 | Reanalysis Team |
| $SO_4^{2-}{}_{(cb\text{-}adj\ US)}$ | Sulfate data for 1980–1981 inclusive, with US-specific adjustment for artifactual sulfate | Based on IPMN and NAD 1980–1981 | | 144 | Reanalysis Team |
| TSP | Total suspended particles | High-volume samplers; based on NAD 1980–1981 | | 156 | Reanalysis Team |
| TSP(IPMN) | Mean total suspended particle mass concentrations | High-volume samplers measuring mass TSP; based on IPMN 1979–1983 | | 58 | Reanalysis Team |

[a] Of the 50 cities for which fine particle data were available, only 3 did not also have sulfate data available; therefore, a total of 154 cities contributed air quality data for the ACS Study.

observation in the dataset used by the Original Investigators, as neither the distribution of the fine particle data (Table 30) nor the relative risks of mortality (Table 31) varied appreciably with the inclusion or exclusion of the Denver data. However, when we used our fine particle data (eg, 1.14 with Denver and 1.17 without Denver for all-cause mortality) the relative risks for mortality were slightly reduced.

For IPMN data, $PM_{2.5}$(DC) was correlated weakly with $PM_{15-2.5}$(DC) ($r = 0.11$), but associated more strongly with $PM_{15}$(DC) ($r = 0.65$). Sulfate, however, was associated positively with fine particles ($r = 0.53$). Sulfate values that had been developed by the Original Investigators were correlated highly with those developed by the Reanalysis Team ($r = 0.92$) for the 144 cities with values in common (Figure 9). The distributions of the two measures of sulfate, $SO_4^{2-}$(OI) and $SO_4^{2-}{}_{(cb\text{-}unadj)}$, also were similar (see Table 30).

**Table 30.** Distribution of the Indices of Particulate Air Pollution (in $\mu g/m^3$) in the Reanalysis of the ACS Study

| Pollutant[a] | Mean | SD | Percentiles | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 5 | 25 | 50 | 75 | 95 | 100 |
| $PM_{2.5}$(OI MD) | 17.5 | 5.1 | 9 | 10 | 13 | 17 | 21 | 25 | 33 |
| $PM_{2.5}$(OI MD) with Denver omitted | 17.5 | 5.1 | 9 | 10 | 13 | 17 | 21 | 25 | 33 |
| $PM_{2.5}$(DC MD) | 17.4 | 5.3 | 8 | 9 | 13 | 17 | 21 | 25 | 33 |
| $PM_{2.5}$(DC MD) with Denver omitted | 17.6 | 5.2 | 9 | 10 | 13 | 17 | 21 | 25 | 33 |
| $PM_{2.5}$(DC) | 20.0 | 5.3 | 10 | 12 | 16 | 2 | 23 | 29 | 38 |
| $PM_{15}$(DC) | 40.0 | 9.3 | 25 | 29 | 33 | 39 | 4 | 59 | 77 |
| $PM_{15-2.5}$(DC) | 20.1 | 7.1 | 9 | 11 | 15 | 19 | 23 | 33 | 42 |
| $PM_{15}$(SSI) | 58.7 | 13.0 | 34 | 40 | 51 | 56 | 66 | 84 | 101 |
| TSP(IPMN) | 74.6 | 16.6 | 42 | 50 | 65 | 71 | 85 | 108 | 113 |
| TSP | 66.4 | 15.3 | 40 | 49 | 56 | 64 | 72 | 101 | 127 |
| $SO_4^{2-}$(DC) | 6.7 | 4.4 | 0.9 | 1.9 | 3.4 | 6.3 | 8.9 | 12.9 | 27.0 |
| $SO_4^{2-}$(OI) | 10.6 | 3.6 | 3.6 | 4.5 | 8.1 | 11.0 | 13.1 | 15.7 | 23.5 |
| $SO_4^{2-}_{(cb\text{-}unadj)}$ | 10.5 | 3.4 | 3.0 | 4.7 | 8.0 | 12.7 | 12.6 | 15.7 | 19.4 |
| $SO_4^{2-}_{(cb\text{-}adj\ US)}$ | 6.7 | 3.2 | 0.0 | 1.4 | 4.3 | 7.0 | 8.8 | 11.6 | 15.0 |
| $SO_4^{2-}_{(cb\text{-}adj\ region)}$ | 5.9 | 3.4 | 0.0 | 1.0 | 2.8 | 6.1 | 8.1 | 11.1 | 17.0 |
| $SO_4^{2-}_{(cb\text{-}adj\ season)}$ | 6.6 | 3.1 | 0.3 | 1.7 | 4.2 | 6.9 | 8.6 | 11.7 | 15.6 |

[a] 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 for the sources of pollutant data. All values are means unless indicated by MD (median).

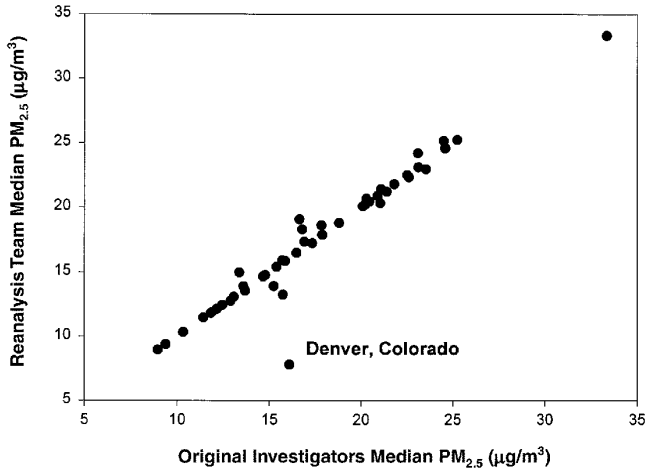



**Figure 8. Comparison of fine particle median values between the Original Investigators of the ACS Study and the Reanalysis Team.** Reanalysis Team values were based on data from the IPMN.

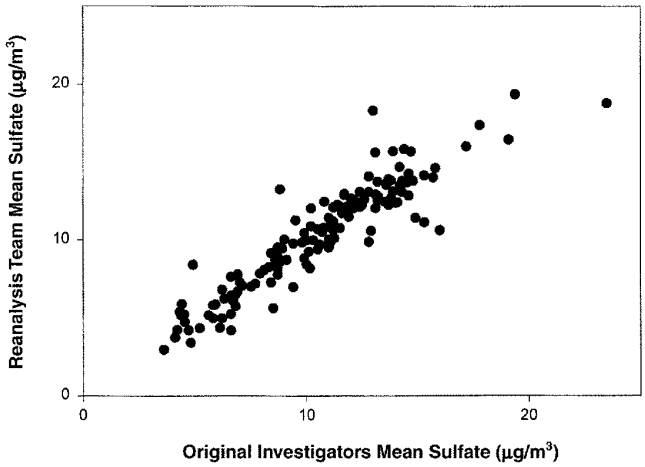



**Figure 9. Comparison of mean sulfate values between the Original Investigators of the ACS Study and the Reanalysis Team.** Reanalysis Team values were based on 1980 and 1981 data from AIRS and the IPMN.

**Table 31.** Relative Risks of Mortality from All Causes, Cardiopulmonary Disease, and Lung Cancer Associated with Various Measures of Air Pollution from 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) |
| $PM_{2.5}$(OI MD) Denver Omitted | 49 | 1.18 (1.10–1.27) | 1.30 (1.17–1.44) | 0.99 (0.78–1.26) |
| $PM_{2.5}$(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 MD) Denver Omitted | 49 | 1.17 (1.09–1.26) | 1.28 (1.15–1.42) | 1.02 (0.81–1.30) |
| $PM_{2.5}$(DC) | 63 | 1.12 (1.06–1.19) | 1.26 (1.16–1.38) | 1.08 (0.88–1.32) |
| $PM_{15}$(DC) | 63 | 1.05 (1.01–1.09) | 1.09 (1.04–1.15) | 1.01 (0.90–1.13) |
| $PM_{15-2.5}$(DC) | 63 | 1.01 (0.97–1.06) | 1.01 (0.95–1.08) | 0.97 (0.83–1.13) |
| $PM_{15}$(SSI) | 59 | 1.02 (0.99–1.05) | 1.07 (1.03–1.11) | 0.98 (0.89–1.08) |
| TSP(IPMN) | 58 | 1.00 (0.98–1.02) | 1.02 (0.99–1.05) | 0.95 (0.89–1.02) |
| TSP | 156 | 0.99 (0.98–1.00) | 0.99 (0.97–1.01) | 0.94 (0.90–0.99) |
| $SO_4^{2-}$(DC) | 51 | 1.17 (1.10–1.23) | 1.29 (1.19–1.40) | 1.09 (0.90–1.33) |
| $SO_4^{2-}$(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) |
| $SO_4^{2-}{}_{(cb\text{-}adj\ season)}$ | 144 | 1.17 (1.09–1.25) | 1.29 (1.17–1.42) | 1.16 (0.93–1.44) |

[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 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender, and race. See Table 19 for a complete list of covariates included in the Extended Model. 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 for the sources of pollutant data. All values are means unless indicated by MD (median).

For lung cancer mortality, relative risks for fine particles varied around 1.0 with almost all 95% confidence intervals including unity, meaning they were not significant. By comparison, the relative risks for all measures of sulfate were high (from 1.16 to 1.33; except for $SO_4^{2-}$(DC), which was 1.09), and two of them were statistically significant [$SO_4^{2-}$(OI) and $SO_4^{2-}{}_{(cb\text{-}adj\ region)}$]. The relative risks of all-cause mortality associated with TSP, TSP(IPMN), $PM_{15}$(DC), $PM_{15-2.5}$(DC), and $PM_{15}$(SSI) were less (in the range 0.99 to 1.05) than those for fine particles and sulfate (ranging from 1.12 to 1.23). We observed a similar pattern for cardiopulmonary deaths.

The relative risks of all-cause and cardiopulmonary mortality associated with our estimates of sulfate values for the 144 cities were similar to those that had been obtained by the Original Investigators using their estimates for 151 cities. When we used sulfate values adjusted for the artifactual sulfate with one equation for the entire United States [$SO_4^{2-}{}_{(cb\text{-}adj\ US)}$], we obtained slightly higher relative risks of mortality from all causes and cardiopulmonary disease than we did when we used the unadjusted sulfate concentrations. We calculated these relative risks for a change in sulfate equal to the difference in mean concentrations between the most-polluted city and the least-polluted city; for the unadjusted sulfate data, this value was 19.9 $\mu g/m^3$; for the adjusted sulfate data, this value was 15.0 $\mu g/m^3$. Evaluating the relative risks on the basis of adjusted sulfate values at their corresponding range reduced the size of the effect to that of the unadjusted values. This is not unexpected, as the adjustment is based on a linear equation. The correlation between the adjusted and unadjusted sulfate values was 0.92. The lung cancer risk, however, was much lower (RR = 1.18, 95% CI: 0.96–1.47) if the adjusted sulfate values were employed. This value is somewhat similar to that obtained using sulfate

values from the IPMN on 51 cities (RR = 1.09, 95% CI: 0.90–1.33). Thus the association between sulfate and lung cancer mortality is sensitive to the air pollution data used.

When we evaluated the relative risks of mortality on the basis of adjusted sulfate values for three regions of the United States, or two seasons, the risks were larger than those that were based on a single adjustment for the entire United States. These risks remained higher even if they were evaluated at the respective ranges.

Because several of the cities involved in the ACS Study had limited sulfate data, resulting in potentially unstable estimates of annual averages, we restricted our analysis to those cities with at least 20 observations for sulfate from AIRS. The relative risk of all-cause mortality on the basis of this restricted sample, which included 126 cities, was 1.26 (95% CI: 1.18–1.34). The relative risk that had been calculated from the Original Investigators' sulfate measurements for these same 126 cities was 1.21 (95% CI: 1.14–1.29). These results suggest that there was some instability in risk estimates resulting from city selection (the Original Investigators' risk estimate calculated from measurements in 151 cities was 1.15), but not from the selection of number of observations per city.

We also examined the influence of monitor location on the association between sulfate and mortality by restricting the monitors selected for data analysis to those whose land use code was residential or urban, thereby excluding sites designated as industrial, agricultural, or mobile. This restriction on land use reduced the number of cities available for analysis from 126 to 120 (on the basis of our selection criterion that required at least 20 observations per year). This resulted in only a marginal change in the relative risk of all-cause mortality (RR = 1.24, 95% CI: 1.16–1.32) compared with relative risk calculated using data from the unrestricted 126 cities (RR = 1.26, 95% CI: 1.18–1.34).

### Seasonal Effects

The additional air pollution data assembled by the Reanalysis Team permitted an assessment of differences in risk by season. Specifically, we examined the association between the gaseous pollutants (CO, $NO_2$, $O_3$, and $SO_2$) and all-cause, cardiopulmonary, and lung cancer deaths for exposures occurring in two periods of the year: the warmer period of April to September and the cooler period of October to March. We found that sulfur dioxide, nitrogen dioxide, and carbon monoxide concentrations tended to be higher in the cooler time period, whereas ozone levels clearly were elevated during the warmer months (Table 32). For all causes and cardiopulmonary causes of death, the relative risks for each of the four gases examined tended to be higher in the warmer period than in the cooler period. Table 32 shows that the pattern was not as consistent, however, for lung cancer mortality.

## FLEXIBLE MODELING

We analyzed the ACS Study data by applying the same flexible spline regression model we used to describe the Six Cities Study data in that Flexible Modeling section. (Further details of this analysis are given in Appendix C.) We used this generalization of the Cox proportional-hazards model to investigate possible nonlinear or time-dependent effects of fine particles and sulfate in the ACS Study. With two exceptions, we used methods similar to those used in the flexible analyses of the Six Cities Study.

First, in our analysis of the Six Cities Study, we had difficulty fully characterizing the shape of the exposure–response

**Table 32.** Relative Risks of Mortality from All Causes, Cardiopulmonary Disease, and Lung Cancer Associated with Gaseous Copollutants by Season from the Reanalysis of the ACS Study[a]

| | | | Cause of Death | | |
|---|---|---|---|---|---|
| Pollutant | Season | Seasonal Mean Concentration | All Causes | Cardiopulmonary Disease | Lung Cancer |
| $SO_2$ (ppb) | April–September | 7.18 | 1.35 (1.25–1.45) | 1.48 (1.33–1.64) | 1.40 (1.10–1.79) |
| | October–March | 11.24 | 1.23 (1.17–1.29) | 1.29 (1.20–1.38) | 1.00 (0.85–1.18) |
| $NO_2$ (ppb) | April–September | 23.65 | 0.96 (0.91–1.02) | 0.96 (0.88–1.04) | 0.79 (0.65–0.96) |
| | October–March | 27.20 | 0.93 (0.89–0.97) | 0.94 (0.88–0.99) | 1.01 (0.87–1.16) |
| CO (ppm) | April–September | 1.33 | 1.02 (0.96–1.08) | 1.00 (0.92–1.09) | 0.80 (0.65–0.99) |
| | October–March | 1.73 | 0.95 (0.90–1.00) | 0.90 (0.84–0.97) | 0.86 (0.72–1.01) |
| $O_3$ (ppb) | April–September | 30.44 | 1.02 (0.96–1.07) | 1.08 (1.01–1.16) | 0.81 (0.69–0.94) |
| | October–March | 15.07 | 0.81 (0.76–0.87) | 0.82 (0.74–0.91) | 0.78 (0.61–0.99) |

[a] Analyses based on the Extended Model; see Table 19 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

curve because observations were available for only six cities. In contrast, the ACS Study included 50 cities in the fine particle cohort and 151 cities in the sulfate cohort, thereby affording a greater opportunity to explore the shape of the exposure–response relation between fine particles and mortality.

The second difference involves the sampling strategy by which we selected random subsets from the ACS cohort, which is much larger than the Six Cities cohort. To conform to the limitations of our flexible modeling software with respect to sample size, we fit the flexible product model to 10 randomly selected disjoint subsets of the ACS Study participants, each including 2,200 individuals. Thus a total of 22,000 individuals, including 1,700 who had died, formed the basis for hypothesis testing using the combined likelihood ratio test discussed in Appendix C. After we accounted for the differences in degrees of freedom, we achieved a level of statistical precision with this combined sample that was comparable to that in the Six Cities Study.

Similar considerations led us to modify our case-cohort approach in order to obtain more stable estimates of the flexible functions of interest. We conducted our modified case-cohort analysis on data from a subset of 2,500 individuals that was created by combining a random subcohort of 1,200 study participants with a random sample of 1,300 deaths.

In our analyses of the 10 random subsets of the ACS cohort, we did not identify a consistent pattern in changes over time on the impact of either fine particles or sulfate on mortality. Whereas the combined likelihood ratio test provided evidence of statistically significant ($P < 0.05$) departures from the Cox proportional-hazards assumption for both fine particles and sulfate, temporal patterns in the hazard ratio varied considerably among subsets, with no pattern being more frequent than any other. The modified case-cohort analyses confirmed the lack of systematic temporal patterns for either fine particles or sulfate; those analyses indicated that the adjusted effects of particles remained nearly constant during the follow-up period (see Figures C.9 and C.13 in Appendix C).

Flexible analyses of the ACS data yielded evidence of nonlinear exposure–response relations ($P < 0.01$) for both fine particles and sulfate. Whereas some differences in subset-specific estimates of the exposure–response relation were apparent, we found evidence of nonlinearity for both fine particles and sulfate. This was confirmed by the case-cohort analysis, which allowed us to estimate the two exposure–response curves more precisely. Figure 10 shows the 3 *df* quadratic spline estimate of the nonlinear effect of fine particles on log–hazard ratio for all-cause mortality, adjusted for pack-years of cigarette smoking for

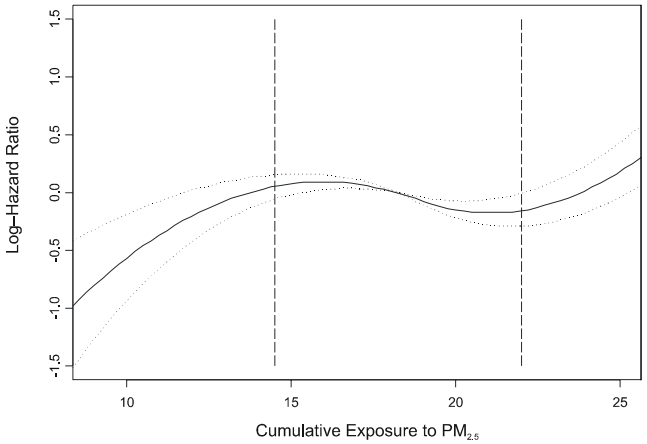



**Figure 10. Impact of cumulative exposure to fine particles in the ACS Study.** Flexible quadratic spline estimate (3 *df*) of the nonlinear effect of increasing the exposure to fine particles on the log–hazard ratio of mortality in a case-cohort subset of the ACS Study, adjusted for BMI, education level, and pack-years of smoking for current- and former-smokers. The log–hazard ratio was associated with a change in fine particles (24.5 $\mu g/m^3$) equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. Along the horizontal axis, the solid curve represents the point estimate of the log–hazard ratio and the dashed curves the point-wise 95% confidence interval. The left and right dashed vertical lines indicate the first and third quartiles of fine particles in the sample of 2,500 individuals included in the ACS Study.

current- and former-smokers, BMI, and education. This analysis suggests that a monotone exposure–response relation may be limited to the lower half of the range of particle exposures, with little difference in response between moderate and high levels of exposure.

Figure 11 shows the case-cohort estimate of the adjusted effect of sulfate on the log hazard in the ACS Study. The

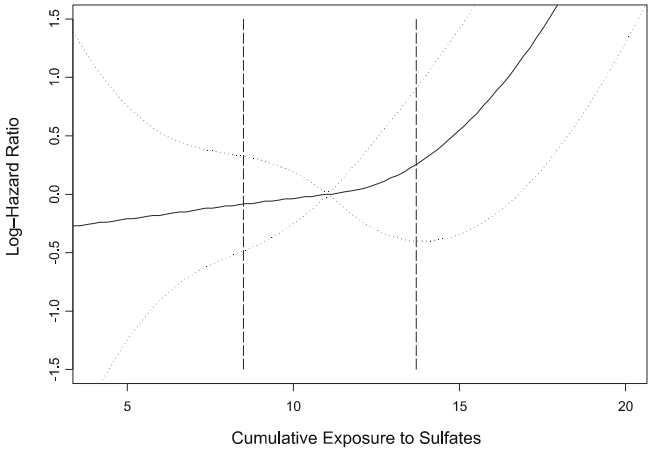



**Figure 11. Impact of cumulative exposure to sulfate in the ACS Study.** Flexible quadratic spline estimate (3 *df*) of the nonlinear effect of increasing the level of exposure to sulfate on the log–hazard of mortality in a case-cohort subset of the ACS Study. The log–hazard ratio was associated with a change in sulfate (19.9 $\mu g/m^3$) equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. The solid curve represents the point estimate of the log–hazard ratio and the dashed curves represent the point-wise 95% condidence interval.

exposure–response curve is nonlinear even though it is monotone. The curve is quite flat in the lower half of the range of observed sulfate levels, corresponding to exposures below about 14 $\mu g/m^3$. At higher exposures, however, sulfate is associated with a relatively sharp increase in mortality. This pattern is consistent with that observed in most of the random subsets (see Figure C.12 in Appendix C).

Although the curve in Figure 11 depicts only the relative impact of changes in sulfate on mortality, we can calculate the magnitude of this impact by multiplying the estimate in Figure 11 by the time-dependent estimate (refer to Appendix C). When we combine the two estimates, our results show that the impact of sulfate on mortality is quite modest; the hazard ratio that corresponds to a change from the minimum to the maximum of the 151 city-specific sulfate levels does not exceed 1.10, which is comparable to the results that had been obtained by the Original Investigators in their analysis of the ACS data.

Using flexible analyses of the ACS data, we also demonstrated a nonlinear relation between BMI and mortality. Figure 12 shows the 3 *df* estimate of the adjusted effect of BMI, based on the case-cohort approach. The relation between BMI and log hazard is U-shaped, as it was in the analysis of the Six Cities Study data, with risk increasing at both low and high values of BMI. This suggests that the association between BMI and mortality may be approximated well by a quadratic function.

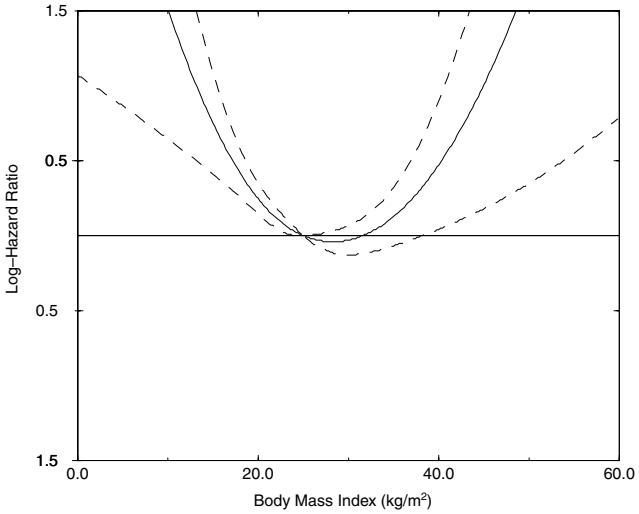



**Figure 12. Flexible nonlinear estimate of the effect of BMI in the ACS Study.** Flexible quadratic spline (3 *df*) estimate of the nonlinear effect of increasing body mass index on the log–hazard of mortality in a case-cohort subset of the ACS Study. The log–hazard ratio is plotted with respect to the mean BMI as reference value. The solid curve represents the point estimates of the log–hazard ratio and the dashed curves represent the pointwise 95% confidence interval.

## ECOLOGIC COVARIATES

Both the Six Cities Study and the ACS Study had included a number of covariates in the risk models that had been developed by the Original Investigators, in addition to the main covariate of interest, namely, ambient particle levels. Individual-level data (data supplied by subjects via questionnaires) were available for each covariate included in the models, except fine particle air pollution, which was measured at the city level. Because particle levels were represented at the ecologic rather than the individual level, it is conceivable that the associations that had been observed between particles (particularly fine particles and sulfate) and mortality in these two studies could have been due at least in part to other city-level characteristics correlated with both air pollution and mortality. To assess the possibility of such ecologic confounding, the Reanalysis Team obtained data on a number of ecologic covariates not considered by the Original Investigators, and examined the effect of including these new city-level covariates on the air pollution–mortality association. Because the Six Cities Study had involved, at most, 5 *df* for incorporating additional ecologic covariates, we restricted our analysis to the ACS Study, which involved 151 cities in the sulfate cohort and 50 cities in the fine particle cohort.

### Selection of Ecologic Covariates

The Reanalysis Team applied several criteria in selecting the additional ecologic covariates to be included in this component of the sensitivity analyses. First, a potential ecologic covariate had to represent a valid measure of a well-defined attribute of each city. Second, there had to be a plausible biological or social mechanism by which a candidate ecologic covariate could affect mortality. And third, we required access to reliable data on those ecologic covariates selected for inclusion in the reanalysis.

There are essentially three related types of ecologic variables. "Aggregated" ecologic variables are derived by aggregating characteristics that have been measured at the individual level to obtain a city-level summary measure. Such aggregated variables are often used as surrogates for measures of individual-level variables. In other words, most aggregated variables are considered to have direct analogs at the individual level. "Group-level" variables represent attributes that have individual analogs, but usually are obtained from measurements at the city level (eg, maximum daily exposure to ozone). "Global" or "contextual" variables refer to attributes of cities that do not have analogs at the individual level (eg, total area of green space, or population density). Although contextual variables represent group-level attributes, they may be

aggregated from individual data. For example, income disparity as measured by the Gini coefficient, which must be calculated from individual income data, has no analog at the individual level (Kaplan et al 1996). Other relevant contextual variables include city-level unemployment or poverty, both of which measure constructs other than individual employment or poverty status.

Although aggregated ecologic variables are sometimes used as substitutes for measurements of the same constructs at the individual level, the results of such analyses often do not represent the level of association that would be measured had individual-level variables been used. This is referred to as ecologic (or cross-level) bias, and has been discussed extensively in the literature (eg, Piantadosi et al 1988; Greenland and Morgenstern 1989; Brenner et al 1992 a,b; Greenland and Robbins 1994).

The ACS Study can be considered a hybrid design, in that detailed individual information had been collected, but the primary exposure variables (fine particles and sulfate) had been derived from measurements taken at the city level. Thus, although the study had provided data on the joint distribution of many covariates across the study population, exposure had been assessed on an ecologic level. This may not be a serious difficulty, depending on the extent to which city-level ambient air pollution concentrations, as estimated from regularly collected data at the beginning of the study period, had represented the relevant exposure metric for individuals. However, if these exposure metrics also had represented certain characteristics inherent to the city, and these were correlated with other city-level characteristics, then it is possible that there could have been residual confounding (on the ecologic level) by these other city-level characteristics. Our purpose in this set of sensitivity analyses was to select plausible ecologic covariates that we could use to address this last concern. We thus attempted to identify variables that, rather than mimicking individual traits, measured essential characteristics of the cities (ie, contextual variables).

In selecting ecologic covariates for this component of the sensitivity analyses, the Reanalysis Team drew upon the literature on the determinants of population health. Evans and Stoddart (1990) outlined a number of contextual risk factors for health, including the social environment, the physical environment, and health care. These three categories guided our search for possible ecologic confounders (Figure 13). We searched Medline to find evidence of links between mortality and specific contextual variables within these categories. For those variables for which the literature indicated a possible health risk, we sought data that had been collected in the early 1980s on counties and metropolitan areas from US government sources. Although data were not available at this level of geographic resolution for all potential contextual variables, we did identify a number of relevant ecologic covariates for inclusion in the reanalysis.

A detailed description of the process we used to select those ecologic covariates included in our sensitivity analyses of the ACS Study is given in Appendix E (which is available on request from the Health Effects Institute). In order to ensure that the ecologic covariate values were representative of the MSAs included in the ACS Study, we carefully examined the geographic area spanned by all 158 MSAs that had been considered by the Original Investigators (details are provided in Appendix F, which is available on request from the Health Effects Institute). The city-specific values of the ecologic covariates we selected are listed in Appendix G (also available on request from the Health Effects Institute).

As described in Appendix E, we selected 20 ecologic covariates suitable to include in the reanalysis from a longer list of 30 potential variables (Table 33). Eight measures of the social environment were considered: population change, percentage of white residents, percentage of black residents, mean income of residents in 1979, poverty level in 1979, income disparity as measured by the Gini

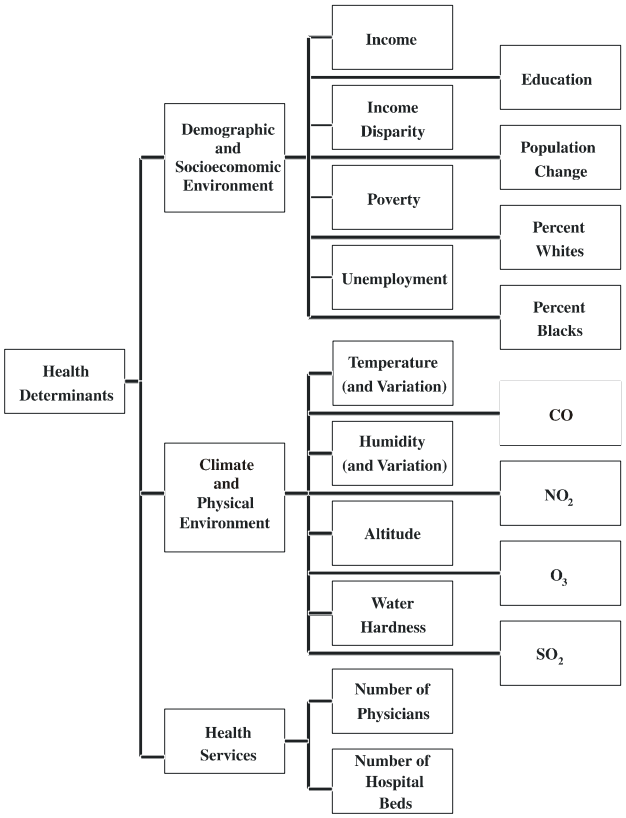



**Figure 13. Summary of selected ecologic covariates.**

**Table 33.** A Summary of the Ecologic Covariates and the Sources of Data Used in the Reanalysis of the ACS Study

| Ecologic Covariate | Number of Cities: Sulfate | Number of Cities: Fine Particles | Description of Covariate and Source of Data |
|---|---|---|---|
| **Demographic Factors** | | | |
| Population change | 139 | 48 | Percentage of net change in number of residents between 1980 and 1986; US Bureau of the Census, 1986 Population Estimates by County with Components of Change[a] |
| Whites | 151 | 50 | Percentage of persons residing in the MSA in 1980 who classified themselves as being of white race; US Bureau of the Census, County Population Estimates (experimental) by Age, Sex, and Race: 1980–1984[a] |
| Blacks | 151 | 50 | Percentage of persons residing in the MSA in 1980 who classified themselves as being of black race; 1980 Census of Population and Housing (April 1, 1980), STF3 data[b] |
| **Socioeconomic Factors** | | | |
| Income | 151 | 50 | Mean annual per capita income in US dollars for 1979; 1980 Census of Population and Housing (April 1, 1980), STF3 data[b] |
| 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; US Bureau of the Census, Current Population Reports, Series P-26, Numbers 86-NE-SC, 86-S-SC, 86-ENC-SC, 86-WNC-SC, and 86-W-SC; and 1980 Census of Population and Housing, STF3 data[a] |
| Income disparity | 151 | 50 | Gini coefficient (see Selection of Ecologic Covariates section for description) calculated from income group data for 1979 as outlined in Shyrock et al 1976; 1980 Census of Population and Housing (April 1, 1980), STF3 data[b] |
| Unemployment | 151 | 50 | Percentage of total civilian labor force who were unemployed in 1986; US Bureau of Labor Statistics, Employment and Unemployment in States and Local Areas, Annual, 1986[a] |
| 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; 1980 Census of Population and Housing (April 1, 1980), STF3 data[b] |
| **Health Services** | | | |
| Physicians | 138 | 48 | Number of professionally active, non-Federal physicians with known addresses per 100,000 residents as of July 1, 1985; American Medical Association's Physician Characteristics and Distribution in the US, 1986[a] |
| Hospital beds | 139 | 48 | Number of hospital beds per 100,000 residents as of July 1, 1985; survey (September 30, 1985) of all hospitals (registered and unregistered) excluding old-age homes, convalescent homes, and sanatoriums; American Hospital Association's Hospital Statistics, 1986[a] |
| **Climate** | | | |
| Temperature | 135 | 46 | Maximum daily temperature (°F) averaged by month for 1980 through 1989; the average of all monthly averages was used as the ecologic covariate; data provided directly to us by the US National Climatic Data Center of the National Oceanic and Atmospheric Administration (NOAA), Asheville NC |
| Temperature variation | 135 | 46 | Variation in maximum daily temperature (°F) averaged by month for 1980 through 1989; the average of the monthly variation was used as the ecologic covariate; data provided directly to us by NOAA |
| Relative humidity | 95 | 37 | Minimum daily relative humidity (%) averaged by month for 1984 through 1989; the mean of all monthly averages was used as the ecologic covariate; data provided directly to us by NOAA |
| Relative humidity variation | 95 | 37 | Variation in minimum daily relative humidity (%) averaged by month for 1984 through 1989; the average of the monthly variation was used as the ecologic covariate; data provided directly to us by NOAA |
| **Physical Environment** | | | |
| Altitude | 110 | 38 | Measured as meters above sea level; US Places (24000+); from Environmental Systems Research Institute (1999) |
| Water hardness | 109 | 49 | Concentration of $CaCO_3$ (ppm) in drinking water, measured ca 1970; National Institutes of Health data cited in Feinleib et al 1979 |
| **Gaseous Copollutants** | | | |
| CO | 107 | 44 | Daily average concentrations averaged by year for 1980; from residential, commercial, or mobile monitors |
| $NO_2$ | 74 | 33 | Daily average concentrations averaged by year for 1980; from residential, commercial, or mobile monitors |
| $O_3$ | 117 | 45 | Daily 1-hour maximum concentrations |
| $SO_2$ | 113 | 38 | Daily average concentrations averaged by year for 1980; from residential, commercial, or mobile monitors |

[a] Cited in the County and City Data Book (1988).

[b] Data from Geolytics Software (1999).

coefficient, unemployment in 1986, and percentage of residents age 25 or older who had completed high school. We obtained two measures of the provision of health care services: number of physicians per 100,000 residents and number of hospital beds per 100,000 residents. In terms of the physical environment, we considered altitude, water hardness, and climate (average maximum temperature, average monthly variation in maximum temperature, average daily relative humidity, and average monthly variation in daily relative humidity). We used four gaseous copollutants in these analyses as well: carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide.

Unfortunately, we were unable to obtain data on certain ecologic covariates for some of the cities included in the ACS Study. In particular, data on relative humidity and the gaseous copollutants were sparse. For this reason, we sometimes conducted the sensitivity analyses that used those ecologic covariates on subsets of the original cohort of cities. The numbers of cities for which we obtained values for the selected ecologic covariates in both the sulfate and fine particle cohort of the ACS Study are given in Table 33.

**Incorporation of Ecologic Covariates in Cox Regression**

The Reanalysis Team examined the effect of these ecologic covariates on the association between particulate air pollution and mortality by incorporating them in the Cox proportional-hazards regression model in the same way that air pollution, itself an ecologic covariate, had been used in the Cox models employed by the Original Investigators. Instead of using the Original Model as the basis of our analyses, however, we used the Extended Model developed in the Alternative Risk Models section for the ACS Study data. This permitted us to make full use of all the individual-level covariates as well as examining the effects of these additional ecologic covariates.

Table 34 summarizes the Extended Model results of including, in turn, each of the 20 ecologic covariates selected by the Reanalysis Team. The first column of data in this table shows the relative risks of all-cause mortality associated with sulfate exposure in a model without the ecologic covariate. Note that because values for some of the ecologic covariates were not available for some cities, the relative risks of mortality associated with sulfate vary somewhat depending on the number of cities for which the ecologic covariate data were available (see Table 33). The second column of data shows the relative risk of all-cause mortality associated with sulfate exposure, with the ecologic covariate included in the Extended Model. The inclusion of most of these ecologic covariates does not appear to have a marked impact on the relative risk of all-cause mortality for sulfate. The inclusion of population change, which has an inverse association with mortality (RR = 0.85, 95% CI: 0.81–0.89) and is correlated negatively with sulfate ($r = -0.40$), decreases the relative risk from 1.15 to 1.06 in the Extended Model, reducing the excess relative risk from 0.15 to 0.06. The inclusion of sulfur dioxide, which has a positive association with mortality (RR = 1.30, 95% CI: 1.23–1.38) and is positively correlated with sulfate ($r = 0.48$), reduces the relative risk from 1.16 to 1.04. The lower confidence limits on the relative risk adjusted for sulfur dioxide (RR = 1.04, 95% CI: 0.98–1.11) is less than 1.00, resulting in the loss of formal statistical significance after adjustment.

Adjustment for the effects of ecologic covariates in this manner requires careful interpretation. Abramowicz and colleagues (2000) have shown that the inclusion of ecologic covariates in the model results in a downward bias, unlike the case of linear regression, in the estimated relative risk of the exposure of primary interest (fine particle air pollution in the present case). Although this bias may be small, some degree of bias toward the null value of unity appears to persist regardless of the strength of the association between the ecologic covariate and mortality, or between the ecologic covariate and particle levels.

The relative risks and associated confidence limits for the ecologic covariates themselves are shown in the last two columns in Table 34. The relative risk of mortality associated with population change in the Extended Model excluding sulfate is 0.85, with a 95% CI (0.81–0.89) that excluded the null value of 1.00. (Inclusion of sulfate in the model increases the relative risk of population change only slightly, from 0.85 to 0.87.) Because population change is thus a strong ecologic predictor of all-cause mortality, the reduction in the relative risk of sulfate (from 1.15 to 1.06) could be an overadjustment. However, the extent of overadjustment is difficult to judge without further information on the nature of the relation between population change and mortality.

Other covariates that appear to be significantly associated with mortality in the absence of sulfate include hospital beds (RR = 1.13, at the range of the values among the cities for which such health services data were available), income (RR = 0.93), income disparity as measured by the Gini coefficient (RR = 0.88), unemployment (RR = 1.12), temperature (RR = 0.88), temperature variation (RR = 1.18), and water hardness (RR = 1.08). With the exception of sulfur dioxide, none of the gaseous copollutants (CO, $NO_2$, and $O_3$) demonstrated a positive and clearly significant association with mortality.

The Reanalysis Team also employed three multivariate models that permitted simultaneous adjustment for more than one ecologic covariate. The first multivariate model

**Table 34.** Relative Risks of Mortality from All Causes Associated with an Increase in Sulfate After Adjusting for Selected Ecologic Covariates[a]

| Ecologic Covariate | Relative Risk from Sulfate | | Relative Risk from Ecologic Covariate | |
|---|---|---|---|---|
| | Without Ecologic Covariate | With Ecologic Covariate | Without Sulfate | With Sulfate |
| **Demographic Factors** | | | | |
| Population change | 1.15 (1.08–1.21) | 1.06 (0.99–1.13) | 0.85 (0.81–0.89) | 0.87 (0.82–0.91) |
| Whites | 1.15 (1.09–1.21) | 1.18 (1.11–1.25) | 1.02 (0.98–1.06) | 1.06 (1.02–1.11) |
| Blacks | 1.15 (1.09–1.21) | 1.17 (1.10–1.24) | 1.01 (0.96–1.06) | 0.96 (0.91–1.01) |
| **Socioeconomic Factors** | | | | |
| Income | 1.15 (1.09–1.21) | 1.15 (1.08–1.21) | 0.93 (0.88–0.97) | 0.93 (0.88–0.97) |
| Poverty | 1.15 (1.09–1.21) | 1.15 (1.09–1.22) | 0.95 (0.91–1.00) | 0.94 (0.90–0.99) |
| Income disparity | 1.15 (1.09–1.21) | 1.15 (1.09–1.21) | 0.88 (0.84–0.93) | 0.88 (0.83–0.93) |
| Unemployment | 1.15 (1.09–1.21) | 1.13 (1.06–1.19) | 1.12 (1.06–1.19) | 1.09 (1.03–1.16) |
| Education | 1.15 (1.09–1.21) | 1.13 (1.06–1.20) | 0.91 (0.86–0.96) | 0.96 (0.90–1.02) |
| **Health Services** | | | | |
| Physicians | 1.15 (1.08–1.21) | 1.14 (1.08–1.21) | 0.95 (0.89–1.01) | 0.96 (0.90–1.01) |
| Hospital beds | 1.15 (1.08–1.21) | 1.13 (1.07–1.20) | 1.13 (1.06–1.21) | 1.12 (1.04–1.19) |
| **Climate** | | | | |
| Temperature | 1.14 (1.07–1.21) | 1.11 (1.04–1.17) | 0.88 (0.85–0.92) | 0.90 (0.86–0.94) |
| Temperature variation | 1.14 (1.07–1.21) | 1.10 (1.04–1.17) | 1.18 (1.11–1.24) | 1.16 (1.09–1.22) |
| Relative humidity | 1.13 (1.05–1.21) | 1.14 (1.05–1.24) | 1.05 (0.99–1.12) | 0.98 (0.91–1.06) |
| Relative humidity variation | 1.13 (1.05–1.21) | 1.16 (1.08–1.25) | 0.96 (0.90–1.02) | 0.92 (0.86–0.98) |
| **Physical Environment** | | | | |
| Altitude | 1.10 (1.04–1.18) | 1.16 (1.08–1.24) | 1.05 (0.99–1.12) | 1.12 (1.04–1.19) |
| Water hardness | 1.11 (1.04–1.18) | 1.12 (1.05–1.19) | 1.08 (1.02–1.13) | 1.08 (1.03–1.14) |
| **Gaseous Copollutants** | | | | |
| CO | 1.14 (1.08–1.21) | 1.14 (1.08–1.21) | 0.98 (0.92–1.03) | 0.97 (0.92–1.03) |
| $NO_2$ | 1.11 (1.04–1.19) | 1.14 (1.06–1.22) | 0.93 (0.89–0.98) | 0.91 (0.87–0.96) |
| $O_3$ | 1.15 (1.08–1.22) | 1.15 (1.09–1.22) | 0.93 (0.87–0.99) | 0.92 (0.86–0.98) |
| $SO_2$ | 1.16 (1.09–1.23) | 1.04 (0.98–1.11) | 1.30 (1.23–1.38) | 1.28 (1.20–1.37) |
| **Multiple Covariate Analyses** | | | | |
| Gaseous copollutants | 1.09 (1.02–1.17) | 1.00 (0.93–1.09) | | 1.36 (1.26–1.46)[b] |
| Socioeconomic status[c] | 1.15 (1.08–1.21) | 1.10 (1.02–1.18) | | |
| 25%[d] | 1.10 (1.02–1.18) | 0.99 (0.90–1.09) | | 1.25 (1.14–1.38)[b] |

[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 sulfate was 19.9 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender, and race. See Table 19 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[b] Whenever $SO_2$ was included in a multivariate model, the relative risk of mortality associated with it is given in the far right column.

[c] Includes population change and the five socioeconomic factors (income, poverty, income disparity, unemployment, and education).

[d] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with the pollutant of interest. In this analysis: population change, temperature variation, altitude, and $SO_2$.

included all socioeconomic variables as well as population change. The second model included all four gaseous copollutants (CO, $NO_2$, $O_3$, and $SO_2$). The third model included all those ecologic covariates that, when analyzed individually in a bivariate model, had resulted in a change of 25% or more in the excess relative risk of mortality associated with the pollutant of interest. Whereas the first ecologic multivariate regression model was intended to provide maximal adjustment for socioeconomic determinants of mortality, the second was designed to isolate the effects of sulfate from gaseous copollutants. The third model, which sought to identify potential confounders empirically, was based on a strategy similar to that employed by Gérin and colleagues (1998); they used logistic regression analysis in a large-scale population-based case-control study of cancer incidence in relation to nearly 400 chemical and other agents found in the workplace.

Some caution is required in the interpretation of the relative risks for sulfate under the multivariate Cox regression models, both because of the possibility of overadjustment noted previously, and because of the moderately high correlation among some of the ecologic covariates considered here (see Appendix G). For example, the correlation between poverty rate and mean income in the sulfate cohort is –0.58 (Table G.7, Appendix G). Similarly, the correlation between mean maximum daily temperature and income disparity is +0.60, because income disparity tends to be greater in the southern United States. The highest correlation ($r$ = –0.96) occurs between percent white and percent black, although none of our multivariate models included both population subgroups.

The relative risk of sulfate alone (RR = 1.15) is reduced following simultaneous adjustment for population change and the five socioeconomic factors (RR = 1.10), although the adjustment is less than that obtained with population change alone (RR = 1.06). This reduced adjustment, which incorporates population change in the multivariate model, is attributable to the complex structure of correlation among the variables in this model. On the other hand, simultaneous adjustment for all four gaseous copollutants leads to a relative risk of sulfate (RR = 1.00) that is less than that following adjustment for sulfur dioxide alone (RR = 1.04). This is similar to the relative risk obtained (RR = 0.99) after adjustment for those covariates (population change, variation in maximum temperature, altitude, and sulfur dioxide) that induced a 25% change in the relative risk from sulfate alone. Again, note that there is a possibility of overadjustment in these latter two cases.

The results of incorporating these same ecologic covariates in the Extended Model for cardiopulmonary and lung cancer mortality are shown in Tables 35 and 36, respectively. A number of ecologic covariates (population change, income, income disparity, unemployment, education, physicians, hospital beds, temperature variation, relative humidity, water hardness, and sulfur dioxide) appear to be associated with cardiopulmonary mortality (Table 35), although etiologic hypotheses underlying these associations are not readily apparent in all cases. Nonetheless, adjustment for these ecologic covariates does not alter the original conclusions concerning the positive association between cardiopulmonary mortality and sulfate exposure. Most of the ecologic covariates do not appear to have a marked impact on estimated relative risks of lung cancer mortality for sulfate (Table 36), although adjustment for altitude reduces the relative risk from 1.24 to 1.14. In the Extended Model runs that ex-cluded sulfate, relative humidity, altitude, and ozone all appear to be associated with lung cancer mortality.

Similar ecologic analyses were carried out for the fine particle cohort. The relative risk of all-cause mortality for fine particles, as with sulfate, was diminished after adjustment for population change or sulfur dioxide (Table 37). This same effect was observed for cardiopulmonary mortality (Table 38). Because lung cancer mortality was not associated with fine particles, no adjustment for ecologic covariates was attempted in this case.

To a certain extent, the effects of the ecologic covariates on the relative risks of mortality for fine particle air pollution can be explained by spatial convergence between the ecologic covariate and exposure to fine particles. Fine particles and sulfate were both highest in the Ohio Valley and around Gary IN, and decreased slightly toward the South and more dramatically toward the West. The two ecologic covariates correlated most highly with both fine particles and sulfate were population change and education. For all-cause mortality, the percentage of the population with high school education or more is inversely associated with mortality from all causes (Tables 34 and 37) and from cardiopulmonary disease (Tables 35 and 38). Our results also bear out the observation that areas where the population has increased tend to have lower mortality.

Although we can postulate a possible biological relation between mortality and exposure to fine particles and sulfate, we cannot suggest that population change is a cause of death. Rather, population change is considered to be an indicator of the economic climate of a metropolitan area. A health effect is associated with the economic climate of a place. Healthy people tend to migrate out of areas of recession to areas experiencing economic well-being, whereas unhealthy people tend to stay where they are. Moreover, areas of heavy manufacturing, which are likely to have

**Table 35.** Relative Risks of Mortality from Cardiopulmonary Disease Associated with an Increase in Sulfate After Adjusting for Selected Ecologic Covariates[a]

| Ecologic Covariate | Relative Risk from Sulfate | | Relative Risk from Ecologic Covariate | |
|---|---|---|---|---|
| | Without Ecologic Covariate | With Ecologic Covariate | Without Sulfate | With Sulfate |
| **Demographic Factors** | | | | |
| Population change | 1.24 (1.15–1.35) | 1.12 (1.03–1.23) | 0.80 (0.75–0.85) | 0.83 (0.77–0.90) |
| Whites | 1.25 (1.16–1.36) | 1.30 (1.20–1.42) | 1.02 (0.97–1.08) | 1.09 (1.03–1.16) |
| Blacks | 1.25 (1.16–1.36) | 1.28 (1.17–1.40) | 1.03 (0.96–1.10) | 0.95 (0.88–1.03) |
| **Socioeconomic Factors** | | | | |
| Income | 1.25 (1.16–1.36) | 1.25 (1.16–1.36) | 0.87 (0.81–0.93) | 0.87 (0.81–0.94) |
| Poverty | 1.25 (1.16–1.36) | 1.26 (1.16–1.36) | 0.99 (0.93–1.05) | 0.97 (0.91–1.04) |
| Income disparity | 1.25 (1.16–1.36) | 1.25 (1.16–1.36) | 0.90 (0.83–0.97) | 0.90 (0.83–0.97) |
| Unemployment | 1.25 (1.16–1.36) | 1.20 (1.11–1.30) | 1.27 (1.16–1.38) | 1.21 (1.11–1.32) |
| Education | 1.25 (1.16–1.36) | 1.21 (1.11–1.32) | 0.84 (0.77–0.92) | 0.92 (0.83–1.00) |
| **Health Services** | | | | |
| Physicians | 1.24 (1.15–1.35) | 1.23 (1.14–1.34) | 0.86 (0.79–0.94) | 0.87 (0.80–0.95) |
| Hospital beds | 1.24 (1.15–1.35) | 1.23 (1.13–1.33) | 1.18 (1.07–1.30) | 1.15 (1.04–1.26) |
| **Climate** | | | | |
| Temperature | 1.22 (1.13–1.33) | 1.19 (1.09–1.29) | 0.87 (0.46–1.64) | 0.89 (0.83–0.95) |
| Temperature variation | 1.22 (1.13–1.33) | 1.17 (1.08–1.28) | 1.26 (1.16–1.36) | 1.22 (1.12–1.32) |
| Relative humidity | 1.21 (1.09–1.34) | 1.20 (1.06–1.35) | 1.11 (1.01–1.21) | 1.01 (0.91–1.13) |
| Relative humidity variation | 1.21 (1.09–1.34) | 1.28 (1.15–1.42) | 0.93 (0.85–1.01) | 0.86 (0.79–0.95) |
| **Physical Environment** | | | | |
| Altitude | 1.20 (1.10–1.32) | 1.26 (1.14–1.39) | 1.02 (0.93–1.12) | 1.12 (1.02–1.23) |
| Water hardness | 1.19 (1.09–1.30) | 1.20 (1.09–1.31) | 1.11 (1.03–1.20) | 1.12 (1.04–1.21) |
| **Gaseous Copollutants** | | | | |
| CO | 1.27 (1.17–1.38) | 1.27 (1.17–1.38) | 0.94 (0.87–1.02) | 0.94 (0.86–1.01) |
| $NO_2$ | 1.25 (1.14–1.38) | 1.29 (1.17–1.42) | 0.93 (0.87–1.01) | 0.89 (0.83–0.97) |
| $O_3$ | 1.26 (1.16–1.37) | 1.27 (1.17–1.38) | 0.98 (0.90–1.08) | 0.96 (0.88–1.05) |
| $SO_2$ | 1.28 (1.18–1.40) | 1.14 (1.04–1.25) | 1.40 (1.29–1.52) | 1.33 (1.22–1.46) |
| **Multiple Covariate Analyses** | | | | |
| Gaseous copollutants | 1.22 (1.10–1.35) | 1.11 (1.00–1.25) | | 1.41 (1.27–1.57)[b] |
| Socioeconomic status[c] | 1.24 (1.15–1.35) | 1.18 (1.06–1.31) | | |
| 25%[d] | 1.20 (1.06–1.36) | 1.17 (0.97–1.41) | | 1.38 (1.17–1.61)[b] |

[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 sulfate was 19.9 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender, and race. See Table 19 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[b] Whenever $SO_2$ was included in a multivariate model, the relative risk of mortality associated with it is given in the far right column.

[c] Includes population change and the five socioeconomic factors (income, poverty, income disparity, unemployment, and education).

[d] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with the pollutant of interest. In this analysis: population change, relative humidity variation, altitude, and $SO_2$.

**Table 36.** Relative Risks of Mortality from Lung Cancer Associated with an Increase in Sulfate After Adjusting for Selected Ecologic Covariates[a]

| | Relative Risk from Sulfate | | Relative Risk from Ecologic Covariate | |
|---|---|---|---|---|
| Ecologic Covariate | Without Ecologic Covariate | With Ecologic Covariate | Without Sulfate | With Sulfate |
| **Demographic Factors** | | | | |
| Population change | 1.31 (1.08–1.58) | 1.30 (1.05–1.61) | 0.91 (0.78–1.06) | 1.00 (0.84–1.18) |
| Whites | 1.33 (1.10–1.61) | 1.34 (1.10–1.64) | 0.96 (0.84–1.10) | 1.03 (0.89–1.19) |
| Blacks | 1.33 (1.10–1.61) | 1.35 (1.10–1.66) | 1.05 (0.89–1.23) | 0.95 (0.80–1.13) |
| **Socioeconomic Factors** | | | | |
| Income | 1.33 (1.10–1.61) | 1.33 (1.10–1.61) | 1.01 (0.86–1.19) | 1.02 (0.86–1.20) |
| Poverty | 1.33 (1.10–1.61) | 1.33 (1.10–1.61) | 0.97 (0.83–1.13) | 0.96 (0.82–1.12) |
| Income disparity | 1.33 (1.10–1.61) | 1.32 (1.09–1.60) | 0.88 (0.73–1.07) | 0.89 (0.73–1.08) |
| Unemployment | 1.33 (1.10–1.61) | 1.31 (1.08–1.60) | 1.13 (0.92–1.38) | 1.05 (0.86–1.29) |
| Education | 1.33 (1.10–1.61) | 1.34 (1.09–1.65) | 0.90 (0.74–1.10) | 1.02 (0.82–1.27) |
| **Health Services** | | | | |
| Physicians | 1.31 (1.08–1.58) | 1.30 (1.07–1.57) | 0.91 (0.74–1.11) | 0.93 (0.76–1.13) |
| Hospital beds | 1.31 (1.08–1.58) | 1.32 (1.09–1.60) | 0.92 (0.73–1.16) | 0.89 (0.71–1.13) |
| **Climate** | | | | |
| Temperature | 1.37 (1.12–1.67) | 1.36 (1.11–1.67) | 0.94 (0.81–1.09) | 0.98 (0.84–1.15) |
| Temperature variation | 1.37 (1.12–1.67) | 1.39 (1.13–1.71) | 1.00 (0.83–1.21) | 0.94 (0.77–1.14) |
| Relative humidity | 1.53 (1.20–1.95) | 1.39 (1.04–1.86) | 1.37 (1.10–1.72) | 1.17 (0.90–1.53) |
| Relative humidity variation | 1.53 (1.20–1.95) | 1.49 (1.16–1.92) | 1.19 (0.96–1.47) | 1.09 (0.88–1.37) |
| **Physical Environment** | | | | |
| Altitude | 1.24 (1.00–1.54) | 1.14 (0.91–1.44) | 0.72 (0.56–0.93) | 0.76 (0.58–0.99) |
| Water hardness | 1.31 (1.06–1.62) | 1.31 (1.05–1.62) | 0.94 (0.78–1.12) | 0.94 (0.79–1.13) |
| **Gaseous Copollutants** | | | | |
| CO | 1.26 (1.03–1.54) | 1.26 (1.03–1.54) | 0.82 (0.68–1.00) | 0.82 (0.68–1.00) |
| $NO_2$ | 1.28 (1.02–1.62) | 1.33 (1.05–1.69) | 0.91 (0.76–1.09) | 0.87 (0.73–1.05) |
| $O_3$ | 1.27 (1.05–1.55) | 1.30 (1.07–1.59) | 0.74 (0.59–0.92) | 0.72 (0.58–0.90) |
| $SO_2$ | 1.31 (1.07–1.62) | 1.36 (1.08–1.72) | 1.06 (0.87–1.30) | 0.93 (0.74–1.17) |
| **Multiple Covariate Analyses** | | | | |
| Gaseous copollutants | 1.31 (1.08–1.58) | 1.20 (0.94–1.54) | | 0.86 (0.66–1.13)[b] |
| Socioeconomic status[c] | 1.42 (1.11–1.82) | 1.61 (1.21–2.14) | | |
| 25%[d] | 1.53 (1.20–1.95) | 1.39 (1.04–1.86) | | |

[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 sulfate was 19.9 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender, and race. See Table 19 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[b] Whenever $SO_2$ was included in a multivariate model, the relative risk of mortality associated with it is given in the far right column.

[c] Includes population change and the five socioeconomic factors (income, poverty, income disparity, unemployment, and education).

[d] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with the pollutant of interest. In this analysis: relative humidity.

**Table 37.** Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles After Adjusting for Selected Ecologic Covariates[a]

| | Relative Risk from Fine Particles | | Relative Risk from Ecologic Covariate | |
|---|---|---|---|---|
| Ecologic Covariate | Without Ecologic Covariate | With Ecologic Covariate | Without Fine Particles | With Fine Particles |
| **Demographic Factors** | | | | |
| Population change | 1.19 (1.10–1.28) | 1.07 (0.99–1.17) | 0.84 (0.80–0.89) | 0.86 (0.81–0.92) |
| Whites | 1.18 (1.09–1.26) | 1.28 (1.18–1.38) | 1.04 (0.98–1.10) | 1.14 (1.07–1.22) |
| Blacks | 1.18 (1.09–1.26) | 1.25 (1.15–1.37) | 1.00 (0.94–1.08) | 0.89 (0.82–0.97) |
| **Socioeconomic Factors** | | | | |
| Income | 1.18 (1.09–1.26) | 1.18 (1.09–1.26) | 0.93 (0.87–0.99) | 0.93 (0.87–0.99) |
| Poverty | 1.18 (1.09–1.26) | 1.22 (1.13–1.32) | 0.91 (0.85–0.99) | 0.86 (0.79–0.93) |
| Income disparity | 1.18 (1.09–1.26) | 1.23 (1.14–1.32) | 0.85 (0.80–0.90) | 0.83 (0.78–0.88) |
| Unemployment | 1.18 (1.09–1.26) | 1.16 (1.08–1.25) | 1.09 (1.02–1.16) | 1.06 (0.99–1.13) |
| Education | 1.18 (1.09–1.26) | 1.17 (1.08–1.27) | 0.94 (0.89–1.00) | 1.00 (0.93–1.06) |
| **Health Services** | | | | |
| Physicians | 1.19 (1.10–1.28) | 1.19 (1.10–1.28) | 0.95 (0.88–1.04) | 0.95 (0.87–1.03) |
| Hospital beds | 1.19 (1.10–1.28) | 1.18 (1.10–1.27) | 1.05 (0.96–1.16) | 1.03 (0.93–1.14) |
| **Climate** | | | | |
| Temperature | 1.13 (1.05–1.22) | 1.12 (1.03–1.20) | 0.86 (0.81–0.90) | 0.86 (0.81–0.91) |
| Temperature variation | 1.13 (1.05–1.22) | 1.07 (0.99–1.16) | 1.18 (1.11–1.25) | 1.16 (1.09–1.23) |
| Relative humidity | 1.19 (1.08–1.30) | 1.19 (1.08–1.31) | 1.03 (0.96–1.10) | 1.00 (0.93–1.07) |
| Relative humidity variation | 1.19 (1.08–1.30) | 1.22 (1.11–1.34) | 0.96 (0.90–1.04) | 0.93 (0.86–1.00) |
| **Physical Environment** | | | | |
| Altitude | 1.11 (1.02–1.20) | 1.14 (1.05–1.24) | 1.06 (1.00–1.13) | 1.09 (1.02–1.16) |
| Water hardness | 1.17 (1.09–1.26) | 1.16 (1.07–1.25) | 1.15 (1.08–1.23) | 1.14 (1.07–1.21) |
| **Gaseous Copollutants** | | | | |
| CO | 1.17 (1.09–1.26) | 1.18 (1.10–1.27) | 0.93 (0.88–0.98) | 0.92 (0.87–0.97) |
| $NO_2$ | 1.15 (1.05–1.25) | 1.22 (1.11–1.33) | 0.95 (0.89–1.01) | 0.90 (0.84–0.96) |
| $O_3$ | 1.16 (1.08–1.25) | 1.18 (1.10–1.27) | 0.90 (0.84–0.97) | 0.88 (0.82–0.95) |
| $SO_2$ | 1.20 (1.11–1.29) | 1.03 (0.95–1.13) | 1.49 (1.36–1.64) | 1.46 (1.32–1.63) |
| **Multiple Covariate Analyses** | | | | |
| Gaseous copollutants | 1.15 (1.05–1.25) | 1.07 (0.96–1.19) | | 1.46 (1.31–1.63)[b] |
| Socioeconomic status[c] | 1.19 (1.10–1.28) | 1.15 (1.04–1.28) | | |
| 25%[d] | 1.09 (0.99–1.20) | 1.33 (1.09–1.61) | | 1.14 (0.90–1.45)[b] |

[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 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender, and race. See Table 19 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[b] Whenever $SO_2$ was included in a multivariate model, the relative risk of mortality associated with it is given in the far right column.

[c] Includes population change and the five socioeconomic factors (income, poverty, income disparity, unemployment, and education).

[d] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with the pollutant of interest. In this analysis: population change, whites, poverty, income disparity, temperature, altitude, $NO_2$, and $SO_2$.

**Table 38.** Relative Risks of Mortality from Cardiopulmonary Disease Associated with an Increase in Fine Particles After Adjusting for Selected Ecologic Covariates[a]

| Ecologic Covariate | Relative Risk from Fine Particles | | Relative Risk from Ecologic Covariate | |
|---|---|---|---|---|
| | Without Ecologic Covariate | With Ecologic Covariate | Without Fine Particles | With Fine Particles |
| **Demographic Factors** | | | | |
| Population change | 1.29 (1.16–1.44) | 1.12 (0.99–1.27) | 0.78 (0.72–0.84) | 0.81 (0.74–0.89) |
| Whites | 1.30 (1.17–1.44) | 1.43 (1.27–1.61) | 1.02 (0.94–1.11) | 1.17 (1.07–1.29) |
| Blacks | 1.30 (1.17–1.44) | 1.39 (1.23–1.58) | 1.04 (0.95–1.15) | 0.88 (0.78–0.99) |
| **Socioeconomic Factors** | | | | |
| Income | 1.30 (1.17–1.44) | 1.30 (1.17–1.44) | 0.90 (0.82–0.99) | 0.90 (0.82–0.99) |
| Poverty | 1.30 (1.17–1.44) | 1.34 (1.20–1.49) | 0.95 (0.85–1.06) | 0.87 (0.78–0.98) |
| Income disparity | 1.30 (1.17–1.44) | 1.35 (1.22–1.50) | 0.86 (0.79–0.93) | 0.82 (0.76–0.89) |
| Unemployment | 1.30 (1.17–1.44) | 1.25 (1.12–1.39) | 1.19 (1.09–1.30) | 1.13 (1.03–1.24) |
| Education | 1.30 (1.17–1.44) | 1.27 (1.13–1.42) | 0.89 (0.82–0.96) | 0.96 (0.88–1.06) |
| **Health Services** | | | | |
| Physicians | 1.29 (1.16–1.44) | 1.30 (1.17–1.44) | 0.88 (0.78–1.00) | 0.88 (0.78–0.99) |
| Hospital beds | 1.29 (1.16–1.44) | 1.28 (1.15–1.43) | 1.16 (1.02–1.33) | 1.13 (0.99–1.30) |
| **Climate** | | | | |
| Temperature | 1.21 (1.09–1.35) | 1.19 (1.07–1.33) | 0.83 (0.77–0.90) | 0.84 (0.77–0.91) |
| Temperature variation | 1.21 (1.09–1.35) | 1.13 (1.01–1.27) | 1.24 (1.14–1.35) | 1.21 (1.10–1.32) |
| Relative humidity | 1.22 (1.07–1.39) | 1.20 (1.04–1.37) | 1.09 (0.99–1.21) | 1.06 (0.96–1.17) |
| Relative humidity variation | 1.22 (1.07–1.39) | 1.27 (1.10–1.45) | 0.94 (0.85–1.05) | 0.90 (0.81–1.00) |
| **Physical Environment** | | | | |
| Altitude | 1.23 (1.09–1.38) | 1.25 (1.11–1.41) | 1.02 (0.93–1.11) | 1.06 (0.97–1.16) |
| Water hardness | 1.28 (1.15–1.43) | 1.26 (1.13–1.41) | 1.21 (1.10–1.32) | 1.19 (1.09–1.31) |
| **Gaseous Copollutants** | | | | |
| CO | 1.30 (1.17–1.45) | 1.32 (1.19–1.47) | 0.92 (0.85–1.00) | 0.74 (0.61–0.90) |
| $NO_2$ | 1.32 (1.16–1.49) | 1.39 (1.22–1.59) | 0.99 (0.91–1.08) | 0.91 (0.83–1.00) |
| $O_3$ | 1.29 (1.16–1.44) | 1.30 (1.17–1.45) | 0.96 (0.86–1.07) | 0.93 (0.83–1.04) |
| $SO_2$ | 1.35 (1.21–1.51) | 1.17 (1.03–1.33) | 1.59 (1.39–1.81) | 1.45 (1.25–1.69) |
| **Multiple Covariate Analyses** | | | | |
| Gaseous copollutants | 1.32 (1.16–1.49) | 1.22 (1.05–1.43) | | 1.42 (1.21–1.65)[b] |
| Socioeconomic status[c] | 1.29 (1.16–1.44) | 1.17 (1.01–1.36) | | |
| 25%[d] | 1.26 (1.12–1.42) | 1.19 (1.00–1.41) | | 1.26 (1.04–1.52)[b] |

[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 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender, and race. See Table 19 for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

[b] Whenever $SO_2$ was included in a multivariate model, the relative risk of mortality associated with it is given in the far right column.

[c] Includes population change and the five socioeconomic factors (income, poverty, income disparity, unemployment, and education).

[d] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with the pollutant of interest. In this analysis: population change, whites, temperature variation, and $SO_2$.

high levels of both fine particles and sulfate, are also likely to have experienced a recession during the 1980s.

Adding ecologic covariates to the Cox proportional-hazards regression models provides one method of controlling for ecologic confounding. However, this method does not enable researchers to control for the spatial autocorrelation that can result from missing or unmeasured ecologic covariates. Moreover, statistical tests of significance are reliable only when researchers can be sure that the residuals of their models are not autocorrelated. For these reasons, the Reanalysis Team used spatial smoothing and filtering techniques (described in the following section) to characterize the spatial patterns in the data and to model the data in a way that makes explicit provision for spatial autocorrelation.

## SPATIAL ANALYSES

An important issue in the analysis of data from the ACS Study is whether or not the observations are independent or correlated. Residents of cities located near one another may be at similar risk of mortality resulting from shared aspects of their social and physical environments, such as socioeconomic influences, access to health care, dietary habits, and environmental or occupational exposures, which lead to spatial autocorrelation in the data. Other covariates used in both the original analyses and the present sensitivity analyses may be spatially correlated as well. Spatial autocorrelation affects the statistical power of associations, with positive spatial autocorrelation in the residuals increasing the likelihood of a false-positive finding. Failure to control for spatial autocorrelation can invalidate traditional tests of significance and lead to biased estimates of coefficients in regression models. Recent studies have shown that when correlation is taken into account, formerly significant findings in ordinary-least-squares regression analyses may become insignificant (Griffith et al 1998).

For the purposes of the ACS data analyses described in the previous sections, the Reanalysis Team assumed the statistical independence of all observations. This assumption was necessary for the application of the standard Cox proportional-hazards regression model of survival that had been used by the Original Investigators. In this section, we consider analytic techniques that allow for the possibility of spatial autocorrelation in the ACS data.

Within the context of the general spatial analysis framework shown in Figure 14, the Reanalysis Team explored different approaches for capturing spatial patterns in the data. The specific approaches included in this framework and their associated results are discussed in later sections. We begin with a description of spatial patterns in the data and the methods used to summarize them in smooth maps of the variables of interest; then we discuss formal tests for spatial autocorrelation. Computationally simple two-stage random effects regression methods, used to take into account spatial clustering at both city and broader regional levels, provide risk estimates that are in close agreement with estimates derived from a new random effects Cox regression model specifically developed by the Reanalysis Team. We also employed spatial filtering methods to remove broad spatial patterns in the data before we applied our two-stage regression models. Further details of the spatial smoothing and spatial filtering methods used by the Reanalysis Team are given in Appendix H, which is available on request from Health Effects Institute.

### Spatial Analysis Framework

Under the Cox proportional-hazards regression model of survival used by the Original Investigators, it had been assumed that the survival of each individual could be represented by statistically independent random variables. However, several processes involved in predicting mortality in space and time may induce some degree of statistical dependence in the data. We have attempted to characterize some of these processes and model the corresponding statistical dependence within the context of the spatial analysis framework shown in Figure 14.

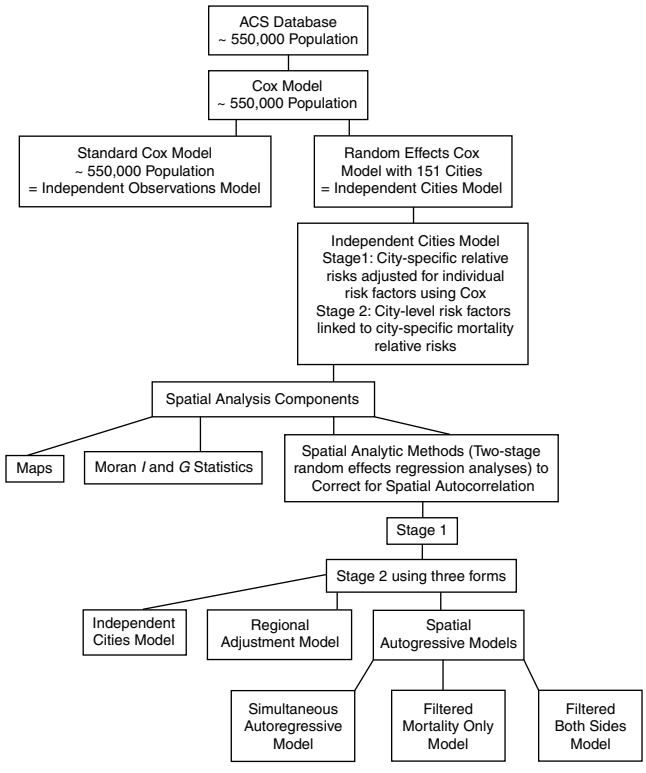



**Figure 14. Paradigm of spatial analyses.**

We discuss in detail in Appendix H the rationale for taking spatial dependence into account. When epidemiologic investigations use health data from contiguous or nearby geographic areas, the data may not provide independent estimates of the dependent variable (in this case, relative risk of mortality). If we account for this lack of independence with covariates that are also spatially autocorrelated, then no statistical problem arises because the error terms from such a model tend to be uncorrelated. However, if areas differ in some unmeasured or unsuspected way that affects mortality, residuals are likely to be correlated (Cook and Pocock 1983). Autocorrelated errors can result in overestimates of significance. Therefore, to ensure reliable significance tests, we needed to account for spatial dependence in the regression models. This could also lead to the identification of new covariates that may explain some of the variation in mortality that manifests as autocorrelation in the residuals. Careful examination and mapping of the residuals can suggest locations where the model fails to predict mortality accurately, thereby providing useful information on omitted covariates.

Following the lead of the Original Investigators, we began by applying the Cox proportional-hazards regression model of survival to individual-level data on members of the sulfate cohort (approximately 550,000 subjects) or the fine particle cohort (approximately 295,000 subjects) from the ACS Study data. This standard Cox model includes a number of risk factors measured at the individual level, with the baseline hazard function stratified by age, gender, and race. Because a key assumption in this model is that the survival times for all subjects are statistically independent, this approach is referred to as the Independent Observations Model.

Next we extended the standard Cox model to allow the baseline hazard function to vary at random among cities, resulting in a random effects Cox model (Appendix I, available on request from the Health Effects Institute). The random effects Cox model is predicated on the assumption that there is more variation in individual risks of mortality than can be explained by the standard Cox model, and that subjects in the same city are expected to have more similar mortality risks than subjects living in different cities. This modeling framework also implies that the city itself is a risk factor for mortality in the sense that even after we control for all available risk factor information at the individual and ecologic level, the city in which a subject lives will have some influence on his or her survival.

Our random effects Cox model assumes that differences in the mortality risks of individuals in different cities are independent of the proximity of those cities, so that mortality is spatially clustered beyond that associated with specific cities. To date, we have not extended the random effects Cox model to incorporate such spatial dependence, although such an extension appears to be technically feasible. Instead, in a two-stage approach, we have exploited spatial regression methods developed for normally distributed data (Getis and Ord 1996) to address the extra spatial variation in mortality beyond that induced by clustering at the city level.

In the first stage, we fitted a standard Cox model to the individual-level data, including an indicator variable for each city. (With this approach, one city must be selected as an index in order to compare mortality between each city and the index city.) No city-level or ecologic variables, including air pollution, were included at this stage. Because estimates of the city-specific mortality rates relative to the index city are, by definition, correlated, we transformed the covariance matrix of the estimated mortality rates in each city relative to the index city to independence using methods developed by Easton and colleagues (1991). We then linked the logarithms of the comparative city-specific relative risks to the ecologic covariates, including air pollution, using a linear model with independent errors of the form $\tau^2 + v_j$, in which $\tau^2$ is the unexplained variation in the true logarithms of the city-specific comparative mortality rates and $v_j$ is the uncertainty in the estimated mortality rate for city $j$ obtained in the first stage. We arrived at estimates of $\tau^2$ by the method of moments (DerSimonian and Laird 1986), and used weighted least squares to estimate the effects of the ecologic covariates and air pollution, with weights given by $1/(\tau^2 + v_j)$ for the $j$th city.

Because both the random effects and two-stage approaches arrive at mortality rates for each city that are assumed to be independent, they are referred to as Independent Cities Models. Although their estimates of the city-level covariate effects and $\tau^2$ are expected to be similar, these estimates will not be equivalent because of the nonlinear structure of the random effects regression model. Under the assumption that there is no extra variation as a result of clustering of mortality rates within a city (ie, $\tau^2 = 0$), the parameter estimates of the covariate effects and their uncertainty under the random effects and the standard Cox models will, however, be identical.

We then questioned the assumption that the cities' mortality rates are independent. Even after we have controlled for available risk factor information at both the individual and ecologic level, the adjusted city-specific risk estimates conceivably could exhibit evidence of spatial autocorrelation. Such spatial dependence in the adjusted risk estimates could result from unidentified processes that vary in space and lead to clustering of mortality rates. As discussed

in Appendix H, the Moran *I* statistic can be used to test for the presence of spatial autocorrelation in the city-specific mortality rates.

We addressed the statistical form of such spatial dependence using four approaches. In the first approach (Regional Adjustment Model) we removed spatial variation in mortality rates by adjusting the city-specific values for broad regional patterns. Specifically, we used the seven regions of the United States (Figure 15) defined in the National Morbidity and Mortality Air Pollution Study conducted by Samet and colleagues (2000), and removed differences in mortality rates between regions together with effects of fine particle air pollution and other variables measured at the city level. Using arbitrary regions, however, provides only limited and ad hoc control for spatial dependence because such regions have not been derived on the basis of prior knowledge or empirical evidence about what processes may have caused the spatial dependence. Thus, it is possible that such regions may overcontrol or undercontrol the actual spatial dependence in the model. As the regions adopted for this analysis were quite large, smaller-area spatial dependence was probably neglected.

Our second spatial analysis approach involved modeling the broader spatial patterns of mortality in city-specific regions using the Moran *G* statistic, which is designed to detect local autocorrelation that arises when variables display nonstationarity (spatial dependence is not the same everywhere in the United States, but varies locally over space). In this approach, the values for relative risk of mortality that surround a city within a given distance are divided by their global average values for the entire United States. Cities that are surrounded by other cities with elevated mortality rates will have significantly elevated values. Then a *G* statistic is calculated for every city in the dataset. Next, the mortality rate at that city is multiplied by the expected value of the city's *G* statistic, and then divided by the actual value. This has the effect of removing spatial dependence from the mortality rate or other covariate of interest, including air pollution. A summary *G* statistic was calculated by averaging the city-specific *G* statisics from all cities.

Two criteria were used to select the distance for defining the regions. First, a graphic technique known as semivariogram analysis assessed the distance at which spatial dependence among mortality, air pollution, and other covariates diminished. Second, we selected the distance that minimized the residual spatial autocorrelation in the variable, as determined by Moran *I,* a global test of spatial autocorrelation. Iterations between these two analyses suggested that regions with a radius of approximately 600 km would remove spatial dependence from the variables without inducing negative autocorrelation (in which, for example, high mortality associates with neighboring low mortality).

This approach is similar to that for time-series mortality studies in which adjustments for temporal trends in mortality rates employ multiday moving-average windows. Similar to time-series models, negative autocorrelation suggests that the filtering procedure has removed too much information from the variable, including some of the attribute value that is not specifically associated with spatial arrangement. The spatially filtered city-specific mortality rates were then regressed on the unfiltered sulfate concentrations (this technique is referred to as the Filtered Mortality Model).

The third modeling approach involved spatially filtering not only the city-specific relative risks of mortality but also the sulfate concentrations and other covariates (referred to as Filtered Both Sides Model, or the Spatial Filtering Model). Here, a 600-km radius also was sufficient to remove any evidence of spatial autocorrelation in the sulfate data. In this approach, we compared mortality rates and sulfate levels after removing broad spatial patterns in both datasets. Clustering of mortality rates by city is taken into account in the filtering approach using weighted least squares regression with weights given by $1/(\tau^2 + v_j)$.

This filtering approach has a number of advantages over the ad hoc regional adjustment. First, because every city is assigned its own region, this method provides a more sensitive adjustment to spatial dependence. Unlike the Regional Adjustment Model, filtering methods rely on actual measured spatial dependence in the data. Second, because it is based on the *G* statistic, the filter deals explicitly with nonstationarities in the variables. Third, this method relies on a linear regression model that is easily interpreted, unlike the simultaneous autoregression technique discussed below. Fourth, the selection of the filter distance forces the analyst to think carefully about what may have caused the spatial dependence.

We found that fairly broad regional patterns with a radius of approximately 600 km appeared to exert a major influence on both mortality and pollution. As mentioned above, it is possible to overfilter the data (ie, by removing not only the spatial pattern, but also some of the attribute value not associated with spatial arrangement) used in the deterministic part of the model, thus removing part of the possible causal relation between air pollution and mortality. One can minimize this problem by carefully selecting the filter distance such that little or no negative autocorrelation is induced in the filtered variables or in the residuals.

Another potential weakness of this approach lies in the binary structure of the spatial weighting matrix. All cities

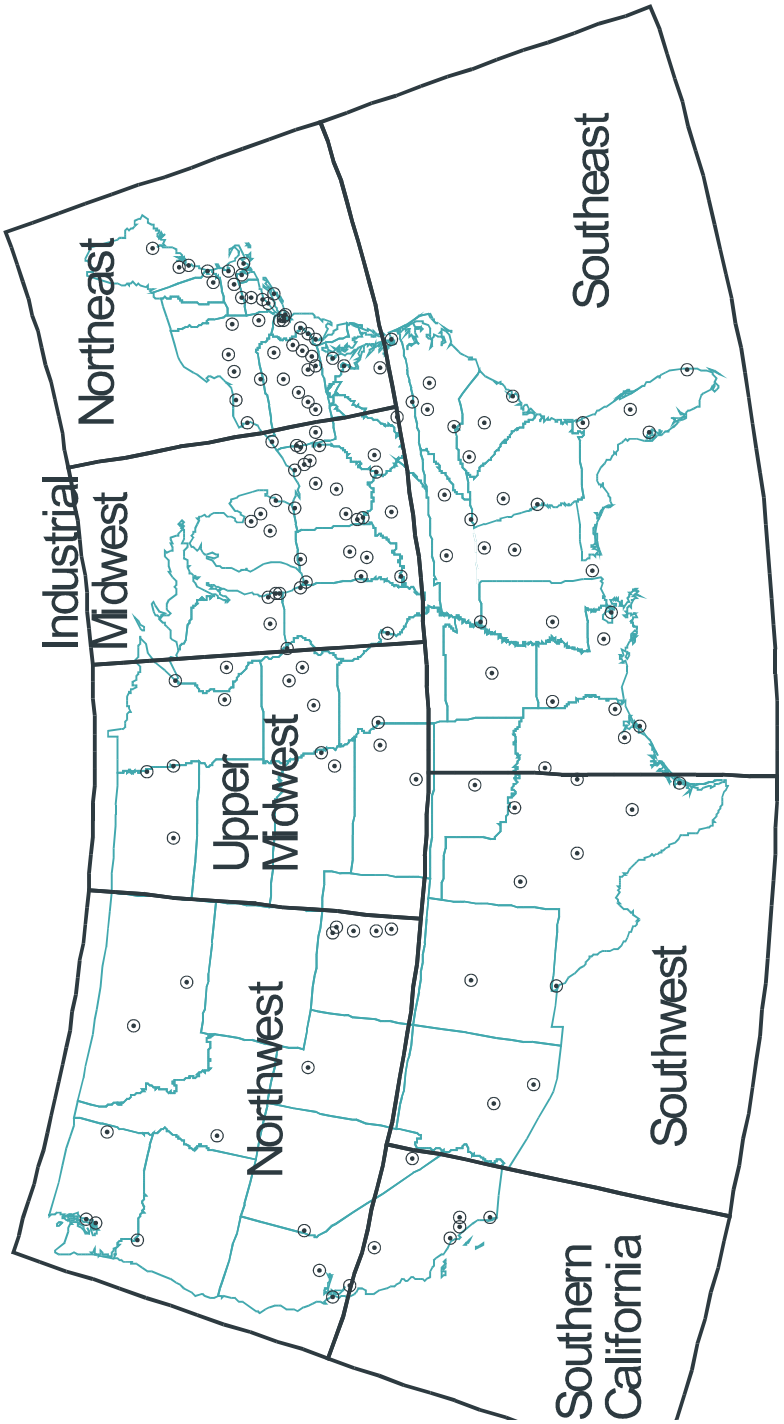



**Figure 15. Regions of the US used for the Regional Adjustment Model.** Cities in the ACS sulfate cohort are noted (Y). The regions were designed for use in Samet and associates (2000).

within the 600-km radius are assigned an equal weight of one, whereas those outside this distance are weighted zero. With many spatial patterns, we would expect to see a distance decay effect, whereby spatial dependence diminishes as a function of distance away from the city of interest. Refinements of the weighting matrix to account for distance decay were not possible in this analysis, but this represents an important area for future research.

We further examined the robustness of our results to the method of controlling for spatial autocorrelation by using a fourth spatial analysis approach referred to as the Simultaneous Autoregressive Model. In this approach, the logarithms of the city-specific mortality rates are the response variables, assumed to be normally distributed, and the city-level or ecologic covariates are used as predictors. The error structure in the Simultaneous Autoregressive Model explicitly incorporates correlation among mortality rates after accounting for city-level predictors of mortality. The correlation structure is predicated on the nearest-neighbor concept, which assumes that one is more likely to be influenced by one's neighbor, no matter how far away that neighbor is, than by one that is not a neighbor.

We defined a city's neighbors in the following manner. First, Thiessen polygons (geographic areas that incorporate all points closer to the given city than to any other) were constructed for each city. The neighbors of any city were then defined as the area enclosed by all the Thiessen polygons touching the polygon of that city. Each city may have a different number of neighbors, and the nearest neighbor may be a different distance away for each city. The correlation structure then derived correlates a city's residual response only with the residual responses of its neighbors; cities that are not neighbors were assumed to be uncorrelated. We assumed a common correlation parameter for the entire dataset, which was estimated simultaneously with the regression parameters using maximum likelihood techniques in S-PLUS statistical software (MathSoft, Seattle WA). We also weighted the analysis by $1/(\tau^2 + v_j)$, thus incorporating the concept of a random effects model in the analysis.

We also considered an adjusted nearest-neighbor approach, in which mortality rates were assumed to be correlated among cities when the cities were nearest neighbors or were within the average distance between cities (111 km for cities with sulfate data and 123 km for cities with sulfur dioxide data). Here we report only the results for the nearest-neighbor approach, because the results obtained using the adjusted nearest-neighbor approach were virtually identical. (Although the data used to generate the correlation matrix using the adjusted nearest-neighbor approach incorporated more cities in the Northeast and Ohio Valley regions than did the data that used nearest neighbors only, the inclusion of these additional cities did not markedly influence the estimate of the common correlation parameter.)

Both approaches we used in the Simultaneous Autoregressive Model (Thiessen polygons and adjusted nearest neighbor) relied on a more localized spatial dependence assumption (the nearest neighbor) than did the Regional Adjustment Model or spatial filtered models. We suggest that spatial interaction among risk factors is most likely to occur among neighbors, regardless of distance. For most places, except parts of the Western United States where the sampled coverage of cities is sparse, this provided a more localized control on spatial autocorrelation. With this type of model, we did not try to understand the mechanisms underlying autocorrelation. Simultaneous estimation of the coefficients and the autoregressive component of the error term did not allow for intensive investigation into spatial relations. Our intention instead was to incorporate, within the error structure of the model, a term that accounts for autocorrelation so that the remaining errors are uncorrelated and therefore amenable to reliable significance testing.

Mortality rates and pollution display an east-to-west trend, whereby the values of both are generally higher in the east than in the west. When spatial relations are not the same in all directions, we refer to the spatial pattern in the data as being anisotropic. In large datasets, it is possible to build in allowance for this directionality. We attempted to remove this trend with a special form of regression known as a trend surface. A trend surface includes the actual geographic coordinates of the cities as independent predictor variables. Both the Simultaneous Autoregressive Model and the Regional Adjustment Model rely implicitly on the assumption that no trend is present (isotropy) in the data. The results of these models must be viewed with this limitation in mind. The filtering procedure, although it implicitly assumes isotropy in the radius around a city, at least removes all autocorrelation from the data. Semivariogram analyses suggested that the filter also removed the east-to-west trend from the data. Thus, the spatial filtering approach has the advantage of producing reliable estimates even when anisotropy is present. Incorporation of this directional trend into future analyses may improve the robustness of the results.

Using each of these four spatial analysis approaches (Regional Adjustment Model, Filtered Mortality Model, Spatial Filtering [Filtered Both Sides] Model, and Simultaneous Autoregressive [Nearest Neighbor] Model) affords an opportunity to examine the extent to which inferences about the association between ambient air pollution and

mortality are influenced by spatial patterns in the data. Under the Independent Observations Model we employed originally, we assumed that all observations on individual cohort members were statistically independent. Our spatial analysis paradigm goes well beyond the Independent Observations Model by allowing for spatial patterns in the data. Specifically, spatial clustering is considered at the city level in the Independent Cities Model, at the regional level in the Regional Adjustment Model, and at the broader spatial level in the Spatial Filtering Model and the Simultaneous Autoregressive (Nearest Neighbor) Model.

An important practical aspect of our work was the use of two-stage regression models to address spatial autocorrelation. This two-stage approach was validated first in the Independent Observations Model by comparing the results with those from the standard Cox model, and then in the Independent Cities Model by comparing the results with those from the random effects Cox model. This validation of the two-stage regression approach supports its use in the more complex spatial filtering models, for which more direct approaches are not yet available.

The different approaches included in our framework of spatial analyses may be viewed as affording greater levels of control for spatial autocorrelation. The Independent Observations Model, which assumes that no spatial autocorrelation exists, represents a baseline with which the results of the spatial analytic techniques may be compared. The Independent Cities Model takes into account clustering of mortality rates by city, but does not acknowledge spatial autocorrelation at a broader regional level. The Regional Adjustment Model does for spatial dependence, but only within seven predetermined regions of the United States. The Spatial Filtering Model allows for more general spatial patterns either in relative risks or in both air pollution and mortality (the filtered both sides model). By filtering out broad spatial patterns in the data, these latter models seek to associate local variations in mortality rates (adjusted for regional mortality rates) with air pollution.

Comparison of the risk of mortality associated with air pollution estimated by the different spatial analytic techniques can suggest whether spatial association exists on the broader regional scale or the narrower subregional scale. We discuss the application of these spatial analytic methods to the ACS data, beginning with visual evidence of spatial patterns in the data.

### Spatial Patterns in the Data

Spatial patterns in the data can be assessed by visualization, exploration, and modeling (Bailey and Gatrell 1995). Graphic visualization is an important first step toward understanding spatial patterns in the variables of interest. We then can use exploratory spatial methods to examine spatial concordance in key variables such as mortality rates and indices of air pollution, along with other ecologic covariates we assembled for the cities included in the ACS Study. After this initial examination, we can use spatial modeling techniques to assess and describe spatial autocorrelation, and to develop spatial regression methods describing any association between the covariates of interest and mortality.

The spatial distributions of sulfate, sulfur dioxide, and fine particles are displayed graphically in Figures 16, 17, and 18, respectively. We derived the smoothed surfaces of pollutant concentrations by using kriging methods to interpolate values between the cities for which direct measurements of these pollutants were available. In these three maps, darker colors represent higher pollution levels. High levels of both sulfate and sulfur dioxide tend to cluster in the Lower Great Lakes area. They exhibit similar spatial patterns, although sulfur dioxide is spatially more concentrated than sulfate. This observation raises the possibility that some of the effect attributed to sulfate pollution in the original ACS Study may have resulted from sulfur dioxide. High values for fine particles are clustered slightly farther south. All three pollutants exhibit higher concentrations in the east than in the west.

The uncertainty in these kriged estimates is considered in Appendix H (see Figures H.3, H.4, and H.5). In general, uncertainty is larger in those areas where the point samples (cities) are less dense. The standard errors of the kriged estimates are largest in the Upper Midwest where the point coverage is most sparse. The standard errors of most of the interpolated sulfur dioxide levels are less than 1.1 ppb, corresponding to a pointwise 95% confidence limit of ± 2.2 ppb or less; in most of the Eastern United States, the confidence limits are within ± 1.37 ppb. For sulfate, the largest errors are also in the Upper Midwest and along the borders of Oregon and Wyoming. In these areas, the contour surfaces are accurate to within ± 1.17 $\mu g/m^3$. For large portions of the Eastern United States, the errors are less than ± 0.39 $\mu g/m^3$.

Uncertainties in the fine particle dataset are somewhat larger because there are fewer cities in the fine particle cohort (50) than in the sulfate cohort (151). The Upper Midwest again displays the largest errors, with estimates of fine particle levels accurate to within ± 2.1 $\mu g/m^3$. The most precise estimates are found for the Lower Great Lakes area and the Southeast, where the monitoring networks are densest. For most of this region, predictions are accurate to within ± 1.37 $\mu g/m^3$.

Spatial overlays of the mortality rates and air quality levels are shown in Figures 19, 20, and 21. We prepared

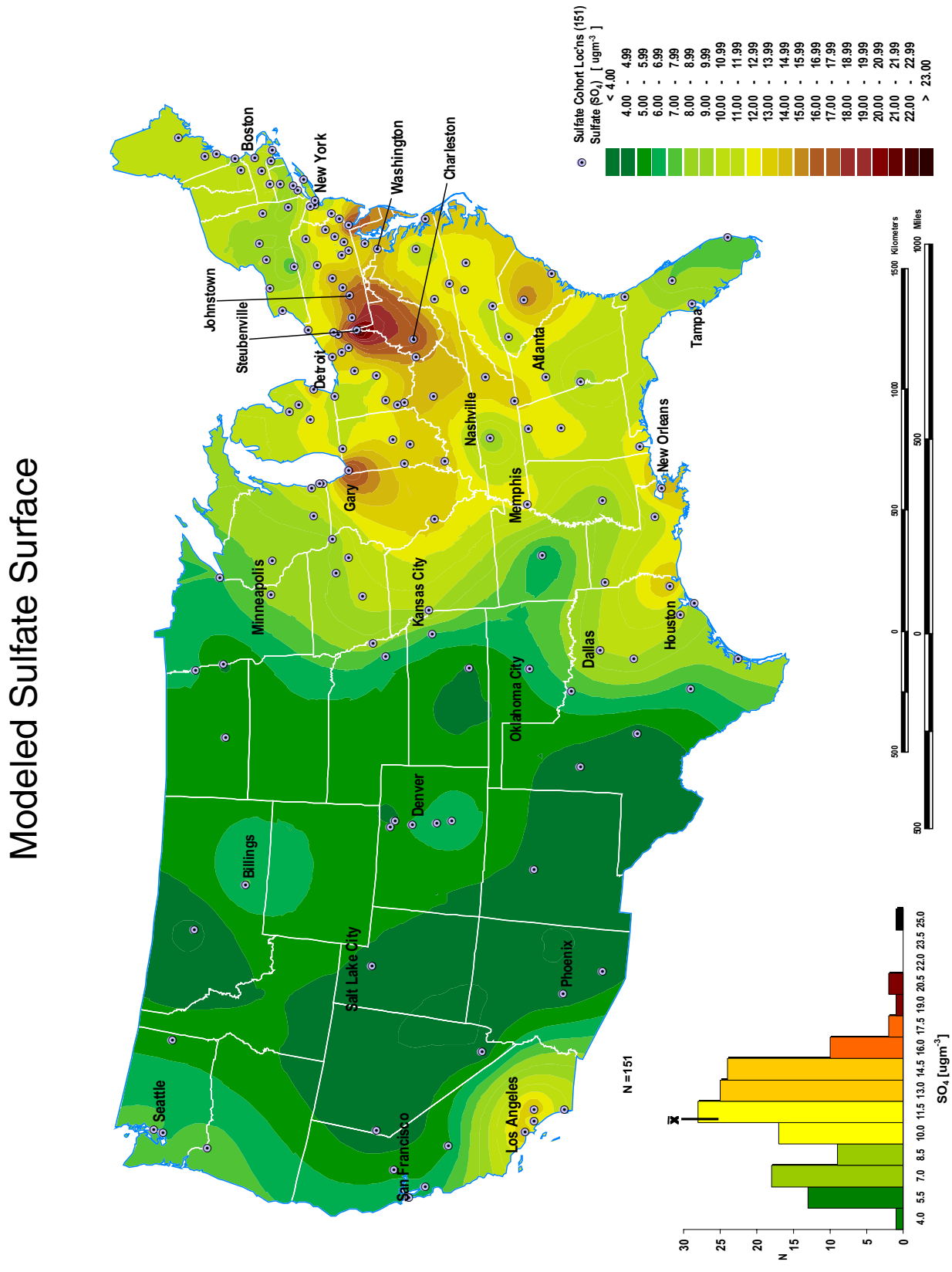



Figure 16. Spatial distribution of sulfate.

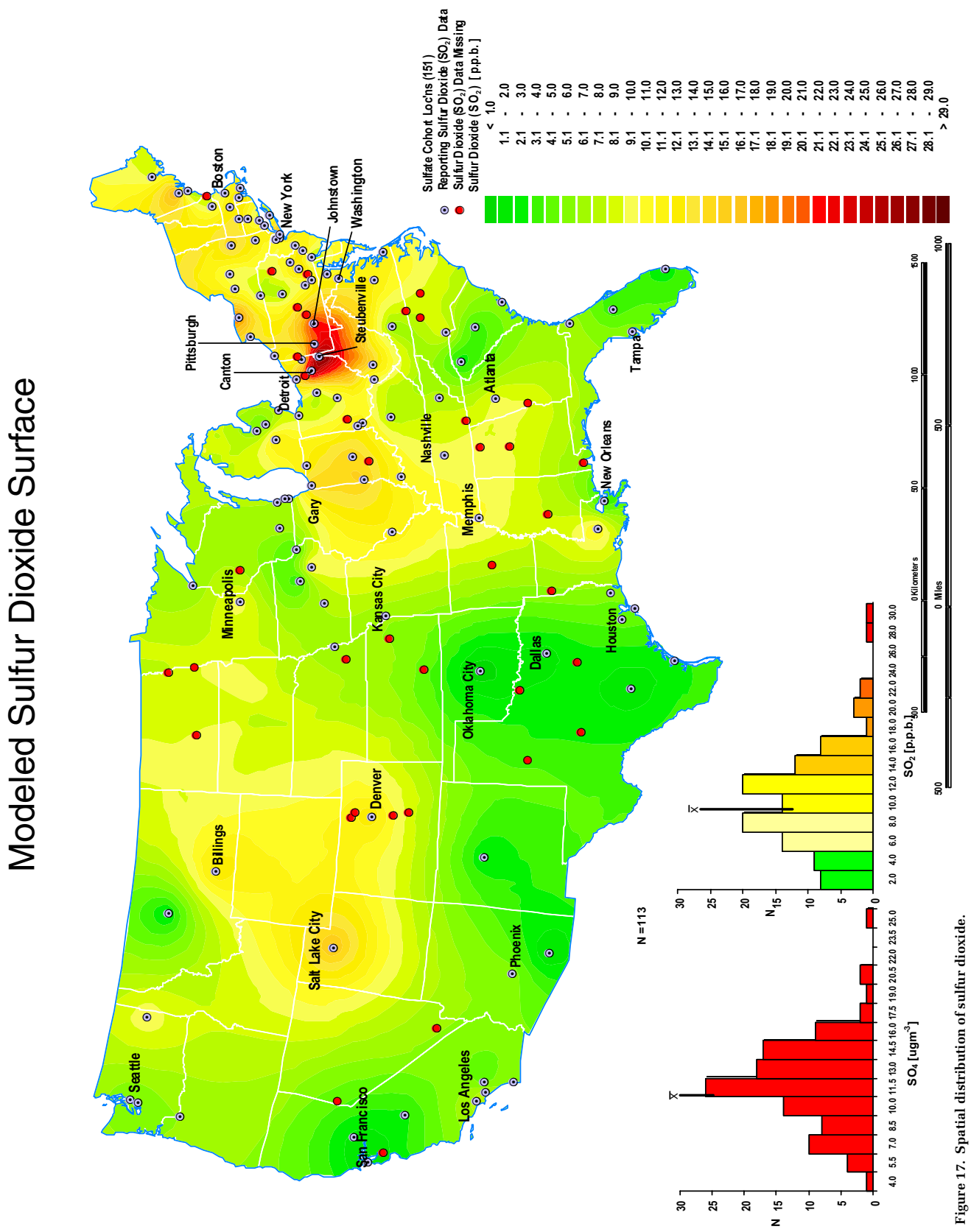



Figure 17. Spatial distribution of sulfur dioxide.

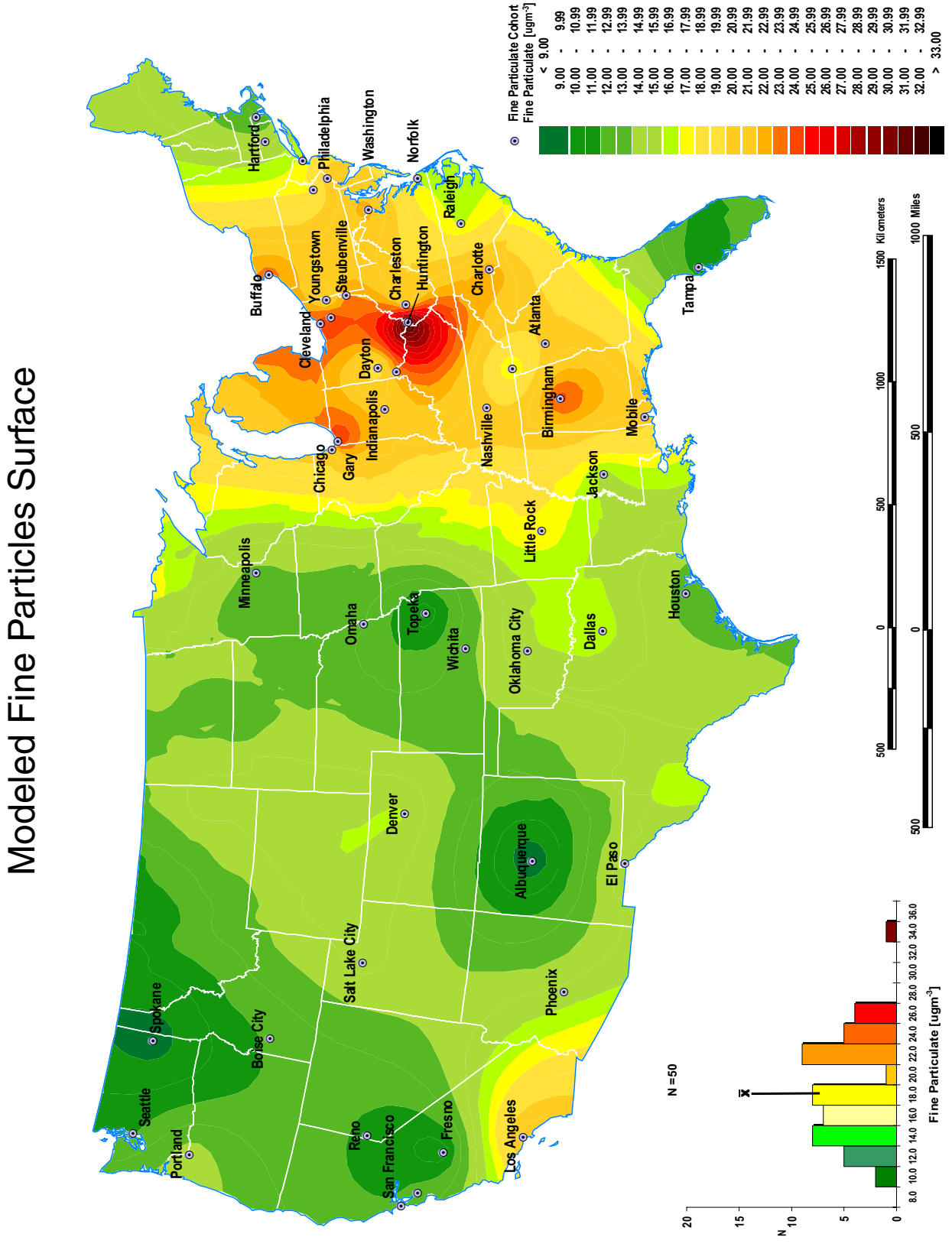



Figure 18. Spatial distribution of fine particles.

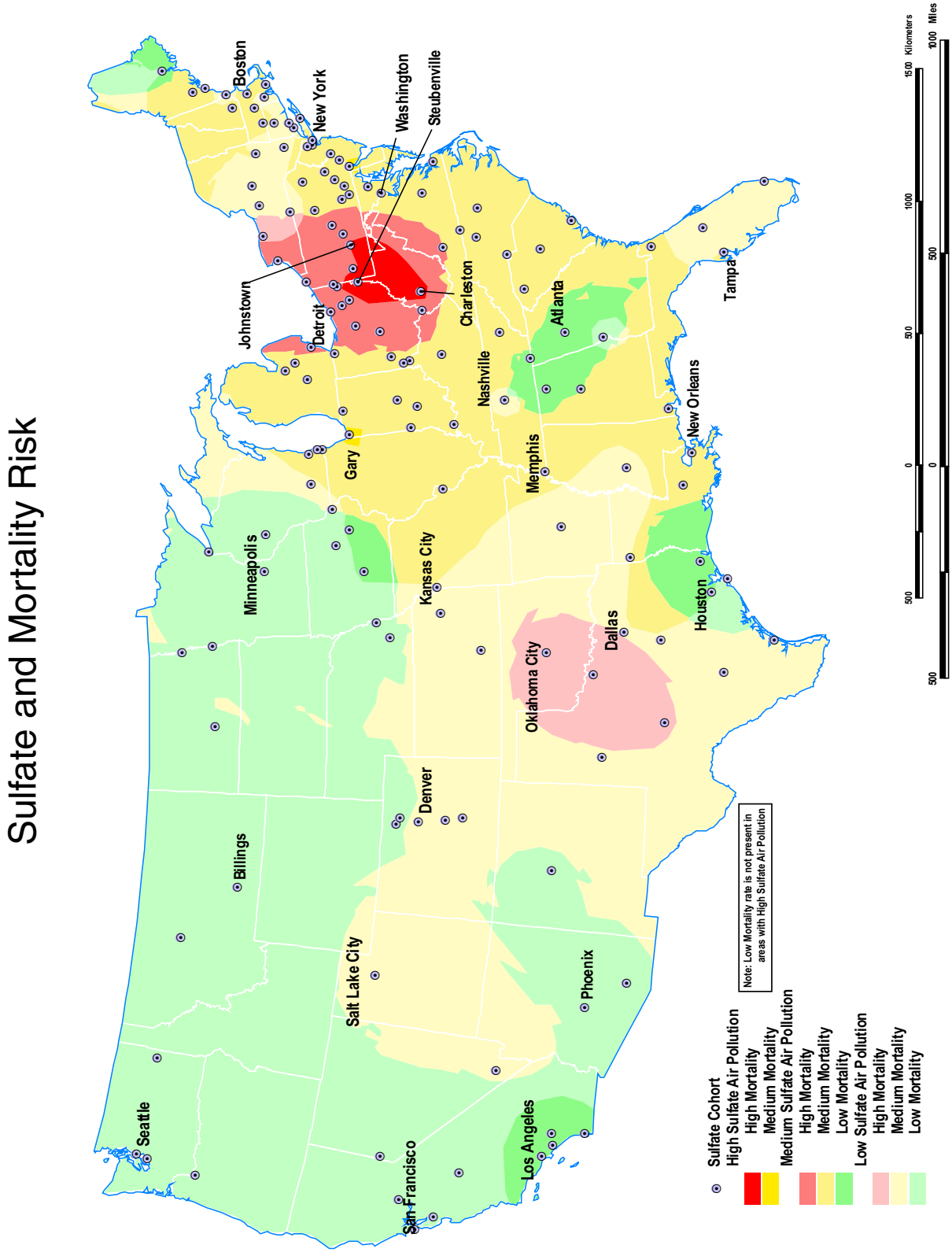



**Figure 19. Spatial overlay of sulfate levels and relative risk of mortality.** Interval classifications for sulfate (in $\mu g/m^3$): low 3.60–10.15; medium 10.15–16.70; high 16.70–23.25. Interval classifications for relative risks of mortality: low 0.924–1.057; medium 1.057–1.14; high 1.14–1.283.

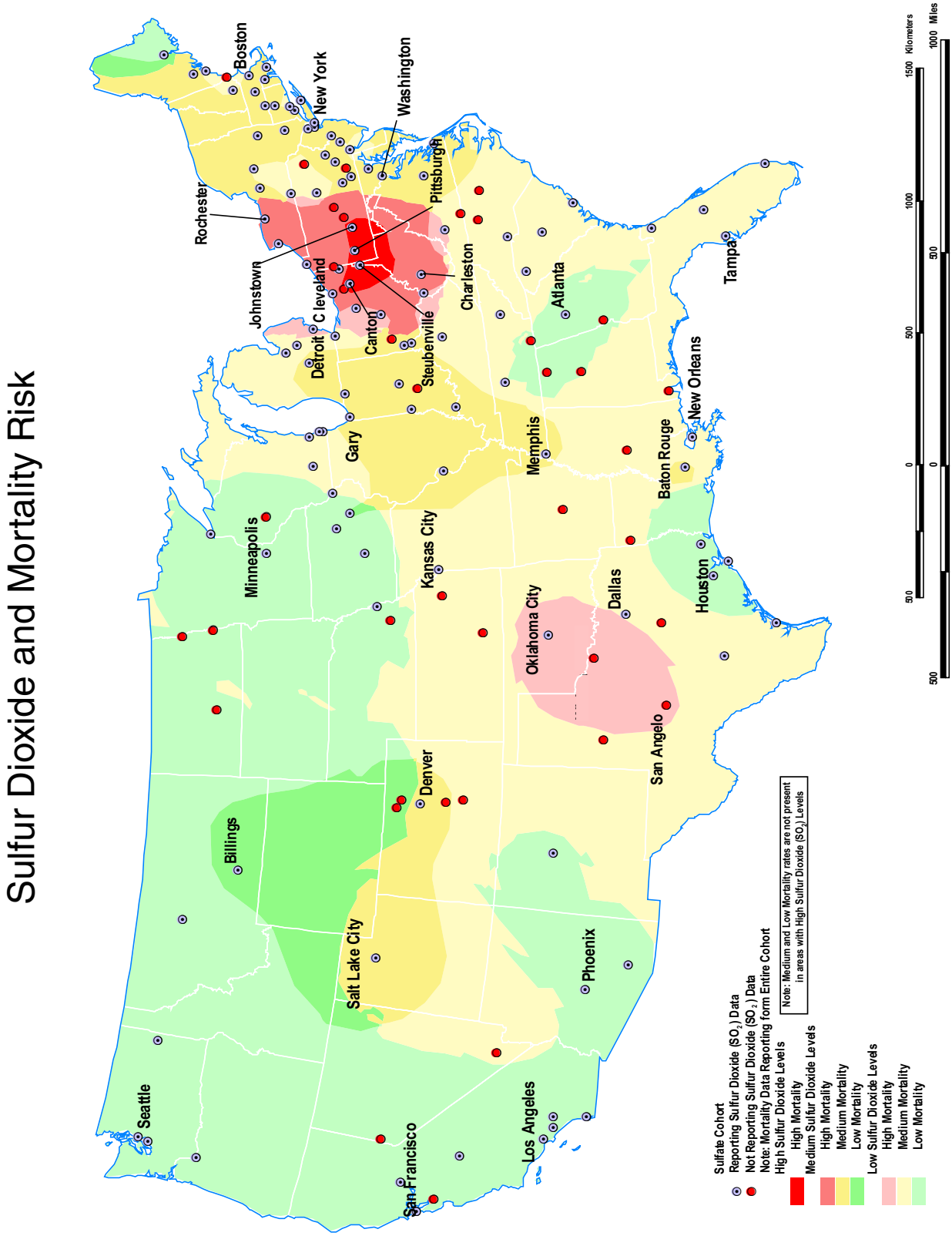



**Figure 20. Spatial overlay of sulfur dioxide levels and relative risk of mortality.** Interval classifications for sulfur dioxide (in ppb): low 0.05–9.78; medium 9.78–19.51; high 19.51–29.25. Interval classifications for relative risks of mortality: low 0.924–1.057; medium 1.057–1.14; high 1.14–1.283.

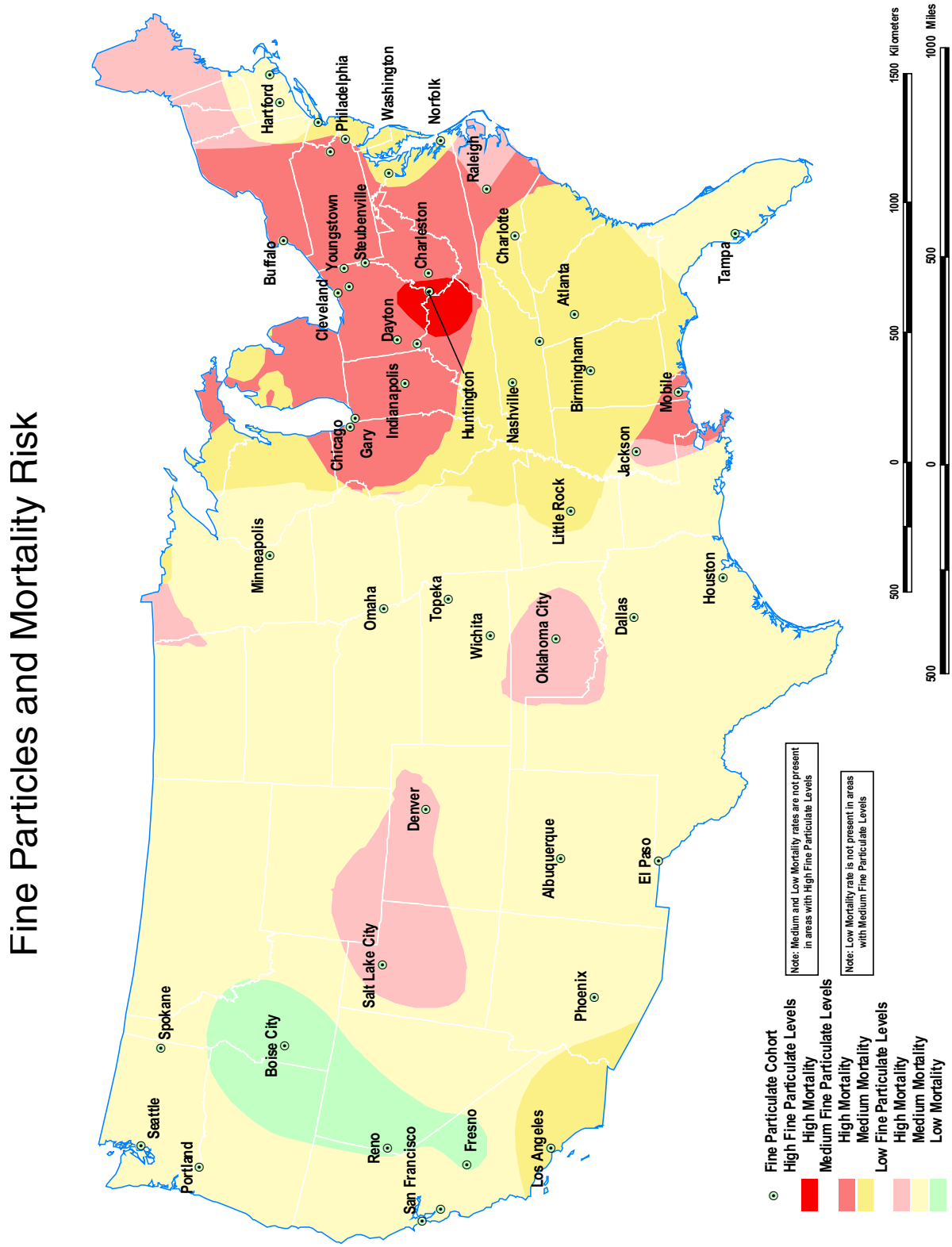



**Figure 21. Spatial overlay of fine particle levels and relative risk of mortality.** Interval classifications for fine particles (in $\mu g/m^3$): low 8.99–17.03; medium 17.03–25.07; high 25.07–33 Interval classifications for relative risks of mortality: low 0.502–0.711; medium 0.711–0.919; high 0.919–1.128.

these displays by first categorizing both mortality rates and pollutant levels into three equal intervals, and then selecting areas of intersection among the three categories of each variable. For the overlay of sulfate and mortality, intersections between high sulfate concentrations and high and medium mortality rates cluster mostly in the Lower Great Lakes area. (There was no intersection between high sulfate concentrations and low mortality rates.) The overlay of sulfur dioxide and mortality is similar, although there are intersections only between high mortality rates and high sulfur dioxide concentrations. (High sulfur dioxide levels do not intersect with either medium or low mortality rates.) Within the low sulfur dioxide category, a cluster of high mortality rates appears along the Texas-Oklahoma border.

The overlay of fine particles and mortality displays a similar pattern in which high levels of fine particle pollution coincide only with high mortality rates. For the medium levels of pollution, intersections exist for high and medium mortality rates, but not for low mortality rates. Only the low fine particle category intersects with the low mortality rate category. The intersection of high fine particle air pollution and high mortality rate is centered on Huntington WV. Areas along the Texas-Oklahoma border display an intersection between low fine particle air pollution and high mortality rate. Overall, these graphic results suggest a certain degree of spatial concordance between high air pollution levels and high mortality rates.

### Testing for Spatial Autocorrelation

We performed exploratory tests for spatial autocorrelation in the response variables (mortality) and predictor variables (air pollution and other ecologic covariates) using global and local indicators of spatial autocorrelation statistics, including the global Moran *I* and *G* statistics (Getis and Ord 1996). We ran these tests using the S-PLUS 2000 spatial statistics package and macro programs developed by Sawada (1999) for Excel 97.

Global autocorrelation tests such as Moran *I* measure the tendency, across all metropolitan areas, for higher (or lower) values to cluster in space with other higher (or lower) values. We evaluated significance against the result expected if the data were randomly distributed in space. Positive correlations with significant *P* values suggest that high values in one metropolitan area tend to depend on values in adjacent regions (ie, higher values will cluster in space with other high values).

Global tests rely on the assumption of stationarity or structural stability over space. Nonstationarity, meaning that the relation among the attributes of interest varies spatially, is quite common. Local indicators of spatial association allow for local instabilities or nonstationarity in the data and point out areas with potential "hot spots" or clusters. The clusters indicate subregions of the study area that may have higher or lower values of attributes, such as risk of mortality, than one would expect by chance.

Results from the exploratory autocorrelation tests indicated significant spatial autocorrelation in the majority of the mortality outcomes considered in the Cox proportional-hazards model. Although they were significant, most of the Moran *I* correlation coefficients were fairly low. The results from the global Moran test indicated that mortality from all causes and from cardiopulmonary disease displays significant positive autocorrelation (Table 39) within the spatial structure of the weight matrix described in Appendix H. This suggests that high values in a given metropolitan area depend partly on other high values in adjacent metropolitan areas. In other words, high values tend to cluster together in space. Positive spatial autocorrelation usually suggests some misspecification in the original model (ie, the Cox proportional-hazards model with individual covariates), such as the omission of relevant covariates, incorrect functional form, or systematic mismeasurement of one of the variables (Odland 1988).

Spatial autocorrelation most often arises when some variable is omitted (Odland 1988), raising the possibility that part of the effect attributed to air pollution may

**Table 39.** Results of Global Tests for Spatial Autocorrelation in the Mortality Rate Ratios Using the Moran *I* and *G* Statistics

| | | Significant Hot Spots? (Moran *G*) | |
|---|---|---|---|
| Cause of Death | Moran *I* | D = 600 km | D = 440 km |
| All causes | 0.225 ($P < 0.001$) | Yes; western lower Great Lakes to the Carolina Coast | Yes; similar but smaller pattern; not as far south |
| Cardiopulmonary disease | 0.197 ($P < 0.001$) | Yes; lower Great Lakes east to Virginia and Maryland | Yes; similar but smaller pattern |
| Lung cancer | 0.0307 ($P = 0.436$) | No | No |

actually be due to some missing variable that is contiguous in space. We addressed this issue using spatial analytic models that incorporate the ecologic covariates assembled by the Reanalysis Team for the ACS Study.

Lung cancer mortality rates showed no significant autocorrelation within the spatial structure used for this analysis. This may be because the processes responsible for this outcome are not autocorrelated, or because the structure of the autocorrelation function differs from that corresponding to the spatial weight matrix. When the data were filtered with the local *G* statistic, we saw significant clustering in rates of all-cause mortality and cardiopulmonary disease mortality (see Table 39).

We conducted a sensitivity analysis to examine spatial dependence at lag distances ranging from 300 to 800 km. This analysis showed that 600 km was the critical distance beyond which spatial dependence decreased; consequently, we chose 600 km as the radius for the spatial filtering techniques discussed below.

Several key points arise from this analysis of spatial autocorrelation of mortality rates. Most of the relative risks of mortality display significant global autocorrelation, which needs to be taken into account in risk modeling. Local autocorrelation is significant as well, particularly in the Lower Great Lakes area. These results appear robust to alternative lag distances.

Sulfate and sulfur dioxide also show significant global autocorrelation, locally tending to cluster in the same pattern as the mortality rates. On the basis of the autocorrelation tests, individual risk factors represented in the Cox model apparently do not explain all of the observed spatial variation in mortality rate in the ACS Study data. The missing variable appears to cluster in areas of high air pollution, although it is difficult to determine whether sulfate, sulfur dioxide, or some combination of both is behind the observed spatial autocorrelation. We used the spatial regression methods discussed below to address this issue.

### Two-Stage Spatial Regression Methods

The Reanalysis Team developed a two-stage regression method to take into account spatial patterns in the mortality rate data and clustering by city. In Stage 1, we regressed risk factor information at the individual level (specifically, those risks included in our Extended Model, discussed in the Alternative Risk Models section) and indicator functions for city (selecting one city as an index) using the Cox model, assuming that the data are statistically independent. For the sulfate cohort, we used Greenville SC as the index city because it had sulfate levels near the mean concentration (11 $\mu g/m^3$). We selected Raleigh NC as the index city for the fine particle cohort. After we adjusted for individual-level risk information, the logarithms of the mortality rates associated with exposure to fine particle air pollution in each city were, in fact, comparable to those in Greenville. Therefore, we note that any index city could have been selected with identical results.

In Stage 2, we regressed the logarithms of the city-specific relative mortality rates on ecologic variables that have common values for all cohort members within each city but vary among cities, including indices of air pollution and the ecologic covariates discussed previously. The statistical uncertainty in the estimated mortality rates in this step is taken into account by weighting the mortality rates by the sum of the variation in relative risks between cities and their estimation errors. (The estimation error is obtained from the Cox model.)

Our method of estimating adjusted city-specific mortality rates has the limitation that the estimate for each city was obtained as a comparison to an index city (Greenville SC). This induces additional covariation in the city-specific mortality estimates and inflates the variance of each estimate. We corrected for this variance inflation using an approach suggested by Easton and colleagues (1991). This approach also yields a variance estimate for the index city, so it can be used in the second step of the analysis, which requires a weight to be assigned to the city-specific mortality rates.

Because the covariance between the estimates of the city-specific mortality rates was almost identical for each city, the Easton adjustment is greatly simplified. The variance estimate for the index city is the average of the covariances of the city-specific estimates, and the adjusted variance for each city is the difference between the variance obtained from the Cox model and the average of the covariances.

Our random effects model assumes that the logarithms of the city-specific mortality rates follow a statistical distribution, with the expected values given by a linear regression model composed of city-level variables and a dispersion parameter that represents the true variation in the logarithms of the city-specific mortality rates, after adjusting for all risk factor information at the city level. (Note we had previously adjusted the mortality rates for individual-level information in Stage 1 of the analysis.) However, we could not observe the true values of the city-specific mortality rates and used estimates from Stage 1 that contained some inherent uncertainty. This uncertainty can be incorporated in Stage 2 by assuming that the variance of the logarithm of the city-specific mortality rate estimates is given by the sum of the true variation in rates between cities and the city-specific estimation error.

Implementation of Stage 2 of the two-stage regression approach involved the following four steps.

1. We obtained an initial estimate of the true variation in mortality between cities, using a method developed by DerSimonian and Laird (1986) that employs no city-level covariates. This method assumes knowledge only of the mean and variance structure of the data and is relatively simple to implement.
2. We used weighted linear regression methods to regress the logarithms of the city-specific mortality rates on city-level covariates, weighted by the inverse of the sum of the initial estimate of the true variance in rates between cities and the city-specific estimation variances.
3. We then used residuals from the model in step 2 to obtain an updated estimate of the true variability in rates between cities.
4. Finally, we repeated step 2 using an updated estimate of between-city variance.

We also estimated the effects on mortality of various indices of air pollution and several other covariates measured at the community level, setting the variation in rates to zero and the residual variance equal to the within-city estimation error. For these analyses, we assumed that the observations were independent and not clustered by city. (This independence assumption was also made in the Cox model.) We compared the results of our two-stage estimation approach to those of the Cox model for these analyses.

Variation in mortality rates between cities incurs a weighting scheme in which the weights are more uniform between cities compared with a scheme in which we assume no such variation (ie, the Independence Cities Model). When weights are more uniform, cities with large sample sizes will carry relatively less weight in the regression model than when we assume the observations are independent. As the estimation of error of the city-specific mortality grows smaller, the weight it is assigned in the second stage of the analysis grows larger. We would assign almost equal weights to every city if the true variation in rates was much greater than the error of the city-specific mortality rate estimates. The relative magnitude of the between-city variation in mortality rates compared with the average of the within-city estimation error determines the weighting scheme used in the analysis.

The Reanalysis Team used logarithms of the estimated city-specific mortality rates adjusted for the individual-level risk factors and their corresponding variances (which include the estimate of the true variation between cities) as input to our spatial analyses. We focused on four different two-stage regression models that afforded increasing control for spatial autocorrelation (see Tables 40 through 49).

***Independent Observations Model*** The two-stage Independent Observations Model, like the standard Cox model, assumes that all observations are statistically independent. We obtained relative risks of mortality 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 standard errors of the relative risks in the second stage. This model provides a baseline against which either model can be compared.

***Independent Cities Model*** The Independent Cities Model, which allows for clustering in mortality rates by city, employs 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 second-stage weights. However, this approach assumes that the city-specific mortality rates are statistically independent, thereby ignoring possible regional patterns in mortality that extend beyond MSA boundaries.

***Regional Adjustment Model*** To allow for the possibility of regional effects, we conducted further analyses in which an indicator variable represented each of the seven regions shown in Figure 15. We then combined these indicator variables in the second stage to allow for residual between-city variation.

***Spatial Filtering Model*** The final analysis summarized in Table 40 uses spatial filtering techniques to remove regional patterns in both mortality and the ecologic predictors of mortality. Variation in relative risks between cities was modeled using the two-stage random effects regression approach on the filtered mortality and ecologic covariate data. In contrast, the previous Regional Adjustment Model adjusts for spatial patterns in mortality, but not in the ecologic covariates used to predict mortality (see Appendix H for a more detailed explanation). The spatial filtering approach compares the relative risk of mortality for a given city to the risks for cities within a specified distance of that city. The distance (600 km) was selected such that the residual spatial autocorrelation was minimized. The results of applying these four two-stage regression methods to the sulfate and fine particle cohorts of the ACS Study are described below.

**Table 40.** Impact of Individual Ecologic Covariates on the Relative Risks of Mortality from All Causes Associated with an Increase in Sulfate Using Two-Stage Spatial Analytic Methods[a]

| | | | Random Effects | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Independent Observations | | Independent Cities | | Regional Adjustment | | Spatial Filtering[b] | |
| Ecologic Covariate | Sulfate | Covariate | Sulfate | Covariate | Sulfate | Covariate | Sulfate | Covariate |
| **Sulfate Alone** | 1.17 (1.07–1.27) | | 1.25 (1.13–1.37)[c] | | 1.19 (1.06–1.34) | | 1.09 (1.01–1.19) | |
| **Demographic Factors** | | | | | | | | |
| Population change | 1.06 (1.00–1.13) | 0.86 (0.81–0.90) | 1.16 (1.05–1.29)[c] | 0.88 (0.80–0.96) | 1.17 (1.02–1.33) | 0.94 (0.84–1.05) | 1.10 (1.00–1.20) | 1.02 (0.86–1.22) |
| Whites | 1.21 (1.14–1.28) | 1.08 (1.04–1.13) | 1.27 (1.15–1.39)[d] | 1.06 (0.99–1.14) | 1.20 (1.06–1.36) | 1.03 (0.95–1.10) | 1.10 (1.01–1.20) | 1.03 (0.95–1.11) |
| Blacks | 1.19 (1.12–1.27) | 0.95 (0.90–1.00) | 1.26 (1.15–1.39)[c] | 0.96 (0.88–1.04) | 1.19 (1.06–1.35) | 0.99 (0.90–1.09) | 1.10 (1.01–1.20) | 0.99 (0.93–1.05) |
| **Socioeconomic Factors** | | | | | | | | |
| Income | 1.16 (1.10–1.23) | 0.88 (0.84–0.93) | 1.23 (1.12–1.35)[c] | 0.91 (0.83–0.99) | 1.18 (1.05–1.33) | 0.90 (0.83–0.97) | 1.09 (1.00–1.18) | 0.91 (0.84–0.98)[e] |
| Poverty | 1.17 (1.11–1.24) | 0.95 (0.91–0.99) | 1.25 (1.14–1.37)[c] | 0.97 (0.89–1.05) | 1.19 (1.06–1.35) | 0.99 (0.91–1.08) | 1.09 (1.00–1.19) | 1.01 (0.94–1.09)[e] |
| Income disparity | 1.17 (1.10–1.23) | 0.87 (0.82–0.92) | 1.24 (1.13–1.36)[d] | 0.92 (0.83–1.01) | 1.19 (1.06–1.34) | 0.95 (0.86–1.06) | 1.10 (1.01–1.19) | 0.96 (0.88–1.06) |
| Unemployment | 1.13 (1.07–1.20) | 1.13 (1.06–1.20) | 1.22 (1.11–1.34)[c] | 1.11 (1.01–1.22) | 1.18 (1.05–1.33) | 1.06 (0.97–1.17) | 1.08 (1.00–1.18) | 1.08 (0.98–1.19) |
| Education | 1.13 (1.06–1.20) | 0.92 (0.86–0.98) | 1.20 (1.08–1.33)[c] | 0.92 (0.82–1.02) | 1.16 (1.02–1.31) | 0.91 (0.80–1.03) | 1.07 (0.98–1.17) | 0.92 (0.83–1.02) |
| **Health Services** | | | | | | | | |
| Physicians | 1.16 (1.10–1.22) | 0.92 (0.87–0.97) | 1.23 (1.12–1.36)[c] | 0.92 (0.84–1.02) | 1.17 (1.04–1.33) | 0.93 (0.85–1.02) | 1.09 (1.00–1.19) | 0.94 (0.86–1.03)[e] |
| Hospital beds | 1.15 (1.08–1.21) | 1.15 (1.07–1.22) | 1.24 (1.13–1.36)[c] | 1.13 (1.02–1.25) | 1.19 (1.05–1.35) | 1.13 (1.02–1.25) | 1.09 (1.00–1.19) | 1.08 (0.99–1.17) |
| **Climate** | | | | | | | | |
| Temperature | 1.12 (1.05–1.19) | 0.90 (0.86–0.94) | 1.23 (1.11–1.36)[c] | 0.94 (0.87–1.01) | 1.20 (1.05–1.37) | 0.98 (0.86–1.13) | NP | NP |
| Temperature variation | 1.11 (1.05–1.18) | 1.18 (1.11–1.25) | 1.22 (1.11–1.35)[c] | 1.13 (1.03–1.25) | 1.18 (1.03–1.34) | 1.12 (0.99–1.26) | 1.08 (0.99–1.18) | 1.07 (0.96–1.19) |
| Relative humidity | 1.14 (1.05–1.24) | 0.99 (0.92–1.06) | 1.17 (1.01–1.35)[c] | 1.02 (0.90–1.16) | 1.15 (0.95–1.39) | 1.06 (0.90–1.24) | 1.12 (0.99–1.26) | 1.10 (1.03–1.18) |
| Relative humidity variation | 1.17 (1.09–1.26) | 0.91 (0.86–0.97) | 1.21 (1.07–1.37)[c] | 0.92 (0.83–1.03) | 1.16 (0.96–1.40) | 0.99 (0.87–1.12) | 1.09 (0.96–1.24) | 0.96 (0.86–1.08) |
| **Physical Environment** | | | | | | | | |
| Altitude | 1.18 (1.10–1.27) | 1.15 (1.08–1.23) | 1.24 (1.09–1.40)[c] | 1.07 (0.95–1.20) | 1.12 (0.96–1.31)[d] | 1.06 (0.94–1.21) | 1.08 (0.97–1.19) | 1.05 (0.95–1.17) |
| Water hardness | 1.14 (1.07–1.21) | 1.09 (1.04–1.15) | 1.24 (1.11–1.39) | 1.07 (0.98–1.17) | 1.17 (1.01–1.36) | 1.05 (0.94–1.16) | 1.08 (0.98–1.19) | 1.08 (0.98–1.20) |
| **Gaseous Copollutants** | | | | | | | | |
| CO | 1.16 (1.10–1.23) | 0.96 (0.91–1.02) | 1.25 (1.14–1.37)[c] | 0.99 (0.90–1.09) | 1.17 (1.03–1.33) | 1.06 (0.97–1.16) | NP | NP |
| $NO_2$ | 1.16 (1.08–1.24) | 0.89 (0.85–0.94) | 1.27 (1.13–1.44)[c] | 0.93 (0.83–1.04) | 1.21 (1.02–1.44) | 0.94 (0.82–1.07) | NP | NP |
| $O_3$ | 1.17 (1.11–1.24) | 0.93 (0.87–0.99) | 1.26 (1.15–1.38)[c] | 0.93 (0.84–1.02) | 1.16 (1.03–1.30) | 1.02 (0.92–1.12) | 1.08 (1.00–1.18) | 0.96 (0.87–1.05)[e] |
| $SO_2$ | 1.05 (0.98–1.12) | 1.31 (1.23–1.40) | 1.13 (1.02–1.25) | 1.27 (1.15–1.40) | 1.10 (0.97–1.24) | 1.23 (1.11–1.36) | 1.05 (0.97–1.14) | 1.19 (1.10–1.29) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] Used the Filtered Both Sides Model. NP = Not possible to remove spatial autocorrelation in this covariate.

[c] The residuals are spatially autocorrelated ($P < 0.05$) confidence using the Moran $I$ statistic.

[d] The residuals are spatially autocorrelated ($P < 0.10$) confidence using the Moran $I$ statistic.

[e] No evidence of spatial autocorrelation was found in the original data for these variables, therefore the Filtered Mortality Only Model was applied.

### Spatial Analysis of the Sulfate Cohort

***All-Cause Mortality*** Using the two-stage methods described above, we calculated the relative risk of mortality from all causes associated with exposure to sulfate (Table 40). For each of the four types of analyses, the first column of results in Table 40 represents the sulfate-exposure-associated relative risk of mortality from all causes, adjusted for each of the ecologic covariates considered; the second column represents the relative risk of all-cause mortality for the ecologic covariate, adjusted for sulfate. Because we were unable to obtain information on some ecologic covariates for certain cities (see Table 33), the relative risk of mortality associated with sulfate alone varied with the set of cities for which data were available for the covariate.

With some exceptions, the relative risk of all-cause mortality associated with exposure to sulfate in each of these subsets of cities was generally comparable to that calculated using all 151 cities. Differences occurred in the Independent Cities Model, in which RR = 1.25 (95% CI: 1.13–1.37) for all-cause mortality associated with sulfate, somewhat higher than the RR = 1.17 (95% CI: 1.01–1.35) in the 95 cities for which data on relative humidity were available. Under the Regional Adjustment Model, the relative risks of mortality associated with exposure to sulfate in these same 95 cities (RR = 1.15, 95% CI: 0.95–1.39) for which relative humidity data were available and the 110 cities (RR = 1.12, 95% CI: 0.96–1.31) for which altitude was available were somewhat lower than the relative risk based on all 151 cities (RR = 1.19, 95% CI: 1.06–1.34). Under the Filtered Both Sides Model, the relative risk of all-cause mortality associated with sulfate exposure was not significant in the subsets of cities for which data were available on education (151 cities), temperature variation (135 cities), relative humidity and relative humidity variation (95 cities), altitude (110 cities), water hardness (109 cities), and $SO_2$ (113 cities).

Under the Independent Observations Model, applied to all 151 cities in the sulfate cohort, the relative risk of mortality from all causes (see Table 40) was estimated to be 1.17 (95% CI: 1.07–1.27). This was similar to the estimate (RR = 1.15, 95% CI: 1.09–1.21) arrived at with the Cox proportional-hazards regression model (see Table 34). The association between exposure to sulfate and all-cause mortality remained significant after adjustment for each of the individual ecologic covariates other than population change and exposure to sulfur dioxide. Whereas population change correlated negatively with mortality when analyzed as the covariate alone, exposure to sulfur dioxide demonstrated a positive association (see Table 40).

When we allowed for clustering by city in the Independent Cities Model, we obtained higher estimates of the relative risk of all-cause mortality from exposure to sulfate than we did in the Independent Observations Model. In the Independent Cities Model, the city-specific weights used in the second stage were more uniform than in the Independent Observations Model, so that larger cities are assigned less weight. In this case, the association between sulfate and mortality remained significant even after adjustment for population change.

Although the Independent Cities Model allows for clustering within cities, it does not allow for clustering at a broader regional level. To evaluate the validity of this analysis, we used the Moran $I$ test for global spatial autocorrelation to test for regional clustering within a radius of 600 km. Except for the analyses adjusted for water hardness and sulfur dioxide, in all cases the residuals demonstrated significant ($P < 0.05$) spatial autocorrelation, indicating the need to allow for regional clustering in the analysis.

When we adjusted for spatial clustering in city-specific mortality rates (Regional Adjustment Model) using the seven regions shown in Figure 15, we obtained relative risk estimates closer to those of the Independent Observations Model, although the confidence limits were somewhat wider. This reduction in risk accompanying regional adjustment suggests that part of the apparent sulfate effect observed with the Independent Cities Model is the result of spatial concordance between mortality and air pollution. We observed little evidence of residual spatial autocorrelation after regional adjustment, indicating that the Regional Adjustment Model removes broad regional trends in the data.

The final analysis summarized in Table 40, which used spatial filtering techniques before regression analysis was applied, removed regional trends in both mortality and each of the ecologic covariates considered. This analysis provided a more complete adjustment for regional patterns in the data without the need to specify regional boundaries as in the Regional Adjustment model. The Spatial Filtering Model resulted in relative risks of all-cause mortality associated with exposure to sulfate that were lower than those from the Regional Adjustment Model. The effect of exposure to sulfate without adjustment for any of the ecologic covariates remained significant (RR = 1.09, 95% CI: 1.01–1.19) but lower than in the Independent Cities Model; again, however, it was no longer significant after adjustment was made for exposure to sulfur dioxide.

We evaluated the stability of the sulfate–mortality association to adjustment for the effects of multiple ecologic covariates by conducting three additional multivariate regression analyses. The first analysis included all four

gaseous copollutants (CO, $NO_2$, $O_3$, and $SO_2$), in addition to sulfate, and was intended to examine the effect of sulfate after adjusting for all of the gaseous copollutants simultaneously. The second included population change and all of the socioeconomic factors (educational attainment, income, poverty rate, income disparity, and unemployment rate) along with sulfate. The third analysis included all ecologic covariates that individually produced a 25% change in the relative risk of mortality associated with sulfate (the covariates included were different for each analysis).

Because sulfur dioxide was the only gaseous copollutant that appeared to be associated strongly with all-cause mortality (Table 41), simultaneous adjustment for all four gaseous copollutants led to sulfate-associated relative risks of mortality somewhat similar to those obtained when we adjusted for sulfur dioxide alone. We did not see a marked impact on the association between sulfate and all-cause mortality when we adjusted simultaneously for all demographic and socioeconomic variables.

***Cardiopulmonary Disease Mortality*** Although exposure to sulfate was significantly associated with cardiopulmonary mortality (Table 42) under the Regional Adjustment Model based on all 151 cities (RR = 1.19, 95% CI: 1.06–1.34), the sulfate-associated relative risk of cardiopulmonary disease mortality was not significant in certain subsets, notably the 95 cities in which data on relative humidity were available (RR = 1.15, 95% CI: 0.88–1.39). Under the Filtered Both Sides Model, the sulfate-associated effect also was not significant in certain subsets of cities for which ecologic data were available (notably education: RR = 1.08, 95% CI: 0.96–1.22; relative humidity: RR = 1.10, 95% CI: 0.91–1.31; relative humidity variation: RR = 1.09, 95% CI: 0.90–1.31; and altitude: RR = 1.12, 95% CI: 0.96–1.29), whereas the relative risk based on all 151 cities (RR = 1.13, 95% CI: 1.01–1.27) achieved nominal statistical significance.

The relative risk of cardiopulmonary disease mortality associated with exposure to sulfate (see Table 42) obtained with the Independent Observations Model was 1.25 (95% CI: 1.12–1.39), again similar to the value of 1.25 (95% CI: 1.16–1.36 [see Table 20, Extended Model]) achieved using the Cox regression. The sulfate-associated effect remained significant after adjustment for any one of the ecologic covariates considered, including sulfur dioxide. As was the case with mortality from all causes, the relative risk of cardiopulmonary mortality associated with exposure to sulfate tended to increase when we used the Independent Cities Model but to decrease when we applied both the Regional Adjustment Model and the Spatial Filtering Models. Although we found consistent evidence of spatial autocorrelation with the Independent Cities Model, we saw little evidence of residual spatial autocorrelation after we applied the Regional Adjustment Model. Cardiopulmonary disease mortality appeared to be associated with the unemployment rate and water hardness in addition to sulfate and sulfur dioxide, although neither unemployment nor water hardness had a marked impact on the association between sulfate and cardiopulmonary mortality. The effect of sulfate was diminished somewhat in multiple covariate models (Table 43), but remained elevated even with maximal adjustment for spatial autocorrelation.

***Lung Cancer Mortality*** Exposure to airborne sulfate was associated with lung cancer mortality (Table 44) in both the Independent Observations Model (RR = 1.31, 95% CI: 1.05–1.65) and the Independent Cities Model (RR = 1.39, 95% CI: 1.09–1.75). None of the other ecologic covariates appeared to be associated with lung cancer, nor did they appreciably alter the association between sulfate and lung cancer mortality. The relative risk of lung cancer mortality associated with exposure to sulfate remained elevated after adjustment for multiple covariates (Table 45). Lung cancer exhibited a high degree of spatial homogeneity and there was no evidence of spatial autocorrelation in the Independent Cities Model; thus no attempt was made to remove it using either the Regional Adjustment Model or Spatial Filtering Model.

### Spatial Analysis of the Fine Particle Cohort

***All-Cause Mortality*** Exposure to fine particles was associated with all-cause mortality (Table 46) under the Independent Observations Model (RR = 1.18, 95% CI: 1.03–1.35). The relative risk increased (RR = 1.29, 95% CI: 1.12–1.48) under the Independent Cities Model, but dropped (RR = 1.16, 95% CI: 0.99–1.37) after we applied the Regional Adjustment Model. We were unable to apply the Spatial Filtering Model, largely because of the limited number of cities (50) in the fine particle cohort.

Sulfur dioxide pollution appeared to be strongly associated with all-cause mortality in the fine particle cohort, as it was in the sulfate cohort. Water hardness also showed an association with all-cause mortality in the fine particle cohort, but it had little effect in the sulfate cohort. The relative risk of all-cause mortality associated with exposure to fine particles remained elevated, if not significant, in the Independent Cities and Regional Adjustment Models. The relative risk of all-cause mortality associated with exposure to fine particles was not altered greatly after adjusting for all demographic and socioeconomic covariates, although the relative risk was reduced markedly in

**Table 41.** Impact of Multiple Ecologic Covariates on the Relative Risks of Mortality from All Causes Associated with an Increase in Sulfate Using Two-Stage Spatial Analytic Methods[a]

| Spatial Analytic Model | Number of Cities | Relative Risk Calculated for Sulfate Alone | Ecologic Covariates Incorporated into Adjusted Analyses | Relative Risk After Adjusting for Ecologic Covariates[b] | |
|---|---|---|---|---|---|
| | | | | Sulfate | $SO_2$ |
| **Demographic and Socioeconomic Factors** | | | | | |
| Independent Observations | 139 | 1.16 (1.10–1.23) | Population change, income, poverty, income disparity, unemployment, education | 1.10 (1.02–1.18) | NC |
| Independent Cities | 139 | 1.24 (1.13–1.37) | | 1.17 (1.05–1.31) | NC |
| Regional Adjustment | 139 | 1.18 (1.04–1.34) | | 1.21 (1.06–1.38) | NC |
| Spatial Filtering[c] | 139 | 1.10 (1.00–1.20) | | 1.11 (1.01–1.21)[d] | NC |
| **Gaseous Copollutants** | | | | | |
| Independent Observations | 58 | 1.11 (1.04–1.19) | $CO, NO_2, O_3, SO_2$ | 1.06 (0.98–1.14) | 1.41 (1.31–1.52) |
| Independent Cities | 58 | 1.25 (1.10–1.43) | | 1.05 (0.93–1.18) | 1.39 (1.24–1.55) |
| Regional Adjustment | 58 | 1.25 (1.03–1.51) | | 1.06 (0.90–1.26) | 1.28 (1.12–1.46) |
| Spatial Filtering[c] | 102 | 1.09 (0.99–1.19) | $O_3, SO_2$ | 1.05 (0.96–1.14) | 1.19 (1.09–1.29) |
| **25%[e]** | | | | | |
| Independent Observations | 44 | 1.12 (1.03–1.21) | Population change, whites, temperature variation, relative humidity variation, altitude, $SO_2$ | 1.18 (1.07–1.30) | 1.22 (1.09–1.37) |
| Independent Cities | 103 | 1.28 (1.16–1.42) | Population change, $SO_2$ | 1.10 (0.99–1.22) | 1.23 (1.11–1.37) |
| Regional Adjustment | 113 | 1.21 (1.07–1.37) | $SO_2$ | 1.10 (0.97–1.24) | 1.23 (1.11–1.36) |
| Spatial Filtering[c] | 50 | 1.05 (0.91–1.22) | Education, relative humidity, altitude, $SO_2$ | 1.09 (0.94–1.26) | 1.07 (0.95–1.22) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] NC = Relative risks associated with $SO_2$ were not calculated in some multivariate models.

[c] Used the Filtered Both Sides Model.

[d] The residuals are spatially autocorrelated ($P < 0.10$) using the Moran $I$ statistic.

[e] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with sulfate.

**Table 42.** Impact of Individual Ecologic Covariates on the Relative Risks of Mortality from Cardiopulmonary Disease Associated with an Increase in Sulfate Using Two-Stage Spatial Analytic Methods[a]

| | | | Random Effects | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Independent Observations | | Independent Cities | | Regional Adjustment | | Spatial Filtering[b] | |
| Ecologic Covariate | Sulfate | Covariate | Sulfate | Covariate | Sulfate | Covariate | Sulfate | Covariate |
| **Sulfate Alone** | 1.25 (1.12–1.39) | | 1.29 (1.15–1.46)[c] | | 1.19 (1.06–1.34) | | 1.13 (1.01–1.27) | |
| **Demographic Factors** | | | | | | | | |
| Population change | 1.11 (1.01–1.21) | 0.82 (0.76–0.88) | 1.17 (1.03–1.33)[c] | 0.84 (0.76–0.94) | 1.16 (0.98–1.37) | 0.91 (0.78–1.05) | 1.12 (1.00–1.25) | 1.08 (0.85–1.37) |
| Whites | 1.30 (1.20–1.42) | 1.10 (1.04–1.17) | 1.32 (1.17–1.50)[c] | 1.07 (0.98–1.18) | 1.24 (1.05–1.46) | 1.03 (0.93–1.13) | 1.14 (1.02–1.28) | 1.04 (0.94–1.16) |
| Blacks | 1.28 (1.18–1.40) | 0.94 (0.87–1.01) | 1.31 (1.15–1.49)[c] | 0.96 (0.86–1.07) | 1.22 (1.04–1.44) | 1.01 (0.89–1.14) | 1.14 (1.01–1.28) | 0.99 (0.91–1.07) |
| **Socioeconomic Factors** | | | | | | | | |
| Income | 1.25 (1.15–1.35) | 0.86 (0.80–0.92) | 1.27 (1.13–1.43)[c] | 0.87 (0.78–0.97) | 1.21 (1.04–1.42) | 0.86 (0.77–0.96) | 1.13 (1.01–1.26) | 0.87 (0.78–0.96)[e] |
| Poverty | 1.25 (1.16–1.36) | 0.97 (0.91–1.04) | 1.29 (1.14–1.46)[c] | 1.00 (0.91–1.09) | 1.22 (1.03–1.43) | 1.04 (0.93–1.17) | 1.12 (1.00–1.26) | 1.06 (0.96–1.16)[e] |
| Income disparity | 1.25 (1.16–1.35) | 0.89 (0.82–0.96) | 1.29 (1.14–1.46)[c] | 0.94 (0.83–1.07) | 1.22 (1.04–1.44) | 1.00 (0.87–1.16) | 1.16 (1.03–1.30) | 1.02 (0.90–1.16) |
| Unemployment | 1.19 (1.09–1.29) | 1.24 (1.14–1.36) | 1.24 (1.10–1.40)[c] | 1.21 (1.07–1.36) | 1.20 (1.02–1.40) | 1.15 (1.01–1.30) | 1.10 (0.99–1.23) | 1.19 (1.05–1.36) |
| Education | 1.20 (1.10–1.31) | 0.90 (0.82–0.99) | 1.22 (1.06–1.39)[c] | 1.50 (1.14–1.98) | 1.17 (0.99–1.38) | 0.85 (0.72–1.00) | 1.08 (0.96–1.22) | 0.86 (0.74–0.99) |
| **Health Services** | | | | | | | | |
| Physicians | 1.23 (1.13–1.33) | 0.86 (0.79–0.93) | 1.25 (1.11–1.41)[c] | 0.85 (0.75–0.96) | 1.17 (1.00–1.37) | 0.85 (0.76–0.96) | 1.10 (0.98–1.23) | 0.85 (0.76–0.96)[e] |
| Hospital beds | 1.22 (1.13–1.32) | 1.16 (1.06–1.28) | 1.27 (1.13–1.44)[c] | 1.15 (1.01–1.30) | 1.20 (1.02–1.41) | 1.14 (0.99–1.30) | 1.11 (0.99–1.25) | 1.08 (0.96–1.20) |
| **Climate** | | | | | | | | |
| Temperature | 1.18 (1.08–1.28) | 0.88 (0.83–0.94) | 1.25 (1.09–1.42)[c] | 0.93 (0.84–1.03) | 1.21 (1.01–1.44) | 0.97 (0.81–1.17) | NP | NP |
| Temperature variation | 1.16 (1.07–1.26) | 1.25 (1.15–1.35) | 1.23 (1.08–1.40)[c] | 1.19 (1.05–1.36) | 1.17 (0.98–1.39)[d] | 1.19 (1.01–1.39) | 1.10 (0.97–1.24) | 1.11 (0.96–1.28) |
| Relative humidity | 1.17 (1.04–1.33) | 1.03 (0.92–1.15) | 1.17 (0.96–1.43)[c] | 1.05 (0.88–1.26) | 1.15 (0.88–1.39) | 1.11 (0.89–1.38) | 1.10 (0.91–1.31) | 1.09 (0.98–1.20) |
| Relative humidity variation | 1.26 (1.14–1.40) | 0.86 (0.79–0.95) | 1.25 (1.06–1.48)[c] | 0.89 (0.76–1.03) | 1.17 (0.91–1.52) | 0.97 (0.81–1.16) | 1.09 (0.90–1.31) | 0.93 (0.79–1.09) |
| **Physical Environment** | | | | | | | | |
| Altitude | 1.27 (1.15–1.40) | 1.15 (1.04–1.26) | 1.28 (1.09–1.52)[c] | 1.04 (0.89–1.22) | 1.23 (0.99–1.53) | 1.01 (0.84–1.21) | 1.12 (0.96–1.29) | 1.02 (0.88–1.19) |
| Water hardness | 1.20 (1.10–1.31) | 1.13 (1.05–1.21) | 1.26 (1.10–1.44)[d] | 1.11 (1.00–1.24) | 1.14 (0.96–1.37) | 1.08 (0.95–1.22) | 1.11 (0.98–1.26) | 1.11 (0.97–1.26) |
| **Gaseous Copollutants** | | | | | | | | |
| CO | 1.28 (1.18–1.39) | 0.93 (0.86–1.01) | 1.32 (1.18–1.48)[c] | 0.94 (0.84–1.05) | 1.24 (1.06–1.45) | 0.98 (0.88–1.10) | NP | NP |
| $NO_2$ | 1.29 (1.17–1.42) | 0.89 (0.82–0.96) | 1.35 (1.18–1.55)[c] | 0.91 (0.81–1.02) | 1.32 (1.07–1.62) | 0.92 (0.79–1.07) | NP | NP |
| $O_3$ | 1.27 (1.17–1.38) | 0.96 (0.88–1.06) | 1.32 (1.18–1.48)[c] | 0.96 (0.85–1.09) | 1.18 (1.01–1.37) | 1.08 (0.96–1.23) | 1.13 (1.01–1.26) | 0.99 (0.88–1.12)[e] |
| $SO_2$ | 1.13 (1.03–1.24) | 1.35 (1.23–1.47) | 1.18 (1.04–1.34) | 1.30 (1.16–1.47) | 1.12 (0.96–1.32) | 1.27 (1.12–1.44) | 1.10 (0.99–1.22) | 1.23 (1.11–1.37) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] Used the Filtered Both Sides Model. NP = Not possible to remove spatial autocorrelation in this covariate.

[c] The residuals are spatially autocorrelated ($P < 0.05$) using the Moran $I$ statistic.

[d] The residuals are spatially autocorrelated ($P < 0.10$) using the Moran $I$ statistic.

[e] No evidence of spatial autocorrelation was found in the original data for these variables, therefore the Filtered Mortality Only Model was applied.

**Table 43.** Impact of Multiple Ecologic Covariates on the Relative Risks of Mortality from Cardiopulmonary Disease Associated with an Increase in Sulfate Using Two-Stage Spatial Analytic Methods[a]

| Spatial Analytic Model | Number of Cities | Relative Risk Calculated for Sulfate Alone | Ecologic Covariates Incorporated into Adjusted Analyses | Relative Risk After Adjusting for Ecologic Covariates[b] | |
|---|---|---|---|---|---|
| | | | | Sulfate | $SO_2$ |
| **Demographic and Socioeconomic Factors** | | | | | |
| Independent Observations | 139 | 1.24 (1.15–1.34) | Population change, income, poverty, income disparity, unemployment, education | 1.15 (1.04–1.28) | NC |
| Independent Cities | 139 | 1.28 (1.13–1.45) | | 1.18 (1.02–1.37)[c] | NC |
| Regional Adjustment | 139 | 1.19 (1.01–1.40) | | 1.21 (1.01–1.44) | NC |
| Spatial Filtering[d] | 139 | 1.12 (1.00–1.26) | | 1.12 (0.99–1.27) | NC |
| **Gaseous Copollutants** | | | | | |
| Independent Observations | 58 | 1.23 (1.11–1.36) | CO, $NO_2$, $O_3$, $SO_2$ | 1.11 (0.99–1.24) | 1.43 (1.29–1.59) |
| Independent Cities | 58 | 1.31 (1.13–1.52) | | 1.11 (0.97–1.27) | 1.42 (1.25–1.61) |
| Regional Adjustment | 58 | 1.36 (1.08–1.72) | | 1.15 (0.93–1.42) | 1.30 (1.11–1.52) |
| Spatial Filtering[d] | 102 | 1.14 (1.02–1.28) | $O_3$, $SO_2$ | 1.10 (0.99–1.23) | 1.33 (1.17–1.51) |
| **25%[e]** | | | | | |
| Independent Observations | 45 | 1.21 (1.07–1.36) | Population change, unemployment, temperature variation, relative humidity variation, altitude, $SO_2$ | 1.02 (0.84–1.25) | 1.37 (1.16–1.62) |
| Independent Cities | 103 | 1.34 (1.18–1.51) | Population change, education, $SO_2$ | 1.07 (0.93–1.24) | 1.29 (1.14–1.46) |
| Regional Adjustment | 113 | 1.25 (1.07–1.47) | $SO_2$ | 1.12 (0.96–1.32) | 1.18 (1.08–1.28) |
| Spatial Filtering[d] | 72 | 1.10 (0.92–1.31) | Education, relative humidity, relative humidity variation, $SO_2$ | 1.20 (1.01–1.43) | 1.19 (1.02–1.38) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] NC = Relative risks associated with $SO_2$ were not calculated in some multivariate models.

[c] The residuals are spatially autocorrelated ($P < 0.05$) using the Moran $I$ statistic.

[d] Used the Filtered Both Sides Model.

[e] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with sulfate.

**Table 44.** Impact of Individual Ecologic Covariates on the Relative Risks of Mortality from Lung Cancer Associated with an Increase in Sulfate Using Two-Stage Spatial Analytic Methods[a]

| | Independent Observations | | Random Effects Independent Cities[b] | |
|---|---|---|---|---|
| Ecologic Covariate | Sulfate | Covariate | Sulfate | Covariate |
| **Sulfate Alone** | 1.31 (1.05–1.65) | | 1.39 (1.09–1.75) | |
| **Demographic Factors** | | | | |
| Population change | 1.27 (1.03–1.57) | 0.97 (0.82–1.15) | 1.36 (1.04–1.77) | 0.99 (0.80–1.23) |
| Whites | 1.33 (1.10–1.62) | 1.04 (0.91–1.20) | 1.39 (1.09–1.78) | 1.02 (0.85–1.22) |
| Blacks | 1.35 (1.11–1.65) | 0.93 (0.79–1.10) | 1.40 (1.10–1.80) | 0.96 (0.78–1.18) |
| **Socioeconomic Factors** | | | | |
| Income | 1.31 (1.08–1.58) | 0.98 (0.84–1.15) | 1.39 (1.09–1.76) | 1.01 (0.82–1.24) |
| Poverty | 1.32 (1.09–1.59) | 1.03 (0.89–1.20) | 1.39 (1.09–1.76) | 0.99 (0.81–1.20) |
| Income disparity | 1.30 (1.08–1.57) | 0.87 (0.72–1.05) | 1.38 (1.09–1.75) | 0.90 (0.71–1.15) |
| Unemployment | 1.27 (1.05–1.55) | 1.13 (0.93–1.38) | 1.34 (1.06–1.71) | 1.15 (0.90–1.46) |
| Education | 1.30 (1.06–1.61) | 0.98 (0.79–1.23) | 1.38 (1.06–1.80) | 1.00 (0.75–1.31) |
| **Health Services** | | | | |
| Physicians | 1.27 (1.05–1.54) | 0.90 (0.74–1.10) | 1.35 (1.06–1.71) | 0.92 (0.72–1.19) |
| Hospital beds | 1.30 (1.07–1.57) | 0.89 (0.71–1.13) | 1.37 (1.08–1.75) | 0.87 (0.66–1.15) |
| **Climate** | | | | |
| Temperature | 1.34 (1.10–1.64) | 0.98 (0.84–1.14) | 1.43 (1.12–1.84) | 0.99 (0.82–1.21) |
| Temperature variation | 1.37 (1.12–1.68) | 0.95 (0.78–1.15) | 1.46 (1.14–1.88) | 0.92 (0.72–1.18) |
| Relative humidity | 1.33 (1.00–1.78) | 1.22 (0.93–1.58) | 1.34 (0.96–1.87) | 1.21 (0.90–1.63) |
| Relative humidity variation | 1.45 (1.13–1.87) | 1.11 (0.89–1.39) | 1.47 (1.10–1.97) | 1.08 (0.84–1.40) |
| **Physical Environment** | | | | |
| Altitude | 1.11 (0.89–1.40) | 0.76 (0.58–0.99) | 1.13 (0.86–1.50) | 0.75 (0.56–1.01) |
| Water hardness | 1.26 (1.03–1.53) | 0.94 (0.79–1.13) | 1.41 (1.08–1.86) | 0.94 (0.75–1.18) |
| **Gaseous Copollutants** | | | | |
| CO | 1.26 (1.03–1.53) | 0.82 (0.67–0.99) | 1.29 (1.03–1.61) | 0.83 (0.66–1.03) |
| $NO_2$ | 1.31 (1.05–1.65) | 0.87 (0.72–1.05) | 1.36 (1.04–1.76) | 0.88 (0.71–1.10) |
| $O_3$ | 1.30 (1.07–1.59) | 0.71 (0.53–0.96) | 1.33 (1.07–1.65) | 0.72 (0.57–0.91) |
| $SO_2$ | 1.37 (1.08–1.73) | 0.94 (0.75–1.18) | 1.39 (1.08–1.81) | 0.94 (0.73–1.20) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] Neither the raw lung cancer relative risks nor the residuals of the Independent Cities Model incorporating spatially autocorrelated sulfate and covariate values were found to be spatially autocorrelated. Therefore, it was not necessary to analyze Regional Adjustment or Spatial Filtering Models.

**Table 45.** Impact of Multiple Ecologic Covariates on the Relative Risks of Mortality from Lung Cancer Associated with an Increase in Sulfate Using Two-Stage Spatial Analytic Methods[a]

| Spatial Analytic Model | Number of Cities | Relative Risk Calculated for Sulfate Alone | Ecologic Covariates Incorporated into Adjusted Analyses | Relative Risk After Adjusting for Ecologic Covariates[b] | |
|---|---|---|---|---|---|
| | | | | Sulfate | $SO_2$ |
| **Demographic and Socioeconomic Factors** | | | | | |
| Independent Observations | 139 | 1.29 (1.07–1.56) | Population change, income, poverty, income disparity, unemployment, education | 1.14 (0.89–1.45) | NC |
| Independent Cities | 139 | 1.36 (1.07–1.74) | | 1.23 (0.90–1.68) | NC |
| **Gaseous Copollutants** | | | | | |
| Independent Observations | 58 | 1.42 (1.11–1.80) | CO, $NO_2$, $O_3$, $SO_2$ | 1.61 (1.21–2.15) | 0.87 (0.65–1.17) |
| Independent Cities | 58 | 1.48 (1.12–1.96) | | 1.63 (1.19–2.23) | 0.90 (0.67–1.21) |
| **25%[c]** | | | | | |
| Independent Observations | 68 | 1.61 (1.22–2.14) | Relative humidity, altitude | 1.39 (0.98–1.99) | NC |
| Independent Cities | 68 | 1.62 (1.21–2.16) | | 1.39 (0.97–2.01) | NC |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] NC = Relative risks associated with $SO_2$ were not calculated in some multivariate models.

[c] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with sulfate.

multiple covariate models that included sulfur dioxide as a copollutant (Table 47). (In contrast, the effect of exposure to sulfur dioxide persisted even in the three multiple covariate analyses considered.)

***Cardiopulmonary Disease Mortality*** Fine particle air pollution alone was associated with cardiopulmonary mortality (Table 48) 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. In the fine particle cohort, as in the sulfate cohort, unemployment appeared to be associated with cardiopulmonary mortality, although adjustment for unemployment rate in the sulfate cohort did not have a marked impact on the relative risk. Sulfur dioxide was strongly associated with cardiopulmonary disease mortality, although the fine particle effect on cardiopulmonary disease mortality was not eliminated by adjustment for exposure to sulfur dioxide. After we applied the Regional Adjustment Model, there was no evidence of residual spatial autocorrelation in cardiopulmonary mortality as there had been for all-cause mortality. Multivariate adjustment (Table 49) reduced, but did not eliminate, the fine particle–cardiopulmonary association.

***Lung Cancer Mortality*** Because we detected no association between exposure to fine particles and lung cancer mortality using Cox regression, we conducted no further spatial analyses.

**Simultaneous Autoregressive Models**

In the preceding section, we used two approaches to adjust for broad spatial patterns in the ACS data. In the first, we used the Regional Adjustment Model to remove spatial variation in mortality rates, adjusting the city-specific values for broad regional patterns. In the second, we used spatial filtering techniques to remove spatial patterns in both the mortality data and the city-level variables before we linked them together. With this analytic approach, after broad regional patterns have been removed, attributes of both predictor and response variables are compared using random effects regression methods.

We further examined the robustness of our results to the method of controlling for spatial autocorrelation by using a third modeling approach, namely the Simultaneous Autoregressive Model described in Appendix H. In this approach the logarithms of the city-specific mortality rates are the response variables and are assumed to be normally distributed. City-level covariates are included as predictors of mortality; however, the error structure incorporates the spatial autocorrelation between mortality rates after accounting for city-level predictors of mortality.

**Table 46.** Impact of Individual Ecologic Covariates on the Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles Using Two-Stage Spatial Analytic Methods[a]

| | | | Random Effects | | | |
|---|---|---|---|---|---|---|
| | Independent Observations | | Independent Cities | | Regional Adjustment | |
| Ecologic Covariate | Fine Particles | Covariate | Fine Particles | Covariate | Fine Particles | Covariate |
| **Fine Particles Alone** | 1.18 (1.03–1.35) | | 1.29 (1.12–1.48)[b] | | 1.16 (0.99–1.37) | |
| **Demographic Factors** | | | | | | |
| Population change | 1.07 (0.98–1.17) | 0.86 (0.81–0.92) | 1.19 (1.01–1.39) | 0.88 (0.77–0.99) | 1.18 (0.97–1.42)[c] | 1.00 (0.85–1.16) |
| Whites | 1.28 (1.17–1.40) | 1.15 (1.08–1.23) | 1.33 (1.16–1.53)[c] | 1.12 (0.99–1.26) | 1.19 (1.01–1.41)[c] | 1.07 (0.96–1.20) |
| Blacks | 1.27 (1.16–1.38) | 0.88 (0.82–0.96) | 1.34 (1.16–1.56)[c] | 0.90 (0.78–1.03) | 1.19 (1.00–1.41) | 0.94 (0.81–1.10) |
| **Socioeconomic Factors** | | | | | | |
| Income | 1.18 (1.10–1.27) | 0.92 (0.86–0.98) | 1.28 (1.11–1.47)[b] | 0.96 (0.84–1.10) | 1.15 (0.99–1.33)[b] | 0.86 (0.77–0.96) |
| Poverty | 1.23 (1.14–1.32) | 0.87 (0.80–0.94) | 1.32 (1.15–1.51)[c] | 0.89 (0.78–1.02) | 1.15 (0.97–1.37)[c] | 1.03 (0.89–1.21) |
| Income disparity | 1.23 (1.14–1.32) | 0.83 (0.78–0.88) | 1.30 (1.15–1.48) | 0.84 (0.75–0.93) | 1.17 (0.99–1.38) | 0.94 (0.83–1.07) |
| Unemployment | 1.16 (1.08–1.25) | 1.07 (1.00–1.14) | 1.28 (1.11–1.48)[b] | 1.02 (0.90–1.15) | 1.16 (0.98–1.37)[c] | 1.02 (0.91–1.13) |
| Education | 1.18 (1.09–1.28) | 0.99 (0.93–1.06) | 1.32 (1.12–1.55)[b] | 1.03 (0.90–1.18) | 1.14 (0.97–1.35)[c] | 0.93 (0.81–1.07) |
| **Health Services** | | | | | | |
| Physicians | 1.19 (1.11–1.28) | 0.94 (0.87–1.02) | 1.30 (1.12–1.51)[b] | 1.00 (0.85–1.18) | 1.18 (0.98–1.41)[c] | 0.99 (0.86–1.14) |
| Hospital beds | 1.19 (1.10–1.28) | 1.02 (0.93–1.13) | 1.30 (1.13–1.50)[b] | 1.02 (0.87–1.21) | 1.18 (0.98–1.42)[c] | 1.03 (0.88–1.21) |
| **Climate** | | | | | | |
| Temperature | 1.12 (1.03–1.21) | 0.86 (0.81–0.91) | 1.22 (1.08–1.39) | 0.85 (0.77–0.94) | 1.14 (0.98–1.33) | 1.02 (0.86–1.20) |
| Temperature variation | 1.08 (0.99–1.17) | 1.16 (1.09–1.24) | 1.19 (1.03–1.36)[c] | 1.15 (1.02–1.29) | 1.11 (0.94–1.31) | 1.06 (0.94–1.20) |
| Relative humidity | 1.18 (1.08–1.30) | 1.00 (0.93–1.07) | 1.23 (1.05–1.44)[b] | 1.04 (0.91–1.19) | 1.10 (0.91–1.34) | 0.86 (0.69–1.07) |
| Relative humidity variation | 1.21 (1.10–1.33) | 0.93 (0.86–1.00) | 1.26 (1.08–1.47)[c] | 0.96 (0.83–1.10) | 1.14 (0.94–1.39) | 0.99 (0.81–1.20) |
| **Physical Environment** | | | | | | |
| Altitude | 1.14 (1.05–1.24) | 1.10 (1.03–1.17) | 1.21 (1.02–1.43) | 1.03 (0.90–1.17) | 1.09 (0.91–1.31) | 1.02 (0.89–1.16) |
| Water hardness | 1.16 (1.08–1.25) | 1.14 (1.07–1.22) | 1.28 (1.11–1.49)[b] | 1.13 (1.00–1.29) | 1.17 (0.98–1.40)[c] | 1.08 (0.94–1.23) |
| **Gaseous Copollutants** | | | | | | |
| CO | 1.18 (1.10–1.27) | 0.92 (0.87–0.98) | 1.28 (1.10–1.48)[c] | 0.95 (0.83–1.09) | 1.17 (0.98–1.39)[b] | 0.97 (0.85–1.10) |
| $NO_2$ | 1.21 (1.11–1.33) | 0.91 (0.85–0.97) | 1.33 (1.12–1.58) | 0.94 (0.81–1.09) | 1.18 (1.00–1.40) | 0.93 (0.80–1.08) |
| $O_3$ | 1.19 (1.10–1.28) | 0.89 (0.83–0.96) | 1.27 (1.11–1.46)[b] | 0.92 (0.80–1.06) | 1.11 (0.96–1.28) | 1.12 (1.00–1.26) |
| $SO_2$ | 1.03 (0.95–1.13) | 1.46 (1.31–1.62) | 1.14 (0.98–1.32) | 1.40 (1.17–1.67) | 1.11 (0.93–1.33) | 1.24 (1.04–1.48) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] The residuals are spatially autocorrelated ($P < 0.05$) using the Moran $I$ statistic.

[c] The residuals are spatially autocorrelated ($P < 0.10$) using the Moran $I$ statistic.

The correlation structure is based on the nearest-neighbor concept, which assumes that a city is more influenced by its nearest neighbor than by any other city, no matter how far away the nearest neighbor is. A city's neighbors are defined in the following manner. First, each of the 151 cities is assigned a Thiessen polygon, a geographic area within which all points within the polygon are closer to the city enclosed than to any other city. Then the neighbors of any city are determined as those in all the Thiessen polygons touching the polygon of that city. Each city may have a different number of neighbors, and the nearest neighbor will be a different distance away for each city. We derived a correlation structure in which a city's residual response correlates only with the residual responses of its neighbors. Cities that are not neighbors are not assumed to be correlated. We assumed a common correlation parameter for the entire dataset and estimated it simultaneously with the regression parameters using maximum likelihood techniques in S-PLUS. We also weighted the analysis by the inverse of the sum of the estimate of the variation in mortality rates between cities and the estimation error for a given city, thus incorporating the concept of a random effects model in the analysis.

We also considered a modified nearest-neighbor modeling approach in which we assumed mortality rates

**Table 47.** Impact of Multiple Ecologic Covariates on the Relative Risks of Mortality from All Causes Associated with an Increase in Fine Particles Using Two-Stage Spatial Analytic Methods[a]

| Spatial Analytic Model | Number of Cities | Relative Risk Calculated for Fine Particles Alone | Ecologic Covariates Incorporated into Adjusted Analyses | Relative Risk After Adjusting for Ecologic Covariates[b] | |
|---|---|---|---|---|---|
| | | | | Fine Particles | $SO_2$ |
| **Demographic and Socioeconomic Factors** | | | | | |
| Independent Observations | 48 | 1.19 (1.11–1.28) | Population change, income, poverty, income disparity, unemployment, education | 1.15 (1.03–1.27) | NC |
| Independent Cities | 48 | 1.30 (1.13–1.50) | | 1.23 (1.02–1.48) | NC |
| Regional Adjustment | 48 | 1.18 (0.98–1.41) | | 1.15 (0.96–1.39) | NC |
| **Gaseous Copollutants** | | | | | |
| Independent Observations | 28 | 1.15 (1.05–1.26) | CO, $NO_2$, $O_3$, $SO_2$ | 1.06 (0.95–1.18) | 1.48 (1.33–1.65) |
| Independent Cities | 28 | 1.31 (1.10–1.56) | | 1.11 (0.95–1.29) | 1.44 (1.23–1.69) |
| Regional Adjustment | 28 | 1.18 (0.99–1.40) | | 1.09 (0.92–1.29) | 1.19 (0.99–1.44) |
| **25%[c]** | | | | | |
| Independent Observations | 22 | 1.09 (0.99–1.21) | Population change, whites, temperature variation, altitude, $NO_2$, $SO_2$ | 1.12 (0.96–1.31) | 1.16 (0.97–1.39) |
| Independent Cities | 32 | 1.32 (1.12–1.54) | Population change, temperature variation, $SO_2$ | 1.06 (0.89–1.26) | 1.28 (1.04–1.57) |
| Regional Adjustment | 27 | 1.21 (0.98–1.50) | Relative humidity, $SO_2$ | 1.05 (0.85–1.30) | 1.25 (0.97–1.61) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] NC = Relative risks associated with $SO_2$ were not calculated in some multivariate models.

[c] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with fine particles.

among cities were correlated when the cities were nearest neighbors or were within the average distance between cities (111 km for the cities with sulfate data and 123 km for the cities with sulfur dioxide data). We report the results obtained using the nearest-neighbor approach only, because the results using the modified nearest-neighbor approach were almost identical. The data used in the latter to generate the correlation matrix incorporated more cities in the Northeast and Ohio Valley regions; however, the inclusion of these additional cities did not influence the estimate of the common correlation parameter and thus had little impact on our estimates of the effects on mortality of exposure to air pollution.

Using the nearest-neighbor approach, our estimated relative risk of all-cause mortality associated with exposure to sulfate (RR = 1.20, 95% CI: 1.06–1.36) was similar to that obtained from the Independent Cities Model (RR = 1.25, 95% CI: 1.13–1.37), which assumes geographic independence, or after applying the Regional Adjustment Model (RR = 1.19, 95% CI: 1.06–1.34). However, we obtained a somewhat lower relative risk of all-cause mortality (RR = 1.09, 95% CI: 1.01–1.19) when we subjected both mortality rates and sulfate levels to spatial filtering techniques. The relative risk of mortality from exposure to sulfur dioxide under the Simultaneous Autoregressive Model was 1.35 (95% CI: 1.16–1.57), a value similar to those obtained by the other methods of analysis considered (Independent Cities Model: RR = 1.33, 95% CI: 1.22–1.45; Regional Adjustment Model: RR = 1.26, 95% CI: 1.15–1.39; Filtered Both Sides Model: RR = 1.27, 95% CI: 1.15–1.40). Note that the range in excess risk [(1 – RR) × 100] was similar for sulfate (24% – 12% = 12%) and sulfur dioxide (35% – 25% = 10%), which suggests that each pollutant was equally sensitive, in absolute terms, to the statistical approach used.

When we modeled sulfate jointly with sulfur dioxide using the Simultaneous Autoregressive Model, the relative risk of mortality from exposure to sulfate was 1.08 (95%

**Table 48.** Impact of Individual Ecologic Covariates on the Relative Risks of Mortality from Cardiopulmonary Disease Associated with an Increase in Fine Particles Using Two-Stage Spatial Analytic Methods[a]

| | | | Random Effects | | | |
|---|---|---|---|---|---|---|
| | Independent Observations | | Independent Cities | | Regional Adjustment | |
| Ecologic Covariate | Fine Particles | Covariate | Fine Particles | Covariate | Fine Particles | Covariate |
| **Fine Particles Alone** | 1.30 (1.11–1.53) | | 1.38 (1.17–1.62)[c] | | 1.24 (1.01–1.52) | |
| **Demographic Factors** | | | | | | |
| Population change | 1.12 (0.99–1.26) | 0.81 (0.74–0.88) | 1.19 (1.00–1.43) | 0.81 (0.71–0.93) | 1.20 (0.95–1.51) | 0.95 (0.79–1.15) |
| Whites | 1.44 (1.28–1.61) | 1.18 (1.08–1.29) | 1.45 (1.23–1.70)[c] | 1.15 (1.00–1.32) | 1.29 (1.05–1.59) | 1.10 (0.97–1.26) |
| Blacks | 1.41 (1.24–1.59) | 0.87 (0.78–0.98) | 1.45 (1.22–1.72)[c] | 0.88 (0.75–1.05) | 1.28 (1.03–1.59) | 0.92 (0.76–1.12) |
| **Socioeconomic Factors** | | | | | | |
| Income | 1.30 (1.17–1.44) | 0.89 (0.81–0.97) | 1.35 (1.15–1.59)[b] | 0.91 (0.78–1.07) | 1.21 (1.01–1.45) | 0.81 (0.71–0.91) |
| Poverty | 1.35 (1.21–1.50) | 0.87 (0.78–0.98) | 1.41 (1.19–1.66)[c] | 0.91 (0.77–1.07) | 1.21 (0.99–1.49) | 1.12 (0.92–1.35) |
| Income disparity | 1.36 (1.22–1.51) | 0.82 (0.76–0.89) | 1.40 (1.21–1.63) | 0.82 (0.73–0.93) | 1.25 (1.02–1.53) | 0.93 (0.79–1.09) |
| Unemployment | 1.25 (1.12–1.39) | 1.15 (1.04–1.26) | 1.33 (1.13–1.57)[b] | 1.10 (0.96–1.27) | 1.23 (1.01–1.50) | 1.11 (0.98–1.27) |
| Education | 1.27 (1.14–1.43) | 0.96 (0.87–1.05) | 1.37 (1.13–1.65)[b] | 0.99 (0.85–1.15) | 1.20 (0.99–1.46) | 0.85 (0.71–1.00) |
| **Health Services** | | | | | | |
| Physicians | 1.30 (1.17–1.45) | 0.86 (0.77–0.97) | 1.36 (1.15–1.61)[b] | 0.91 (0.76–1.10) | 1.22 (0.98–1.52) | 0.88 (0.74–1.05) |
| Hospital beds | 1.29 (1.16–1.43) | 1.13 (0.98–1.29) | 1.37 (1.16–1.62)[b] | 1.14 (0.94–1.38) | 1.23 (0.98–1.53) | 1.13 (0.93–1.37) |
| **Climate** | | | | | | |
| Temperature | 1.19 (1.07–1.33) | 0.83 (0.77–0.90) | 1.27 (1.09–1.47) | 0.83 (0.74–0.93) | 1.22 (1.00–1.50) | 0.99 (0.80–1.24) |
| Temperature variation | 1.14 (1.01–1.28) | 1.22 (1.11–1.33) | 1.21 (1.04–1.42)[b] | 1.21 (1.06–1.38) | 1.17 (0.94–1.45) | 1.09 (0.92–1.28) |
| Relative humidity | 1.20 (1.04–1.37) | 1.07 (0.97–1.19) | 1.26 (1.03–1.54)[c] | 1.12 (0.95–1.33) | 1.17 (0.90–1.53) | 0.89 (0.66–1.21) |
| Relative humidity variation | 1.27 (1.11–1.46) | 0.90 (0.81–1.01) | 1.33 (1.09–1.63)[c] | 0.92 (0.77–1.11) | 1.19 (0.92–1.53) | 0.85 (0.66–1.10) |
| **Physical Environment** | | | | | | |
| Altitude | 1.26 (1.12–1.42) | 1.08 (0.99–1.19) | 1.30 (1.06–1.59) | 1.00 (0.85–1.17) | 1.18 (0.92–1.52) | 1.03 (0.86–1.24) |
| Water hardness | 1.27 (1.14–1.41) | 1.20 (1.09–1.31) | 1.34 (1.13–1.58) | 1.19 (1.03–1.37) | 1.22 (0.99–1.51) | 1.17 (1.00–1.37) |
| **Gaseous Copollutants** | | | | | | |
| CO | 1.32 (1.19–1.47) | 0.90 (0.83–0.98) | 1.38 (1.17–1.64) | 0.90 (0.78–1.05) | 1.26 (1.02–1.56) | 0.90 (0.77–1.06) |
| $NO_2$ | 1.39 (1.22–1.59) | 0.91 (0.83–1.00) | 1.51 (1.24–1.83) | 0.91 (0.78–1.07) | 1.34 (1.05–1.70) | 0.87 (0.71–1.08) |
| $O_3$ | 1.31 (1.18–1.46) | 0.94 (0.84–1.05) | 1.38 (1.17–1.63)[b] | 0.98 (0.83–1.17) | 1.18 (0.97–1.43) | 1.20 (1.02–1.41) |
| $SO_2$ | 1.17 (1.03–1.33) | 1.47 (1.28–1.70) | 1.25 (1.05–1.49) | 1.40 (1.14–1.72) | 1.23 (0.97–1.55) | 1.26 (1.00–1.58) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute. Data are RRs with 95% CIs.

[b] The residuals are spatially autocorrelated ($P < 0.05$) using the Moran $I$ statistic.

[c] The residuals are spatially autocorrelated ($P < 0.10$) using the Moran $I$ statistic.

CI: 0.91–1.28), whereas that for exposure to sulfur dioxide was 1.31 (95% CI: 1.12–1.28). Joint modeling produced a larger reduction in the sulfate-associated relative risk of mortality (1.20 to 1.08) than in the sulfur dioxide relative risk (1.35 to 1.31). The sulfate relative risk varied slightly less (8%) in terms of absolute amount [(1 – RR) × 100] (Independent Cities Model: RR = 1.13, 95% CI: 1.02–1.25; Regional Adjustment Model: RR = 1.10, 95% CI: 0.97–1.24; Filtered Both Sides Model: RR = 1.05, 95% CI: 0.97–1.14; Simultaneous Autoregressive Model: RR = 1.08, 95% CI: 0.91–1.28) than did the relative risk associated with sulfur dioxide (12%) (Independent Cities Model: RR = 1.27, 95% CI: 1.15–1.40; Regional Adjustment Model: RR = 1.23, 95% CI: 1.11–1.36; Filtered Both Sides Model: RR = 1.19, 95% CI: 1.10–1.29; Simultaneous Autoregressive Model: RR = 1.31, 95% CI: 1.12–1.54) when both pollutants were examined together.

### Random Effects Cox Models

The original regression analyses of both the Six Cities Study and the ACS Study using the standard Cox model had been predicated on the assumption that the vital status of all study participants represented statistically independent

**Table 49.** Impact of Multiple Ecologic Covariates on the Relative Risks of Mortality from Cardiopulmonary Disease Associated with an Increase in Fine Particles Using Two-Stage Spatial Analytic Methods[a]

| Spatial Analytic Model | Number of Cities | Relative Risk Calculated for Fine Particles Alone | Ecologic Covariates Incorporated into Adjusted Analyses | Relative Risk After Adjusting for Ecologic Covariates[b] | |
|---|---|---|---|---|---|
| | | | | Fine Particles | $SO_2$ |
| **Demographic and Socioeconomic Factors** | | | | | |
| Independent Observations | 48 | 1.30 (1.17–1.45) | Population change, income, poverty, income disparity, unemployment, education | 1.16 (1.00–1.35) | NC |
| Independent Cities | 48 | 1.38 (1.16–1.63) | | 1.19 (0.98–1.45) | NC |
| Regional Adjustment | 48 | 1.22 (0.97–1.52) | | 1.13 (0.91–1.40) | NC |
| **Gaseous Copollutants** | | | | | |
| Independent Observations | 28 | 1.32 (1.16–1.50) | CO, $NO_2$, $O_3$, $SO_2$ | 1.22 (1.05–1.42) | 1.45 (1.16–1.80) |
| Independent Cities | 28 | 1.48 (1.22–1.80) | | 1.28 (1.05–1.57) | 1.40 (1.13–1.73) |
| Regional Adjustment | 28 | 1.40 (1.08–1.80) | | 1.26 (0.96–1.66) | 1.21 (0.89–1.65) |
| **25%[c]** | | | | | |
| Independent Observations | 32 | 1.27 (1.12–1.43) | Population change, whites, temperature variation, $SO_2$ | 1.18 (1.00–1.40) | 1.23 (1.02–1.48) |
| Independent Cities | 32 | 1.41 (1.17–1.69) | Population change, temperature variation, $SO_2$ | 1.10 (0.91–1.34) | 1.27 (1.00–1.61) |
| Regional Adjustment | 38 | 1.34 (1.07–1.70) | $SO_2$ | 1.23 (0.97–1.55) | 1.26 (1.00–1.58) |

[a] Effects were evaluated for the respective range of each covariate specified in Appendix G, which is available upon request from the Health Effects Institute.

[b] NC = Relative risks associated with $SO_2$ were not calculated in some multivariate models. Data are RRs with 95% CIs.

[c] Incorporated all ecologic covariates that, when analyzed individually in a bivariate model, were found to produce a change of 25% or more in the excess relative risk associated with fine particles.

outcomes. Because the life and death of each individual depends in a complex way on a number of health determinants, including characteristics of the city within which the subject resides, it was important to account in the analysis for individual heterogeneity as well as potential intracity correlation.

As we noted previously, the Reanalysis Team used two-stage models to address spatial clustering by city and region. We also employed two-stage spatial filtering methods to take into account more complex spatial patterns in the data. In addition to the two-stage random effects methods used to address spatial autocorrelation at different levels, we developed powerful new methods of incorporating random effects into the Cox regression model (Appendix I). Specifically, we considered a Cox proportional-hazards model with a random effect that represents the unique characteristics of each city. This approach avoids the approximations inherent in the two-stage random effects models by estimating the regression parameters and random effects within a single integrated estimation framework.

The random effects Cox model assumes that, given the city-specific random effects, the hazard functions for individuals are conditionally independent, with the hazard function for individual $j$ from city $i$ given by

$$h_{ij(s)}(t) = h_s(t)u_i \exp(\beta^T \mathbf{x}_{ij(s)})$$

at time $t$, where the subscript $s$ denotes different strata within the age-stratified and gender-stratified cohort. The city-specific random effects $u_i$ are assumed to follow flexible Tweedie distributions with unit mean and variance $\tau^2$. The regression vector $\beta$ reflects the effects of the covariate vector $\mathbf{x}_{ij(s)}$ on the baseline hazard $h_s(t)$ in each stratum $s$. Further details of the statistical methods used to fit the random effects Cox model are given in Appendix I.

Although the opportunity to characterize intercity variation is limited by the number of cities in the Six Cities Study, this is not the case in the ACS Study, which involved 151 cities in the sulfate cohort and 50 cities in the fine particle cohort. Table 50 shows the relative risks of mortality from all causes for exposure to both fine particles and sulfate based on our random effects Cox model fit to

**Table 50.** Relative Risks of Mortality from All Causes Associated with Sulfate and Sulfur Dioxide in the Reanalysis of the ACS Study Comparing Single and Multiple Pollutants in a Standard Cox Model, a Two-Stage Model, and a Random Effects Cox Model

| Pollutant | Number of Cities | Standard Cox Model[a] | Two-Stage Independent Cities Model[b] | | Random Effects Cox Model[b] | |
|---|---|---|---|---|---|---|
| | | RR (95% CI) | RR (95% CI) | $\tau^2$ | RR (95% CI) | $\tau^2$ |
| **ACS Fine Particle Cohort** | | | | | | |
| Single-pollutant model | | | | | | |
| $PM_{2.5}$ | 52 | 1.18 (1.10–1.27) | 1.31 (1.14–1.51) | 0.0067 | 1.31 (1.14–1.49) | 0.0056 |
| $SO_2$ | 38 | 1.53 (1.40–1.68) | 1.55 (1.32–1.81) | 0.0036 | 1.50 (1.29–1.74) | 0.0034 |
| Multiple-pollutant model | | | | | | |
| $PM_{2.5}$ | 38 | 1.02 (0.94–1.12) | 1.14 (0.98–1.33) | 0.0041 | 1.13 (0.97–1.31) | 0.0034 |
| $SO_2$ | 38 | 1.52 (1.37–1.68) | 1.44 (1.20–1.72) | | 1.40 (1.18–1.66) | |
| **ACS Sulfate Cohort** | | | | | | |
| Single-pollutant model | | | | | | |
| $SO_4^{2-}$ | 38 | 1.16 (1.10–1.23) | 1.25 (1.13–1.37) | 0.0050 | 1.22 (1.12–1.34) | 0.0040 |
| $SO_2$ | 151 | 1.33 (1.25–1.41) | 1.33 (1.22–1.46) | 0.0028 | 1.31 (1.21–1.43) | 0.0023 |
| Multiple-pollutant model | | | | | | |
| $SO_4^{2-}$ | 113 | 1.05 (0.98–1.12) | 1.13 (1.02–1.25) | 0.0029 | 1.12 (1.02–1.23) | 0.0023 |
| $SO_2$ | 113 | 1.30 (1.22–1.39) | 1.27 (1.15–1.39) | | 1.25 (1.14–1.37) | |

[a] This model had the same covariate specifications used by the Original Investigators.

[b] $\tau^2$ is the dispersion parameter.

the ACS data, along with the relative risks based on both the standard Cox model used by the Original Investigators and our two-stage Independent Cities Model. In the fine particle cohort, the relative risk of all-cause mortality associated with fine particle air pollution based on the random effects Cox model (RR = 1.31, 95% CI: 1.14–1.49) is virtually identical to that based on the two-stage approach (RR = 1.31, 95% CI: 1.14–1.51), which confirms the validity of the approximate but computationally simpler two-stage random effects approach. However, these relative risks are notably greater than that based on the standard Cox model (RR = 1.18, 95% CI: 1.10–1.27), which does not acknowledge intracity correlation. The overdispersion parameter $\tau^2 = 0.0067$ based on the two-stage method also is comparable to the value of $\tau^2 = 0.0056$ achieved by the full random effects Cox model.

When we calculated the relative risk of mortality associated with exposure to fine particles using the standard Cox model, it was notably lower than that based on the random effects Cox model. This occurred because, as in two-stage regression, the random effects Cox model took into account heterogeneity among cities as measured by the overdispersion parameter $\tau^2$. The inclusion of this between-city variation in the weighting scheme gave less weight to larger cities, which in this case resulted in an increased relative risk.

We conducted a similar analysis on the fine particle cohort using sulfur dioxide in place of fine particles. As was the case with fine particles, the relative risk of all-cause mortality associated with exposure to sulfur dioxide obtained with the random effects Cox model (RR = 1.50, 95% CI: 1.29–1.74) was similar to that obtained with the two-stage Independent Cities Model (RR = 1.55, 95% CI: 1.32–1.81). In this case, however, we obtained a similar relative risk from the standard Cox model (RR = 1.53, 95% CI: 1.40–1.68) as well. This occurred because the heterogeneity among cities was lower for sulfur dioxide ($\tau^2 = 0.0036$ under the two-stage model) than for sulfate ($\tau^2 = 0.0067$). Because sulfur dioxide exhibited less overdispersion, the city-specific weights used in the two-stage Independent Cities Model were similar to those in the two-stage Independent Observations Model, which, as shown previously, produced relative risks similar to those from the standard Cox model.

When we included both fine particles and sulfur dioxide as predictors of mortality in the same random effects Cox model, we reduced the relative risk of mortality associated with fine particles from 1.31 to 1.13. Note,

however, that the relative risk of mortality from all causes associated with exposure to fine particles remained elevated even after adjustment for the effects of sulfur dioxide.

Because the overdispersion parameter $\tau^2 = 0.0034$ in the single-pollutant sulfur dioxide model was identical to that in the model that included both sulfur dioxide and fine particles, fine particles did not appear to predict variation in all-cause mortality among cities beyond estimates provided by sulfur dioxide alone.

The sulfate cohort exhibited patterns similar to those just described for the fine particle cohort. Specifically, the two-stage random effects Independent Cities and random effects Cox models led to similar results, with exposure to sulfur dioxide in air pollution explaining more of the variation in mortality than did exposure to sulfate. However, the effects of sulfate remained significant even after we adjusted for sulfur dioxide under the two-stage Independent Cities Model and the random effects Cox model.

### Effects of Sulfate and Sulfur Dioxide by Region

Our spatially filtered analysis compares high (low) mortality rates for a spatially local area (600 km in radius) to high (low) air pollution levels in the corresponding area. Thus, we remove broad spatial patterns before we link the variables together. This type of analysis is conducted to remove the possibility that coincidental broad spatial patterns in both variables will influence the associations between mortality and air pollution. This type of adjustment is of interest because there may be important risk factors for mortality that we have not accounted for in our analysis.

Spatial filtering can adjust for risk factors, such as dietary habits, that aggregate at a broad spatial level. When we compared relative risks obtained from the Independent Cities Model and the Spatial Filtering Model, we could estimate how much of the air pollution effect on mortality was attributable to broader spatial patterns and where the effect existed on a more local level. Reduction in the relative risk associated with sulfate exposure from 1.25 (Independent Cities Model) to 1.19 (Regional Adjustment Model) to 1.09 (Spatial Filtering Model) suggests that most of the association between sulfate and mortality resulted from the spatial coincidence of these variables on a relatively large scale.

The seven regions selected for our Regional Adjustment Model were similar in size to the area needed to remove spatial autocorrelation in the spatial filtering analysis. The main difference between these two types of analyses is that the latter removes the broad spatial patterns in sulfate before sulfate values are linked with the spatially filtered mortality rates. There may be some concordance in space between mortality rates and sulfate exposure that is not accounted for by the Regional Adjustment Model. We examined this possibility by conducting separate analyses by region.

Four of the regions originally examined had too few cities with either sulfate or sulfur dioxide data (the Northwest had only 16 cities with sulfate data and 10 cities with

**Table 51.** Relative Risks of Mortality from All Causes Associated with Sulfate and Sulfur Dioxide in the Reanalysis of the ACS Study by Region Using a Two-Stage Model[a]

| | Sulfate | | | | Sulfur Dioxide | | | |
|---|---|---|---|---|---|---|---|---|
| Region | Number of Cities | Mean ($\mu g/m^3$) | Range ($\mu g/m^3$) | RR (95% CI)[b] | Number of Cities | Mean ($\mu g/m^3$) | Range ($\mu g/m^3$) | RR (95% CI)[b] |
| **Single-Pollutant Model** | | | | | | | | |
| Northeast | 41 | 11.5 | 12.8 | 1.14 (0.93–1.40) | 36 | 11.8 | 15.6 | 1.20 (1.00–1.45) |
| Industrial Midwest | 34 | 13.3 | 14.6 | 1.29 (1.07–1.55) | 30 | 11.1 | 25.7 | 1.24 (1.11–1.38) |
| Southeast | 30 | 11.6 | 11.9 | 1.25 (1.01–1.54) | 19 | 6.6 | 13.4 | 1.29 (0.98–1.70) |
| West[c] | 46 | 7.1 | 11.0 | 0.91 (0.71–1.17) | 28 | 5.9 | 16.5 | 1.30 (1.00–1.67) |
| **Two-Pollutant Model** | | | | | | | | |
| Northeast | 36 | | | 1.03 (0.85–1.24) | 36 | | | 1.19 (0.98–1.45) |
| Industrial Midwest | 30 | | | 1.09 (0.88–1.35) | 30 | | | 1.19 (1.04–1.38) |
| Southeast | 19 | | | 1.30 (0.99–1.70) | 19 | | | 1.10 (0.82–1.48) |
| West[c] | 28 | | | 0.91 (0.72–1.16) | 28 | | | 1.31 (1.01–1.69) |

[a] The Random Effects Cox Model assumes cities are statistically independent.

[b] Relative risks were calculated at the range for each pollutant across the entire study dataset.

[c] Data from the Northwest, Southern California, Southwest, and Upper Midwest were combined to form the West region.

sulfur dioxide data; Southern California, 6 and 5; Southwest, 10 and 6; and Upper Midwest, 14 and 7, respectively). Data for these four regions were combined to form a West region. The Independent Cities Model, which assumed that the cities within each region were statistically independent, was run for sulfate alone, sulfur dioxide alone, and both pollutants together for each of the four regions (Northeast, Industrial Midwest, Southeast, and West).

Both sulfate and sulfur dioxide levels were high in the Northeast and Industrial Midwest, with lower concentrations in the West (Table 51). Sulfate was correlated weakly with sulfur dioxide in the Northeast ($r = 0.18$) and West ($r = 0.17$), correlated moderately in the Southeast ($r = 0.44$), and correlated highly in the Industrial Midwest ($r = 0.69$).

Three of the four regions exhibited positive associations between exposure to sulfate and deaths from all causes. We observed an inverse association in the West where mean sulfate levels are lowest. We observed positive associations between mortality and exposure to sulfur dioxide in all four regions, with the largest relative risk of mortality from all causes found in the West. The relative risk of mortality associated with sulfur dioxide was larger than that associated with sulfate in three regions, with only the Southeast region displaying a greater sulfate effect based on the two-pollutant model specifications. The two-pollutant model, with its strong negative association with sulfate in the West and corresponding strong positive association with sulfur dioxide, suggests why sulfur dioxide accounts for much of the sulfate effect on mortality when all cities are examined together. The sulfur dioxide effect was insensitive to adjustment for sulfate in all four regions; the sulfate effect, however, changed considerably in all but one of the four regions (the Southeast) after adjustment for sulfur dioxide.

## DISCUSSION

The association between fine particle pollution in ambient air and cardiorespiratory morbidity and mortality has been explored in a number of epidemiologic investigations; both time-series and cohort studies have shown positive associations between ambient fine particles and mortality. The Six Cities Study and the ACS Study provided important information on this association and were the basis for the promulgation of the first US National Ambient Air Quality Standard (NAAQS) for fine particles. Positive associations between ambient fine particles and mortality had been demonstrated in the original analyses of these two large-scale cohort studies. For instance, in the Six Cities Study, the adjusted mortality rate ratio for the most-polluted city compared to the least-polluted city was 1.26 (95% CI: 1.08–1.47). In the ACS Study, the all-cause mortality risk ratio for the most-polluted city compared with the least-polluted city was 1.17 (95% CI: 1.09–1.26).

### DESIGN OF THE ORIGINAL STUDIES

Although these two studies produced comparable results, they differed markedly in design. The Six Cities Study was a prospective cohort study, with subjects recruited between 1974 and 1977 from six cities (Watertown MA, Harriman TN, and Steubenville OH, St Louis MO, Portage WI, and Topeka KA) and followed for up to 16 years. The cities, located in the Midwest and Northeast United States, had been chosen to represent a gradient in ambient air pollution. The original cohort comprised 8,111 white adults, 25 to 74 years of age. All subjects had completed a standardized questionnaire that elicited information concerning age, gender, weight, height, education level, complete smoking history, occupational exposures, and medical history.

The Six Cities Study had a number of strengths, including random selection of study subjects; reasonably high participation rates; personal interviews with all respondents at the time of enrollment; subsequent follow-up at intervals of 3, 6, and 12 years; and pulmonary lung function testing using appropriate spirometric techniques. Exposure monitoring was conducted largely by ambient air pollution monitors developed and operated by the Original Investigators at Harvard University, although data from the US EPA's AIRS database also were used. The baseline questionnaire administered at the time of enrollment was extensive and included items on age, gender, weight, height, education level, complete smoking history, occupational exposures, and health status. Residence histories before and after enrollment were recorded, which permitted direct assessment of residential mobility of the study subjects.

The ACS Study drew on a larger cohort from the CPS-II, which involved approximately 1.2 million individuals. The cohort assembled by the Original Investigators included 552,138 persons in 154 United States cities located in all 50 states. Participants were at least 30 years old and were members of households with at least one individual 45 years old or older. Because the CPS-II had not been designed expressly to address the relation between ambient fine particle concentrations and mortality, the Original Investigators did not develop questionnaire items specific to this purpose. Nonetheless, the ACS

questionnaire included a rich set of items providing information on health status, demographic characteristics, smoking history, alcohol use, and occupational exposures to pollutants.

The ACS Study cohort was recruited in 1982, with mortality follow-up through 1989. Vital status was ascertained by personal inquiries by volunteers in September 1984, 1986, and 1988. Automated linkage using the National Death Index (NDI) maintained by the National Center for Health Statistics was used to extend the follow-up to December 31, 1989. Ambient levels of fine particles and sulfate were obtained from two sources. Mean concentrations of sulfate air pollution for 1980 were obtained from the EPA's NAD and the EPA's IPMN. Median fine particle concentrations for 1979 through 1983 were calculated from the EPA's IPMN using dichotomous samplers. Whereas sulfate air pollution data were available for 151 United States cities, fine particle data were taken from previously published data for only 50 United States cities.

The Six Cities Study and the ACS Study possess complementary strengths and limitations. Although the Six Cities Study had been designed specifically to test the hypothesis that long-term exposure to fine particle air pollution is associated with increased mortality rates, the study involved only six cities within a limited geographic region of the United States. Because only one pollution monitor was positioned in each city, all individuals within the city were assigned the same level of exposure for each of the pollutants considered. Thus, although a large number of individual covariates had been recorded for each of the 8,111 subjects in the Six Cities Study, the limited nature of the pollution monitoring reduced the effective number of data points in the exposure-response gradient to six and uncertainty in estimating the citywide averages effectively reduced the number of data points even further. Further adjustment for the effects of other ecologic covariates in the Six Cities Study was not practical because of the limited number of degrees of freedom (at most 6 *df*) for further analyses. The ACS Study, which involved 154 cities with a wide range of pollutant concentration profiles, was not seriously affected by this limitation.

The different nature of the two studies provided the Reanalysis Team with opportunities to explore the sensitivity of the original findings to alternative analytic approaches and to incorporate additional data not explicitly considered in the original publications.

## LIMITATIONS OF THE ORIGINAL STUDIES

The Six Cities Study and the ACS Study had certain limitations, including the inability to strictly characterize the long-term exposure of study participants to fine particles (Vedal 1997). In both studies, exposure to ambient air pollutants necessarily had been gauged using fixed-site ambient monitors, as personal dosimetry for such large cohorts would have been both impractical and prohibitively expensive. Abbey and colleagues (1999) also relied on fixed-site ambient monitors maintained by the California Air Resources Board in the Seventh-Day Adventist Study. The use of such area monitors leads to some degree of exposure measurement error (Clayton et al 1993; Kotchmar et al 1987; Leaderer et al 1999), the consequences of which have been discussed below. Nonetheless, fixed-site monitors are widely used in large-scale studies of air pollution and population health, including informative time-series studies of the association between ambient fine particles and morbidity and mortality in the general population (Burnett et al 1995, 1998; Samet et al 2000).

Other potential limitations of the Six Cities Study and the ACS Study cited by other investigators include inadequate control of age and sedentary lifestyle (Moolgavkar and Luebeck 1996), and insufficient control of cigarette smoking, both active and passive (US EPA 1996). Our analytic plan (Krewski et al 1998) called for our reanalysis to exert the maximal control possible for potential confounding due to these and other covariates on which information was available. For the ACS Study, we also assembled and used a series of additional ecologic covariates that represented potential determinants of population health in a further attempt to control for confounding.

Gamble (1998) prepared a detailed critique of the Six Cities Study and the ACS Study. He focused particularly on the ecologic nature of the exposure measurements resulting from the use of fixed-site ambient monitors, as noted previously. Gamble suggested that lung function (as measured by $FEV_1$) and sedentary lifestyle also could be important confounding variables, and that there could be residual confounding from a failure to consider nonlinear effects of alcohol consumption and body weight. To address these latter concerns, the Reanalysis Team accounted for possible nonlinear effects of these covariates and included spirometric pulmonary function measurements in the reanalysis.

Information on population mobility was lacking in both studies. To evaluate population mobility in the Six Cities Study, we coded the residence histories that had been recorded, but not examined in detail, by the Original Investigators. Because residential addresses were available only at the time of recruitment into the cohort in 1980 in the ACS Study (and at the time of death for those subjects who died during the period of follow-up), we could not evaluate mobility in the ACS Study cohort.

## REPLICATION AND VALIDATION

The results of the Reanalysis Team's replication and validation of the original findings are presented in Part I of the Investigators' Report. We validated those findings by comprehensively auditing all variables that had been used in the original published analyses, comparing the original information (eg, from questionnaires and air pollution monitors) with the data in the analysis files. Our replication involved duplicating the selection process that had defined the subcohorts in the original analysis and replicating the original numerical results using the same analytic methods reported by the Original Investigators. Although we identified some discrepancies in questionnaire-based items and vital status, we found the data from both studies to be of generally high quality. We could not trace all the original air pollution data from the Six Cities Study; nonetheless, there was sufficient evidence to confirm the integrity of the long-term average fine particle levels for each of the six cities in the study. Although we noted some discrepancies in the selection and follow-up of the subcohorts used in both the Six Cities Study and the ACS Study, these discrepancies did not dramatically affect the risk estimates in either study. The Reanalysis Team, using the same data and analytic techniques that had been used by the Original Investigators, concluded that the original findings in both studies were substantiated.

## DATA QUALITY AUDIT

Part I of the reanalysis included a detailed audit of all variables that had been used by the Original Investigators. In keeping with our intent to audit all variables involved in the reanalysis, we subjected individual-level variables used for the first time in Part II to the same rigorous audit standards. As in Part I, we found few errors in most variables, although we did find a number of errors in the occupational coding that had been assigned in the ACS Study. Consequently, our ability to control for occupational confounding in the ACS Study was limited by the quality of the occupational data.

## SENSITIVITY ANALYSES

The Reanalysis Team conducted a number of different sensitivity analyses to further explore the associations between mortality and fine particles or sulfate. First, we explored the sensitivity of the Original Investigators' risk estimates to the inclusion of additional variables in the Cox proportional-hazards model, and to different ways of characterizing variables such as education, which we considered explicitly in the Original Models. These analyses had two related but distinct objectives: to identify potential confounding variables of the association between mortality and fine particles, and to identify variables that modify the effect of fine particle air pollution.

Using two new aggregate indices, we also investigated in detail the possibility of confounding due to occupational exposures. The first index provided a seven-level ordinal measure of the overall dirtiness of specific jobs and occupations of the study subject; the second provided a binary indicator of ever/never having been exposed in the workplace to agents accepted as being associated with increased lung cancer risk. Members of the Reanalysis Team who have extensive experience in occupational exposure assessment developed these aggregate occupational exposure indices on the basis of occupational and industrial codes that had been assigned by the Original Investigators.

In the Six Cities Study, the availability of additional data on study subjects at 3, 6, and 12 years after the collection of baseline data upon enrollment permitted us to assess changes in key covariates, such as tobacco consumption and BMI, over time. Likewise, we were able to assess the impact of population mobility on estimates of risk because detailed residence histories had been included in this study. The ACS Study, which involved 154 MSAs from across the United States, allowed us to assess changes in risk associated with a number of auxiliary sociodemographic and environmental variables derived from publicly available data sources. We used random effects methods and flexible nonparametric risk models to assess variation in mortality rates among cities.

We outlined these sensitivity analyses in the Analytic Plan prepared before we began the reanalysis (Krewski et al 1998). In addition to the planned analyses, we applied modeling techniques that controlled for spatial autocorrelation in measures of fine particle air pollution and other ecologic covariates.

Two of our planned analyses were not attempted. Specifically, we didn't make comparisons by race because of the small number of minority subjects in both cohorts, and we didn't perform the proposed exploration of critical exposure-time windows (ie, the period of exposure most strongly associated with mortality) in the Six Cities Study for several practical reasons. First, the residential mobility information needed to accurately characterize exposure for the period before enrollment is incomplete. (The Reanalysis Team did, however, construct postenrollment residence histories on the basis of information from the follow-up questionnaires and postcards.) Second, postenrollment mobility was limited; only 18.5% of the study subjects left the original city of residence during the follow-up period. And third, historical records of fine particle levels are not

available for these cities before 1980, which precluded evaluating fine particle exposures in the early years of the Six Cities Study. Despite these limitations, the Six Cities Study does present an opportunity to evaluate the effects of changes in exposure over time, including possibly important exposure-time windows. This analysis would be most informative if exposures in all residences outside the six cities were assessed by spatial interpolation methods, a complicated task that is outside the scope of the reanalysis.

The results of the sensitivity analyses conducted in Part II of the reanalysis are summarized below.

### Alternative Risk Models

We considered an extensive series of alternative risk models. The Reanalysis Team found little evidence that questionnaire variables had led to confounding in either study, thereby strengthening the conclusion that the observed association between fine particle air pollution and mortality was not the result of a critical covariate that had been neglected by the Original Investigators. Although this analysis is reassuring, it does not rule out the possibility of confounding by unmeasured covariates. The Reanalysis Team also found that the risk estimates in both studies were not sensitive to the manner in which individual covariates were characterized.

The Reanalysis Team tested the goodness of fit of the Cox proportional-hazards model in the Six Cities Study. Although the model did not demonstrate a significant lack of fit overall, there was some evidence that the effects of both fine particles and sulfate on mortality varied with time.

### Controlling for the Effects of Age

Because the original study outcomes were strongly dependent on age, and because of the possibility of differing age structures across the cities represented in the two studies, we attempted to account more precisely for the effects of age. One method is to use age as the time axis, rather than calendar year, in the proportional-hazards model (Breslow and Day 1987). For most causes of death, these two methods of controlling for the effects of age produced comparable results.

### Controlling for Other Covariates

In the original analyses, the data had been stratified by age (5-year categories) and gender. The ACS Study also had been stratified by race (white, black, and other). The following covariates had been included in the original analyses for the Six Cities Study: an indicator variable for current- or former-smokers, number of pack-years for current-smokers, number of pack-years for former-smokers, an indicator variable for less than high school education, and BMI (weight in kilograms divided by the square of height in meters; also referred to as the Quetelet Index). For the ACS Study, the statistical adjustments had included an indicator variable for current-smokers; an indicator variable for pipe- and/or cigar-smoker only; number of years smoked for current-smokers; number of cigarettes per day for current-smokers; number of years smoked for former-smokers; number of cigarettes per day for former-smokers; number of hours per day exposed to environmental tobacco smoke; BMI; number of drinks per day of alcoholic beverages; an indicator variable for less than high school education; and an indicator variable for regular occupational exposure to any asbestos, chemicals/acids/solvents, coal or stone dust, coal tar/pitch/asphalt, diesel engine exhaust, or formaldehyde.

We extended these statistical models by incorporating a wide range of individual covariates that included finer levels of adjustment, adding quadratic terms for some variables and considering gender differences (statistical interactions) in the effects of these variables. We examined as separate subgroups those individuals who, at the beginning of the study period, reported selected diseases (high blood pressure, heart disease, stroke, diabetes, chronic bronchitis and emphysema, asthma, or any cancer). In addition, we examined the potentially confounding effect of physical exercise on the relation between air pollution and mortality by including the self-reported amount of physical exercise (none or some, moderate, or heavy) at time of enrollment in the model. Because we postulated that illness causes stricken individuals to exercise less than healthy persons, we examined the group that had not reported having the selected diseases in order to minimize the potential that level of exercise was a variable in the causal pathway. Again, the results were essentially identical to those from the other models. We concluded that finer levels of control for these measured covariates did not alter the original findings of an association between air pollution and mortality.

### Influence of City

In studies involving multiple cities, the overall results may be unduly influenced by a single city. This is particularly likely in the Six Cities Study, which involved a small number of communities. In an attempt to identify strong leverage points, we estimated the effect that each city had on the estimated hazard ratios by excluding in turn each city from the analysis (comparable to deletion regression diagnostics). We found that the results were not influenced by the exclusion of any of the six cities. This means that the form of the exposure-response pattern, as well as the

estimated slope, was not seriously influenced by cities with less pollution (Portage WI) or more pollution (Steubenville OH). We conducted a similar regression analysis for the ACS Study and found that no single city exerted an undue influence on the association between air pollution and mortality.

Because the original air pollution monitoring records in the ACS Study were unavailable for audit, the Reanalysis Team constructed alternative air pollution data on the basis of monitoring data accumulated by the US EPA. Although the city-specific fine particle air pollution levels that had been assembled by the Original Investigators correlated highly with those developed by the Reanalysis Team, there were notable differences in fine particle levels for Denver. However, inclusion or exclusion of Denver from the reanalysis had no appreciable effect on the overall mortality risk ratios.

### Identification of Sensitive Subpopulations

The Reanalysis Team examined the changes in relative risk estimates associated with air pollution for specific subgroups of the study populations (statistical interactions), conducting separate analyses for well-defined categories of each of the following variables: age at enrollment; gender; educational attainment; marital status; smoking status; diseases reported at time of enrollment; amount of time lived in neighborhood at time of enrollment; self-reported occupational exposure to toxic air (dust, gases, and fumes); and our own lung carcinogen occupational dirtiness indices.

In the ACS Study, we found no important differences in relative risk of mortality by gender or age at enrollment. Although the estimates of the relative risk associated with air pollution differed for other variables, the 95% confidence intervals overlapped in all instances, so that the differences could be formally explained by chance alone.

The Reanalysis Team did find strong evidence of effect modification for some variables. Education notably modified the air pollution–mortality association (for both fine particles and sulfate); individuals who did not complete high school had the highest relative risks of mortality. Conversely, individuals who completed high school did not appear to have had increased risk. The Reanalysis Team concludes that this modifying effect is not necessarily attributable to education per se, but could indicate that education is a marker for a more complex set of socioeconomic variables that impact upon the level of risk.

### Comparison of Results Between Studies

Estimates of risk of mortality associated with exposure to fine particles and sulfate were insensitive to the set of covariates included in the risk model (the Original, Full, and Extended Model specifications yielded almost identical risks for the Six Cities Study and the ACS Study). In both studies, we obtained similar relative risks whether we used calendar year or age as the time axis. Also in both studies, cardiovascular disease mortality had the highest relative risk associated with exposure to air pollution. We found no associations between air pollution and death from respiratory disease in either study. In the Six Cities Study, the relative risks of other causes of death were similar to those for death from all causes, whereas the relative risks of other causes of death were much lower in the ACS Study. In the ACS Study, we observed slightly larger relative risks for the other cancers group (RR from 1.08 to 1.14) compared with those in the Six Cities Study (RR 1.03 to 1.04).

Although the air pollution effect was less among married persons in the ACS Study, the relative risks of mortality in the Six Cities Study were independent of marital status. Gender did not modify the mortality effect of fine particle air pollution in the ACS Study, but did so in the Six Cities Study.

The relative risks of mortality associated with an increase in exposure to fine particles or sulfate, by underlying cause of death and educational attainment, are shown in Table 52. Although relative risks clearly declined with increasing educational attainment for all causes of death examined in the ACS Study, this pattern was not as consistent in the Six Cities Study.

### Flexible Risk Models

Under the Cox proportional-hazards regression 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 levels of pollution are proportional. In addition, this model assumes that the relative increase in mortality is described by a specific parametric form; specifically, that the logarithm of the hazard rate is a linear function of the covariates.

To evaluate the applicability of this model to the Six Cities Study, the Reanalysis Team considered more flexible models, based on regression spline generalizations of the Cox model, to describe the relation between mortality and fine particles and sulfate. This flexible modeling approach indicated that the linearity assumption implicit in the Cox model was appropriate for fine particles. However, there was some evidence of departure 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.

**Table 52.** Relative Risks of Mortality by Cause of Death Associated with an Increase in Fine Particles or Sulfate 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%] |
| **Fine Particles** | | | | | | |
| 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) |
| **Sulfate** | | | | | | |
| All causes | 1.27 (1.13–1.42) | 1.20 (1.08–1.33) | 1.05 (0.96–1.14) | 1.47 (1.14–1.89) | 1.30 (0.97–1.73) | 0.99 (0.72–1.36) |
| Cardiopulmonary disease | 1.39 (1.20–1.62) | 1.31 (1.13–1.53) | 1.11 (0.98–1.25) | 1.28 (0.91–1.79) | 1.38 (0.94–2.02) | 1.42 (0.90–2.24) |
| Cardiovascular disease | 1.44 (1.23–1.69) | 1.42 (1.21–1.67) | 1.19 (1.05–1.36) | 1.30 (0.90–1.87) | 1.59 (1.06–2.37) | 1.40 (0.87–2.26) |
| Respiratory disease | 1.11 (0.74–1.66) | 0.78 (0.52–1.18) | 0.66 (0.47–0.93) | 1.05 (0.40–2.72) | 0.29 (0.07–1.24) | 1.73 (0.26–11.38) |
| Lung cancer | 1.49 (1.02–2.18) | 1.39 (0.99–1.95) | 1.19 (0.89–1.59) | 2.82 (1.15–6.90) | 0.51 (0.11–2.25) | 0.91 (0.27–3.02) |
| Other cancers | 0.97 (0.76–1.24) | 1.28 (1.06–1.54) | 1.04 (0.89–1.21) | 1.44 (0.80–2.60) | 1.56 (0.81–2.99) | 0.59 (0.29–1.22) |
| Other causes | 1.16 (0.86–1.56) | 0.71 (0.55–0.94) | 0.84 (0.68–1.04) | 1.66 (0.86–3.19) | 0.64 (0.28–1.44) | 0.67 (0.30–1.50) |

[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 $\mu g/m^3$ and for sulfate it 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 it was 19.9 $\mu g/m^3$. Time axis was calendar year. Percentage of sample in educational group is given in square brackets. Data are RRs with 95% CIs.

Although the Cox proportional-hazards assumption did appear to be appropriate for most of the study period, there was some evidence that the effects of both fine particles and sulfate varied somewhat with time. (Recall that tests for lack of fit of the Cox proportional-hazards regression model also provided some evidence that the effects of fine particles and sulfate may vary over time.) The pattern of time dependency suggests that the multiplicative effect of recent exposures on hazard rates may be associated more strongly with mortality than are exposures that occurred many years before death.

Analyses of the ACS Study cohort did not identify a consistent pattern in changes over time of the impact of either fine particles or sulfate on mortality. However, flexible analyses of the ACS Study data yielded evidence of nonlinear exposure-response relations for both fine particles and sulfate, with sulfate demonstrating a comparatively shallow exposure-response relation at concentrations below 10–15 $\mu g/m^3$. Flexible analyses of the ACS Study data also demonstrated, as in the Six Cities Study, a nonlinear (U-shaped) relation of BMI with mortality.

### Occupational Confounding

Although occupational exposures had been considered to some extent by the Original Investigators, the original analysis had been restricted in the Six Cities Study to self-reported occupational exposure to dust and fumes and in the ACS Study to a selected number of toxic air pollutants. The Reanalysis Team was concerned about the possibility of occupational confounding. For example, individuals in cities with high air pollution levels might tend to work in jobs that incurred high exposure to other agents associated with increased mortality. Consequently, our reanalysis used additional information on occupational exposures derived from the occupational histories available in both studies.

The Reanalysis Team developed and applied two aggregate indices of occupational exposures to the Six Cities Study and the ACS Study. The first index provided a mea-

sure of the overall dirtiness of the environments in which the subjects had worked. The second index reflected occupational exposure to accepted lung carcinogens.

The dirtiness index can be conceptualized as a variable that encompasses and integrates all exposures in the workplace, including exposure to pollutants that are pathogenic. But it can also be conceptualized as a variable that captures an aspect of social class that is correlated with, but distinct from, educational attainment—the other social class variable that had been used by the Original Investigators. The lung carcinogen index is a binary indicator variable that reflects whether or not a subject (ever/never) has been exposed occupationally to agents that have been identified as increasing risk of lung cancer.

We emphasize that there are four limiting factors associated with using the new indices to control confounding. First, the occupational information collected from study subjects did not represent detailed lifetime work histories. Second, the validity of the occupation coding has not been established in relation to the actual jobs and occupations held; because the Six Cities Study used a more detailed occupation coding system than did the ACS Study, there is greater potential in the former for valid attribution of both the dirtiness index and the lung carcinogen index. Third, the indices themselves are crude simplifications of complex exposure circumstances. In a sense, the indices are ecologic variables that establish an individual's presence within a potentially hazardous environment but do not measure individual exposure. Fourth, the two indices constructed focus on the dirtiness of jobs and subjects ever/never having been exposed to known lung carcinogens. It is recognized that the dirtiness index may be more useful in the case of deaths from respiratory conditions than deaths from cardiovascular disease. The lung carcinogen index is specifically designed to control for potential confounding by exposure in the workplace to agents known to increase lung cancer risk.

The impact of these limitations is to lessen the ability of the analyses to adequately adjust for potential confounding variables; that is, whatever bias in the original results might be due to confounding by occupational exposure would be diminished, but not necessarily eliminated, in our reanalyses. Nevertheless, we believe that this approach to controlling occupational confounding is an improvement over the original analyses. The new indices appeared to perform their intended function in that they were correlated with other variables in an expected way. The Six Cities Study had higher dirtiness scores, and higher prevalence of occupational exposure to carcinogens, than the ACS Study, compatible with what is known about the respective study populations. The dirtiness index was not correlated with air pollution in the ACS Study, but it was in the Six Cities Study. Although the dirtiness index was not a risk factor for mortality in the ACS Study, it was in the Six Cities Study.

The inclusion of these new variables had almost no impact on the relative risks of air pollution for cardiopulmonary mortality and mortality from all causes. In the ACS Study, we found excess risks for lung cancer from exposure to sulfate pollution but not fine particle pollution; lung cancer risks exhibited little change after adjusting for occupation. In the Six Cities Study, we found a nonsignificant excess in lung cancer risk related to fine particle air pollution, although this risk was attenuated considerably when the occupational confounders were included. There was a particularly high risk of lung cancer among never-smokers (RR = 9.03, 95% CI: 0.63–129.28) in the Six Cities Study even after adjusting for occupation, although this may have been a statistical anomaly resulting from the very small number of lung cancer deaths (8) among never-smokers.

Although our attempt to control for occupational exposure was constrained by the limitations in data quality, the findings nevertheless increase our confidence that the apparent increase in risk of general mortality—and in particular cardiopulmonary disease mortality associated with fine particle air pollution—was not the result of uncontrolled confounding by occupational exposures. In the ACS Study, even after the lung carcinogen index has been applied, the possibility of some residual confounding by occupation for mortality from lung cancer cannot be ruled out.

In both studies, occupational dirtiness rating exerted some effect modification. The air pollution effects tended to be stronger among subjects with high occupational dirtiness ratings, although the trends were not strictly monotonic. Education similarly was an effect modifier, and our attempts to disentangle the relative impacts of these two covariates did not produce a clear distinction. (It is important to remember that these two variables—education and occupational dirtiness—not only are correlated but also measure some of the same underlying social traits of the study subjects.)

### Time-Dependent Covariates

In long-term cohort mortality studies, the values of important covariates may change over time, which leads to concomitant temporal changes in risk. Although all covariate values used in the ACS Study had been determined when the cohort was defined in 1982, longitudinal information on covariates was available for the Six Cities Study from the follow-up questionnaires administered at 3, 6, and 12 years after enrollment. Using Poisson regression,

**Table 53.** Relative Risks of Mortality from All Causes Associated with Selected Indices of Fine Particle Air Pollution[a] Based on the Multivariate Poisson Regression Model

| Model | Fine Particle Index of Exposure | Relative Risk[b] (95% CI) |
|---|---|---|
| 1 | Exposure to $PM_{2.5}$ for each city remained fixed over the entire follow-up period | 1.31 (1.13–1.52) |
| 2 | Exposure to $PM_{2.5}$ for each city was defined according to 13 calendar periods[c] | 1.16 (1.02–1.32) |
| 3 | Exposure to $PM_{2.5}$ was assigned based on the city-specific mean exposure estimate for the earliest year available | 1.19 (1.08–1.30) |
| 4 | Time-dependent estimate of $PM_{2.5}$ exposure received during the 2 years before death | 1.16 (1.02–1.31) |
| 5 | Time-dependent estimate of $PM_{2.5}$ exposure received 3–5 years before death | 1.14 (1.02–1.27) |
| 6 | Time-dependent estimate of $PM_{2.5}$ exposure received > 5 years before death | 1.14 (1.05–1.23) |

[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 $\mu g/m^3$.

[b] Relative risks were adjusted for age, gender, body mass index, education, number of years smoked (at baseline), number of cigarettes smoked weekly, and occupational exposures.

[c] Exposures were defined according to 13 calendar periods: earlier than 1979, 1979, 1980, 1981, ..., 1989, and 1990 or later.

we found that incorporating information on changes over time in cigarette smoking and BMI had little effect on the association between fine particles and mortality. Allowing for the general downward trend in the average annual concentration of fine particles in the six cities, however, resulted in somewhat lower risk (RR = 1.16; 95% CI: 1.02–1.32) than we found with Poisson regression based on fixed-in-time long-term average fine particle levels (RR = 1.31; 95% CI: 1.12–1.52).

As discussed in the Time-Dependent Covariates section, the strong correlations that we observed between city-specific indices of fine particles did not allow us to discriminate among the risks of mortality for exposures received at various time intervals before death. For example, as shown in Table 53, the relative risk of mortality was roughly equivalent for exposures received within 2 years of death, 3 to 5 years before death, and more than 5 years before death. Multivariate models that included these indices simultaneously were highly collinear, so risk estimates were unstable (data not presented within this report). Further exploration of the variations in risk associated with fine particles is necessary before we can determine whether long-term or short-term exposure is most predictive of increased mortality. Such analyses will require detailed individual exposure information in which large changes in fine particle concentrations have occurred over an extended period of time.

An ideal analysis would include time-dependent exposure profiles for each individual in the study (Murdoch et al 1992). The construction of such profiles would require accurate information on study subject mobility linked to ambient fine particle monitoring data for each residence occupied during the period of interest, or even personal monitors. The development of residence histories and time-dependent exposures could be more informative for the ACS Study than for the Six Cities Study because the former exhibited greater variation in exposure patterns among participants and a larger number of persons who had moved.

### Population Mobility

Population mobility is an important consideration in long-term follow-up studies, because cohort members may change residences, and hence change exposure, during the observation period. Mobility is particularly important in studies of environmental factors that affect population health, as the level of exposure may vary substantially with geographic location.

Population mobility is difficult to assess in the ACS Study, because subjects' residence changes were not generally monitored subsequent to 1982 enrollment. The Six Cities Study afforded a greater opportunity to assess mobility within the cohort. The Reanalysis Team constructed postrecruitment residence histories for cohort members using the follow-up interviews and the annual contacts with study participants.

Mobility within the Six Cities Study cohort was limited; only 18.5% of participants left their original city of residence during the follow-up period. The relative risk of mortality from all causes in the subcohort of nonmovers was similar to that in the entire cohort.

Movers were younger and better educated than nonmovers, and did not exhibit a significantly elevated relative risk of fine particle–associated mortality from all causes

(RR = 1.08, 95% CI: 0.67–1.76). However, relative risks declined with increasing educational attainment, decreasing from 1.56 (95% CI: 0.67–3.64) among movers with less than a high school education to 0.96 (95% CI: 0.40–2.30) among those with more than high school education. As the subgroup of movers was small, relative risks were estimated with less precision than in the much larger subgroup of nonmovers.

We also evaluated pre-enrollment mobility using the reported number of years subjects had lived in the original city of residence before they enrolled in the study. Including residency duration as a predictor of mortality from all causes did not appreciably alter the relative risk of mortality associated with exposure to fine particles.

**Alternative Air Quality Data**

In the Six Cities Study, the Original Investigators had monitored ambient air pollution levels throughout the study period using data from federal and state monitoring stations, as well data from their own monitors developed specifically for that study. In the ACS Study, 1980 data had been obtained for sulfate (151 cities) and fine particles (50 cities) from AIRS and from the EPA's IPMN. The Six Cities Study data have been subjected to several independent audits, including that by the Reanalysis Team. Our audit of the ACS air pollution data was more difficult because of the limited information about how the database was constructed.

In order to test the sensitivity of the relative risk estimates that had been obtained by the ACS Study Original Investigators, the Reanalysis Team developed several alternative indices of exposure to fine particle air pollutants. We examined all available AIRS data for the period 1980–1989, and constructed exposure indicators for 133 of the ACS Study cities from fine particle air pollution data for 1980–1981. With the AIRS data and additional data from the IPMN, we were able to assemble alternative sulfate data for 144 of the 151 cities in the ACS Study. These alternative sulfate data led to risk estimates similar to those obtained by the Original Investigators. However, correcting the sulfate data for a known artifact in the high-volume samplers used to generate the AIRS data reduced the sulfate concentrations by approximately 50%, and somewhat increased the multiplicative risk estimates for all-cause and cardiopulmonary disease mortality. These alternative sulfate data reduced the estimate of lung cancer mortality associated with sulfate concentration from 1.33 (95% CI: 1.10–1.61) using the original sulfate data to 1.18 (95% CI: 0.96–1.47) using the adjusted sulfate data.

Using data derived from the IPMN, we obtained fine particle measurements for 63 cities, rather than the 50 cities in the original ACS Study's fine particle cohort. These data led to estimates of risk slightly lower than those obtained by the Original Investigators for all-cause, cardiopulmonary disease, and lung cancer mortality.

Further analysis by the Reanalysis Team failed to reveal increased risks of mortality for inhalable particles ($PM_{15}$), the coarse particle fraction ($PM_{15-2.5}$), or total suspended particles in the approximately 60 cities for which such data were available from the IPMN. We noted no increased association between all-cause mortality and total suspended particles in the 154 cities for which total suspended particle data were available from AIRS.

**Gaseous Copollutants**

Air pollution is a complex mixture of not only fine particles and sulfate, but also gaseous copollutants including carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide. These gases, present in varying degrees in virtually all urban centers in the United States, are often highly correlated both spatially and temporally. They have been associated with cardiorespiratory morbidity and mortality in time-series studies, and it is possible that long-term exposure to these gases also contributes to the observed association between mortality and exposure to either fine particles or sulfate. Because of the strong interrelations among these copollutants, it is difficult to separate their effects. This is recognized as an area of high priority for future research (National Research Council 1998, 1999).

The Six Cities Study, with its small number of cities and high degree of correlation among the air pollutants monitored, did not permit a clear distinction among the effects of gaseous and fine particle pollutants. Indeed, estimates of the relative risk of mortality from all causes were similar for exposure to fine particles, sulfate, sulfur dioxide, and nitrogen dioxide. Of the gaseous copollutants in the Six Cities Study, only ozone did not display an association with mortality.

The ACS Study, which involved a much larger number of cities with more diverse ambient air pollution profiles, afforded a greater opportunity to evaluate the effects of the gaseous copollutants. The supplementary data assembled by the Reanalysis Team on sulfur dioxide, ozone, nitrogen dioxide, and carbon monoxide permitted us to roughly evaluate the impact of these gaseous pollutants on mortality. Although no positive associations were found in the Cox regression models between ozone, nitrogen dioxide, or carbon monoxide and mortality from all

causes, cardiopulmonary disease, or lung cancer, sulfur dioxide did demonstrate a significant association with all-cause and cardiopulmonary disease mortality. In the ACS Study, the association between sulfur dioxide and mortality persisted after we made adjustments for spatial autocorrelation (see below).

### Sulfur Dioxide

We observed a stronger association between sulfur dioxide levels and mortality from all causes in the ACS Study than between either fine particles or sulfate and all-cause mortality. This difference in the strength of the association with mortality could result from the stability of the city-specific pollutant exposure estimates. Sulfate and fine particle mass data were obtained only every six days, whereas the gaseous pollution data were obtained hourly and averaged daily. Thus, city-specific average concentrations for gaseous pollutants comprised six times as many observations as the fine particle averages.

We therefore constructed a new exposure measure for sulfur dioxide, the gaseous pollutant most strongly associated with mortality. We used only those days in 1980 in each city for which there was also an available sulfate measurement. On the basis of this limited dataset, the relative risk of all-cause mortality associated with sulfur dioxide was 1.32 (1.24–1.40), a value similar to that based on all available observations (RR = 1.30; 95% CI: 1.23–1.38). Thus, the fact that sulfur dioxide was a stronger predictor of mortality than was sulfate does not appear to be due to the larger number of sulfur dioxide measurements.

We examined the association between mortality and exposure to sulfur dioxide for subjects who had not completed high school (RR = 1.28; 95% CI 1.15–1.43), subjects who had completed high school (RR = 1.50; 95% CI 1.35–1.67), and subjects who had had more than high school education (RR = 1.17; 95% CI 1.07–1.29). The sulfur dioxide effect on mortality risk was diminished for the best-educated subjects, a pattern we also observed with exposures to fine particles and sulfate. However, the sulfur dioxide effect, unlike the fine particle effect, was not the strongest for the least-educated subjects.

### Acid Aerosols

Acid aerosols may mediate the association between fine particle air pollution and adverse health outcomes (Spengler et al 1990; Lippmann and Thurston 1996). We found an association with acid aerosols (RR = 1.12; 95% CI: 0.97– 1.30) in the Six Cities Study. However, we could not test this hypothesis for the ACS Study because no measurements of acid aerosols were available. In the two time-series studies reporting exposure to acid aerosols, no associations were found (Dockery et al 1992; Schwartz et al 1996). Lippmann and Thurston (1996) found that sulfate correlated well with acid aerosols; therefore, because sulfate-associated mortality risks were present in both studies under review here, an association between mortality and acid aerosols may exist for the ACS Study as it does for the Six Cities Study.

### Ecologic Covariates

Gamble (1998) suggested that ecologic covariates other than the gaseous copollutants may have confounded the relation between fine particles and mortality in the ACS Study data. To address this concern, the Reanalysis Team considered 20 such ecologic covariates. (This analysis was necessarily restricted to the ACS Study; the inclusion of even five ecologic covariates other than air pollution in analyses of the Six Cities Study data would have resulted in a saturated risk model, in which the number of city-level covariates equals the number of cities.)

In order to avoid introducing ecologic covariates that may be artifactually associated with mortality, we identified a list of a priori covariates for which there was some plausible basis for suspecting an association with mortality. In this regard, we considered the main determinants of population health, including genetic, biological, environmental, occupational, social, and behavioral determinants, as well as health services. We obtained covariate values for the relevant metropolitan areas in the ACS Study from publicly available data sources such as the US Census Bureau and the US National Oceanic and Atmospheric Administration (NOAA).

When they are included in the Cox regression model, a number of these ecologic covariates appeared to be correlated with mortality. Specifically, population change, income, unemployment, education, income disparity, number of hospital beds, temperature, temperature variation, water hardness, sulfur dioxide, nitrogen dioxide, and ozone were significantly associated with mortality in the sulfate cohort ($P < 0.05$). However, because income disparity and nitrogen dioxide were negatively correlated with mortality, and water hardness was positively correlated, these ecologic associations require careful interpretation.

The diminished effect of sulfate on mortality risk estimates after we adjusted for either population change or exposure to sulfur dioxide warrants some discussion. The statistical effects of including ecologic covariates in the Cox proportional-hazards regression model are not well understood. Consequently, the Reanalysis Team investigated these effects by computer simulation under controlled conditions in which the true effect of the ecologic covariate is known (personal communication from Michal Abrahamowicz to the Ranalysis Team 2000). We found that including ecologic covariates in the Cox regres-

sion model reduced the estimated relative risk of the exposure of primary interest (in this case, fine particle air pollution). Unlike the case in linear ecologic regression, this effect was observed regardless of the strength of the association between the ecologic covariate and mortality, or the correlation between the ecologic covariate and the primary exposure. This downward bias in the relative risk of the primary exposure persisted even when the correlation between the covariate and exposure was negligible. This bias was small in many circumstances, but could be 20% or higher when the ecologic covariate was highly correlated with air pollution. The most important factor in determining the extent of this downward bias was the strength of the association between the covariate and mortality. Still, to obtain as accurate an estimate as possible of the sulfate-associated relative risk of mortality, our results suggest that it is better to adjust for relevant ecologic covariates than not.

**Contextual Ecologic Effects**

The Reanalysis Team made extensive efforts to identify ecologic covariates that would contribute to spatial variation in mortality rates among the cities in the ACS Study, and might confound the association between mortality and fine particle air pollution. Our multivariate Cox regression models identified a number of ecologic variables that altered the relative risk of mortality associated with fine particles or sulfate by more than 25%. Of the variables flagged as potential confounders in this way, population change, altitude, and sulfur dioxide were significant predictors of mortality in several of our multivariate Cox regression models. Although individual-level covariates, as had been used by the Original Investigators, are generally preferred over ecologic covariates in epidemiologic analysis, we used ecologic information on income because individual income was not recorded for the ACS Study. Variables such as population change and unemployment rate inherently represent community-level or contextual effects.

Certain variables can influence mortality at both the individual and the community level. For example, educational attainment was included as an individual covariate in our models, but also in our two-stage spatially filtered multivariate regression models for all-cause and cardiopulmonary disease mortality in the sulfate cohort.

Although this study focused on the association between fine particle air pollution and mortality, the contextual effects of education and other ecologic covariates on mortality warrant further exploration elsewhere. Useful guidance on the interpretation of the contextual education effect can be derived from recent work in the Netherlands (Schrijvers et al 1999). This study showed that inequalities in health, associated with inequalities in educational attainment, can be explained by a combination of behavioral and material factors. Behavioral factors include smoking, drinking, exercise, and dietary habits. Material factors include environmental quality (broadly defined to include housing, noise, and other pollution exposures) and factors such as the psychosocial stress of struggling to survive with the knowledge that others have much more material wealth. The relative risk of dying appears to take a fairly consistent ordering across educational strata and so do the material and behavioral risk factors. Behavioral and material factors together contribute to the health inequalities, but material factors contribute both directly (eg, through poor housing and environments) and indirectly (through modified behavior), which increases the importance of material factors.

This and other studies have suggested at least two possible explanations of the educational effect. One is differential exposure; less-educated persons appear less likely to avoid the risks of ambient air pollution (Hamilton 1995), and other factors that may influence health, than persons with higher education (Link and Phelan 1996). In a recent, ongoing study in Hamilton, Ontario, Jerrett (1999) found that enumeration areas (similar to the census block units in the United States) with high proportions of individuals with less than high school education were 2.5 times more likely to be within high pollution zones than areas populated more by educated individuals. This effect persisted even when researchers controlled for other potential predictors of exposure, including income and dwelling value.

The second possible explanation for the educational effect involves what can be called a healthy/unhealthy contagion phenomenon. Economic geographers use this concept to help explain the diffusion of technological innovation within specific regions (Miron 1984), and medical geographers use the term to characterize the movement of disease over space (Cliff and Haggett 1988). This concept might also be relevant for lifestyle behavior. Possibly, within better-educated communities, there is a propensity toward healthier living simply because people who live in close proximity are likely to imitate good behavioral traits in others around them. In other words, the interaction creates what could be a healthy community effect. The opposite, an unhealthy community effect, may possibly occur in less-educated communities. We would expect individuals in healthy communities to be better able to cope with a range of health risks, including air pollution, because of the relative absence of other risk factors. Likewise, we would expect to see air pollution exert a significantly greater effect in unhealthy communities.

A growing and impressive body of literature using multilevel models suggests that both personal characteristics and place of residence can help to explain health inequalities (see, for example, Duncan and Jones 1996). In our reanalysis of the ACS Study, we found some evidence that education was important in both individual and ecologic regression models. In the individual-level models, the pollution effect diminished or became insignificant when the model was stratified by education, and the ecologic models suggested that a community-wide educational effect may be at work. The individual model findings, combined with the importance of the ecologic education variable, lend more support to the possibility that exposure tends to vary with education.

This effect modification may well be due to the combination of spatial variation in intracity distributions of pollution, segregation of neighborhoods with low education, and the resulting inequitable exposure to pollution for persons of low education and places of high unemployment. In this case education becomes a marker for exposure misclassification, and although some of the effect modification by education may still result from contagious healthy or unhealthy living associated with community-wide education, the majority of the effect modification still results from exposure to pollution.

The association between mortality and air pollution found in the ACS Study may have been influenced mostly by persons of relatively low educational status who live in areas of high pollution. This interpretation would join a growing body of literature on environmental justice or equity (Jerrett 1997; Institute of Medicine 1998) that connects socioeconomic and racial status to disproportionate pollution exposures. Although much remains to be investigated regarding the health effects of such exposures, indications are that at least part of the socioeconomic and racial inequalities in health observed in the United States and other countries arise from the higher exposures of disadvantaged groups.

Some variables that we expected would have a significant effect on mortality were not strongly associated in our analyses. For example, although still controversial (Judge et al 1998), many studies (Kawachi and Kennedy 1997; Kaplan 1996; Wilkinson 1996) have suggested that income disparity (measured in our analyses by Gini coefficients) is an important determinant of health in the United States and that lower-income groups consistently display higher levels of age-standardized mortality. In the United States, income inequalities often translate into spatial inequalities (Massey and Denton 1993); because of residential segregation, disadvantaged individuals are subject to greater exposures from ambient fine particles, which may lead to misclassification bias.

These spatial inequalities may translate into exposure inequalities and a higher degree of exposure misclassification within the MSAs. Yet the Gini coefficient was not strongly associated with mortality in the ACS cohort. In the few models in which the Gini coefficient did achieve significance, it was negatively correlated. This unexpected finding might arise from the different locations for income disparity and high relative risk of mortality associated with air pollution. In the ACS Study, income disparity centered mostly in the Deep South around Mississippi, and the relative risks, as mentioned, were highest in the Lower Great Lakes region.

**Spatial Autocorrelation**

In the original analyses of both the Six Cities Study and the ACS Study, the possibility of spatial autocorrelation in both mortality rates and exposure to fine particle air pollution had not been considered. In addition, other covariates used in both the original analyses and the reanalysis may have been autocorrelated spatially. The presence of spatial autocorrelation affects the statistical power of the associations, with positive spatial autocorrelation in the residuals increasing the likelihood of a false-positive finding. In the ACS Study, which spanned the breadth of the continental United States, the existence of regional differences could lead to spatial autocorrelation, and we conducted additional analyses to take this into account.

The spatial analysis focused on city-specific mortality rates adjusted for all individual-level covariates, but not air pollution, using a risk model selected from a large number of alternative models fit to the ACS Study data. We then examined the association between these adjusted city-specific mortality rates and ecologic covariates, including fine particle levels and gaseous copollutant concentrations, using spatial regression methods. We detected significant positive spatial autocorrelation for most covariates, including the adjusted mortality rates, ambient air pollutant levels, and supplementary ecologic covariates such as education.

The analyses conducted by the Reanalysis Team to account for spatial autocorrelation in the ACS Study data are summarized in Figure 22. Both the standard Cox model that had been used by the Original Investigators and our two-stage regression Independent Observations Model assume statistical independence among all observations, and are included as points of reference.

We considered five additional two-stage random effects model specifications to account for spatial patterns in the data. The Independent Cities Model acknowledges the possibility that subjects living in the same city are more likely to have similar mortality rates than subjects living in

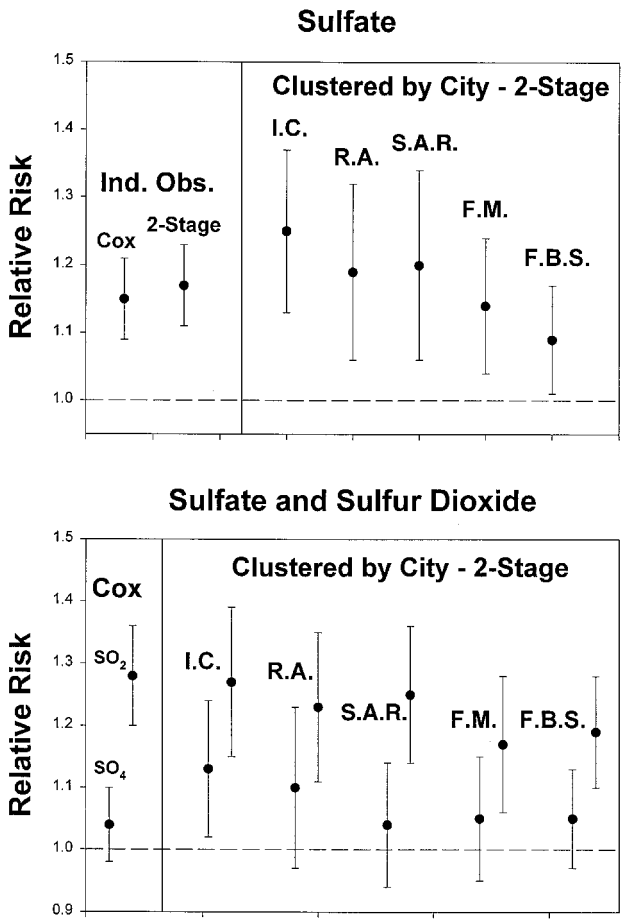



**Figure 22. Effects of sulfate or sulfate and sulfur dioxide on relative risks of mortality from all causes using the ACS Study data.** Top panel: Relative risks of mortality associated with an increase in sulfate concentrations of 19.9 μg/m$^3$ by type of statistical model for the dependency among subjects and cities. Bottom panel: Sulfate and sulfur dioxide were both included in each model and the relative risk of morality associated with each pollutant was calculated. In the left sections, the Independent Observations Models assume subjects are statistically independent (standard Cox model; two-stage regression assumes error variance equal to city-specific estimation error). In the right sections, all Clustered by City Models assume that the population's mortality is clustered within each city; risks were calculated using two-stage random effects regressions. In the Independent Cities Model (I.C.), data in different cities were assumed to be independent. In the Regional Adjustment Model (R.A.), mortality rates were adjusted for seven US regions. In the Simultaneous Autoregressive Model (S.A.R.), cities were assumed to be spatially dependent and analyses included an error structure based on nearest-neighboring cities. In the Filtered Mortality Only Model (F.M.), city-specific relative risks were spatially filtered before being linked with air quality data. In the Filtered Both Sides Model (F.B.S.), both relative risks and air quality data were spatially filtered. Error bars represent ±2 SE.

different cities. To look for evidence of clustering of mortality by city, we compared variation in the logarithms of the estimated city-specific relative risks obtained in the first stage of our two-stage regression approach to their standard errors. If the observed variation was similar to the estimation error, then cities could not be distinguished in terms of mortality rates. However, if there was additional variation in these estimates after we controlled for risk factors such as city-level air pollution measurements, then we modeled the variation in mortality rates among cities by including a random effect for each city with a common variance. This additional variation affects the estimates of the influence of city-level and ecologic covariates as well as their uncertainty.

In the first (Independent Cities) random effects model, we assumed that the mortality rates for cities are statistically independent. Under this model, the relative risk of all-cause mortality associated with exposure to airborne sulfate was increased over that in models assuming independence among subjects because both estimation error and variation in risk among cities were included in the weighting scheme for combining risk estimates across cities. This type of weighting scheme generates more uniform weights among cities than that used in the Independent Observations Model, in which the weights depend only on the estimation error. The degree of uniformity depends on the magnitude of the intercity variation in risk relative to the average within-city estimation error. Under the random effects model, if the variation among cities is comparatively large, then the city-specific weights will be similar and the larger cities are weighted less. If the mortality rates in these larger cities do not conform to a predictive model for sulfate-associated mortality, they will have less influence on the analysis, thus increasing the relative risk of mortality associated with exposure to sulfate.

Confidence intervals on the relative risk estimates for all-cause mortality obtained under the Independent Cities random effects model are much larger than those for the standard Cox model because the standard error of the logarithm of the sulfate relative risk was twice the size of that obtained from the Cox model. This indicates that we do not really have over half a million (the sample size) independent observations in the ACS Study with respect to determining air pollution effects; rather, the effective sample size in the ACS Study is approximately half the total sample size (ie, the number of subjects divided by the variance inflation factor of 2).

We then questioned the assumption that mortality risks were independent among cities. Even after we controlled for available risk factor information at the individual and ecologic level, there was evidence of residual spatial autocorrelation among the city-specific risk estimates. Thus there was some unidentified process that varied in space and resulted in broader regional clustering of mortality rates. We addressed the statistical form of this spatial dependence from four approaches. In the first (Regional Adjustment Model), we adjusted the city-specific relative

risks of seven regions of the United States by using indicator functions for each region in the two-stage random effects regression model. The sulfate-associated relative risk of mortality estimated under the Independent Cities Model (RR = 1.25) decreased by about 32% under this Regional Adjustment Model (RR = 1.19), suggesting that some of the association between sulfate and mortality was the result of broader regional associations in these variables. Statistical tests for spatial autocorrelation in the residuals from the Regional Adjustment Model provided little evidence of further spatial dependency in the data ($P > 0.10$).

We also attempted to remove spatial autocorrelation in the stochastic error structure of the model, as opposed to addressing spatial autocorrelation through the deterministic part of the model (as in the Regional Adjustment Model), using our simultaneous autoregressive modeling approach. In this case, we considered residuals to be spatially autocorrelated if they were a nearest-neighbor under the assumption that cities closer to one another have more similar mortality experiences than cities farther part. As with the Regional Adjustment Model, the sulfate-associated relative risk of mortality under the Nearest-Neighbor Model (RR = 1.20) was lower than that obtained from the Independent Cities Model (RR = 1.25). This modeling approach also eliminated much of the evidence of spatial autocorrelation in the residuals ($P > 0.10$).

Our third approach to the issue of spatial autocorrelation involved modeling spatial patterns in the data directly. Here, the relative risk of each city was compared with the risks for neighboring cities within a distance selected such that the residual spatial autocorrelation was minimized; we used all cities within a 600-km radius to determine an average risk for adjustment purposes. (This approach is similar to that for time-series mortality studies in which temporal trends in mortality rates are removed by using multiday moving-average filters.) This approach has the advantage over the Regional Adjustment Model that the data themselves effectively select the size of the regions and control for spatial autocorrelation at each city. To explore the impact of filtering only the mortality and not the pollution data (Filtered Mortality Only), we regressed sulfate concentrations on the spatially filtered city-specific mortality rates. The resulting sulfate-associated relative risk (RR = 1.14) was lower than it was under the other methods used. Thus, it appears that in the relation between sulfate and mortality there is subregional spatial structure that the Regional Adjustment Model did not remove.

The final approach (Filtered Both Sides) involved filtering not only the city-specific relative risks of mortality, but also the sulfate concentrations. Here, a 600-km radius was sufficient to remove any evidence of spatial autocorrelation in the sulfate data. With this approach, we compared mortality rates and sulfate levels after we removed broad spatial patterns in both variables, representing both sides of the regression equation relating mortality and air pollution. The estimated sulfate-associated relative risk was lower under the Filtered Both Sides Model (RR = 1.09) than under the Filtered Mortality Only Model (RR = 1.14), further suggesting that broad spatial patterns in sulfate concentrations account for some of the association with mortality.

These analyses provide strong evidence that mortality rates are clustered by city and that effects in neighboring cities are more similar than are those in distant cities. The spatial regression methods suggest that part of the relation between sulfate and mortality is probably due to some unobserved variable or group of confounding variables. In particular, we see that the sulfate-associated effect drops from a relative risk of 1.25 with the Independent Cities Model, to 1.19 with the Regional Adjustment Model, and to 1.09 with the Filtered Both Sides Model. Subtracting the results of the Regional Adjustment and Filtered Both Sides Models from the Independent Cities Model gives a possible range (RR of 0.6–0.16) over which the sulfate-associated effect results from spatial autocorrelation in the data. When we convert this to a percentage on the basis of the relative risk of 1.25 from the Independent Cities Model, it suggests that uncontrolled spatial autocorrelation accounts for 24% to 64% of the observed relation. Nonetheless, all our models continue to show an association between elevated risks of mortality and exposure to airborne sulfate.

### Spatial Analysis of the Joint Effects of Sulfate and Sulfur Dioxide

Our standard Cox model analysis of ecologic covariates indicated that adjustment for sulfur dioxide, a gaseous copollutant, reduced the sulfate-associated relative risk of mortality. We examined the possible effects of spatial autocorrelation on this association, and the results are shown in the bottom panel of Figure 22. In all models considered, the relative risk of all-cause mortality associated with exposure to sulfur dioxide was greater than that for sulfate. Furthermore, when sulfur dioxide was included as a covariate, the sulfate-associated relative risk did not achieve formal statistical significance ($P < 0.05$) in any model except the Independent Cities Model. The relative risk associated with sulfur dioxide was statistically significant in all models examined. After we adjusted for sulfur dioxide levels, the variation in city-specific relative risks of mortality was much lower than after we adjusted for sul-

fate or fine particle concentrations. This suggests that sulfur dioxide accounted for much more of the variation in between-city mortality than sulfate. The addition of sulfur dioxide into the models with sulfate removed spatial autocorrelation in the residual mortality rates. However, the sulfur dioxide effect was also sensitive to the method of analysis; the relative risk for all-cause mortality based on the Independent Cities Model (RR = 1.27) exceeded that for the Filtered Both Sides Model (RR = 1.19). Thus, the effect observed at broad spatial levels (RR = 1.27 − 1.19 = 0.08) was less than that observed at local levels (RR = 1.19 – 1.00 = 0.19). In contrast, sulfate demonstrated a stronger effect at the broad spatial level (RR = 1.25 − 1.09 = 0.16) than at the local level (RR = 1.09 – 1.00 = 0.09). This may result from the degree of spatial autocorrelation in the air pollution data; using Moran *I*, the spatial autocorrelation for sulfur dioxide was 0.27 whereas that for sulfate was 0.39.

## EXPOSURE MEASUREMENT ERROR

A potentially important source of exposure measurement error in both the Six Cities Study and the ACS Study is that data from fixed-site monitors rather than personal dosimeters necessarily were used to evaluate individual exposures to ambient air pollutants. For a number of cities in the ACS Study, data were available from more than one monitor, and those data were averaged to provide an indicator of exposure for all individuals in the city.

Air pollution exposure is an ecologic index that refers to cities and not individuals. As an ecologic variable, it has limitations associated with its use, including, among others, levels of air pollution before the studies began, variations within and between cities during follow-up, declining levels in ambient particles over time, and the changing chemical makeup of air pollution.

When fixed-site monitors are used and other internal sources of particles of comparable toxicity are excluded, measurement error should bias associations toward the null hypothesis of no effect and decrease statistical precision (Zidek et al 1996). If exposure measurement errors can be characterized, statistical methods exist to adjust risk estimates for those errors (Fung and Krewski 1999a,b). Empirical data on the exposure measurement error incurred from using fixed-site monitors to represent individual long-term average exposures are unavailable at present. Moreover, it will be difficult to generate such data because of the need to collect individual exposures over an extended period of time.

We attempted to gauge the potential impact of exposure measurement error on estimates of mortality risks associated with long-term exposure to fine particle air pollution by examining the variation among fixed-site monitors in the same metropolitan area. Intermonitor variation provided some information; specifically, for individuals with limited intracity mobility, the difference between the ambient pollutant concentration at the nearest monitor and the average of all city monitors provides a rough indication of the extent of exposure measurement error. However, the average of the multiple city monitors provides a better indication of long-term average exposure for highly mobile individuals within a city. This suggests that within-city intermonitor variation can roughly indicate the extent of exposure measurement error incurred when fixed-site ambient air pollution monitors are used instead of personal dosimeters. To the extent that there is a high degree of population mobility within a given city, this may actually overestimate the degree of exposure measurement error.

The Reanalysis Team employed within-city intermonitor variation as a rough indicator of exposure measurement error for fine particles to calculate, using the nonparametric simulation extrapolation method developed by Carroll and colleagues (1995), adjusted estimates of the relative risk of mortality based on a simplified Cox regression model that included fine particles and smoking. Because the degree of measurement error varied among cities, we prepared adjusted estimates for a range of possible degrees of measurement error.

The results indicate that this type of random exposure measurement error could lead to substantial underestimation of risk associated with long-term exposure to fine particle air pollution. In the Six Cities Study, for example, the estimated relative risk of 1.26 for all-cause mortality might be in the range of 1.30 (low measurement error) to 1.50 (high measurement error), if we could adjust for this source of error. However, because the true extent of exposure measurement error remains unknown, these adjusted risk estimates are only indicative, and they need to be interpreted with caution.

A more complete quantitative evaluation of the potential impact of exposure measurement error would require that additional sources of error be incorporated into the analysis. For instance, instrumentation error (both random and systematic) inherent in daily readings from the fixed-site monitors requires consideration. However, this source of error may be small in relation to the spatial variation in pollutant levels within a large metropolitan area. The complex interrelation between indoor and outdoor sources of exposure to fine particles also warrants consideration, as do time-activity patterns reflecting the time individuals spent outdoors.

It should be clear that, as in other studies of ambient air pollution, the estimates of increased mortality associated

with exposure to ambient air pollution exclude exposure to fine particles and other pollutants from indoor sources. The implicit assumption in such analyses is that total personal exposure can be partitioned into two components representing airborne fine particles from outdoor and indoor sources. Two questions that arise are whether this assumption is correct, and whether the effects observed in this and other studies were confounded by indoor air pollution.

With regard to the first question, fine and ultrafine airborne particles do penetrate indoors (Dockery and Spengler 1981a,b; Spengler et al 1981; Spengler and Sexton 1983), and individuals will be exposed to ambient fine particles regardless of their activity patterns. For example, Dockery and Spengler (1981a,b) estimated that the indoor concentration of fine particles of outdoor origin was about 70% of the outdoor value, although full air-conditioning could reduce this to about 30%.

Leech and colleagues (1996) estimated that North Americans spend almost 88.6% of their time indoors, 6.1% outdoors, and 5.3% in vehicles; thus one would expect indoor air to be important in these time-series studies. The level of exposure to fine particle air pollution from indoor sources varies by individual, depending on personal activity patterns. The main argument for partitioning the two components of fine particles is that particles generated indoors will be different from ambient air fine particles. Outdoor particles consist of coarse particles from dust, and finer fractions of sulfate and carbon particles generated mostly by internal combustion. Indoor air fine particles are generated by indoor sources and activities, such as cigarette smoke, radon, indoor combustion of fuels, molds, fungi, shedding of human skin, and personal grooming habits (Spengler and Sexton 1983; Wallace 1996).

If these levels are approximately constant across cities, then the differential effect on rates of mortality will be minimal and the indoor component should not confound the effects of the outdoor component. The fact that smoking status had little effect on the association between fine particles and mortality provides some support for this position. Neither the Six Cities Study nor the ACS Study included information on environmental tobacco smoke in the home and the workplace. However, because the effects of passive smoking on mortality are generally much smaller than the effects of active smoking, these effects could also be minor.

Although most cross-sectional studies have found very low correlations between personal exposures and indoor and outdoor levels of exposure to air pollution (Dockery and Spengler 1981b; Wallace 1996), a recent within-subject study suggested much higher correlations (Janssen et al 1998). The within-subject longitudinal component of variability answers the primary question of whether personal exposure, averaged across individuals, correlates with levels measured outdoors. This is very important in time-series studies, because the analysis focuses on day-to-day variations in air pollution, but it is not critical in an analysis that uses fixed values.

## ACCURACY OF MORTALITY DATA

We have assumed, as did the Original Investigators, that the underlying causes of death were accurately reported and accurately coded. It has been found, however, that the accuracy of coding varies with cause of death (Alderson and Meade 1967; de Faire et al 1976; Engel et al 1980; Percy et al 1981). Cancer deaths usually are coded with more than 80% accuracy, but deaths from respiratory and cardiovascular diseases are often confused. In particular, when persons had these conditions concurrently and both contributed to death, there can be some uncertainty about which should be selected as the primary underlying cause. In other instances, there may be errors in selecting one underlying cause in a complex chain of health events (eg, cancer leading to pneumonia and then to respiratory failure). Largely for these reasons, the Original Investigators combined cardiovascular and respiratory diseases in their analyses. As part of our sensitivity analyses, we also conducted separate analyses for these causes of death. In the absence of differential errors between cities in reporting the underlying cause of death in either study, we would expect that such errors would dilute the true associations. Unfortunately, we have no data to confirm such an absence; obtaining such information would be a major undertaking and was outside of the scope of this project.

## SELECTION BIAS

The results of the Six Cities Study and the ACS Study have influenced the development of national air pollution control policy in the United States. Therefore, it is important to consider the extent to which the studies' results are applicable to the general United States population.

There are two issues, one related to generalizability and the other to bias, regarding the representativeness of these findings. If study subjects were not representative of their entire communities, it could compromise the generalizability of the findings. For instance, if the study undersampled persons of low social class or some other socioeconomic or demographic indicator, then the findings strictly are applicable only to the proportion of the population that matches the profiles of the subjects who were included. In the ACS Study, for example, 94% of the population was white; thus the results may not apply to other racial groups. Still, it

can be argued that relevant biological processes are likely to be identical across racial groups, so that air pollution is likely to have similar effects on all segments of the population.

Another possibility is that study subjects were not representative of their target populations and differed in certain key characteristics from community to community. Statistical analyses could adjust for those differences for which individual data were available. However, these adjustments might not capture all important differences. Intangible and unmeasured factors, related perhaps to the sociodemographic profiles of the communities, could have a bearing on who was recruited into the studies. Statistical adjustments for such contextual ecologic effects could be attempted, although the completeness of such ecologic adjustments would be difficult to assure. A bias in estimating mortality effects from air pollution would occur only if the reasons for being included or excluded from the study differed city by city and if these reasons were also correlated with mortality rates.

In the Six Cities Study, potential subjects, selected from a sampling frame of addresses, had been included in the study if they were contacted successfully and agreed to participate. The methods used to select subjects from the sampling frames were based on sound statistical sampling procedures. If the structure or nature of the sampling frames (household voting lists or private census for commercial listings) differed from city to city, or if the fieldwork procedures varied in any way that could influence the likelihood of participation, then there could be differential subject enrollment in the different cities. Ferris and colleagues (1979) compared the age-gender distributions in the Six Cities Study to the 1970 US census, and found important deviations from the expected numbers of subjects enrolled in the various age strata as well as in some broad occupational groups. This suggests that subjects were not representative of the occupational and age distributions of the target populations in all cities. The authors concluded that the largest deviations occurred in Harriman.

Other than age, gender, and occupation, we have no information about the characteristics of the sampling areas and whether they were comparable to each other sociodemographically. Subjects had been enrolled over a 4-year period (1974 until 1979) and, unless those years saw secular changes in socioeconomic situations in these cities, we would not expect prolonged enrollment to affect the composition of the study population. Response rates (mean 77%) varied from a low of 73% in Watertown and Steubenville to a high of 81% in Portage and Harriman (Ferris et al 1979). This is a fairly narrow range and does not admit a great deal of latitude for serious discrepancies to occur between cities. Face-to-face interviews had been conducted with subjects. A bias could occur if study personnel had changed dramatically over this period and if different techniques had been used to elicit information from study subjects. Because most questions were not subject to interpretation, we would not expect this to be a major factor.

In the ACS Study, conversely, subjects had been enrolled by volunteers; standard statistical and epidemiological methods had not been used to select individuals

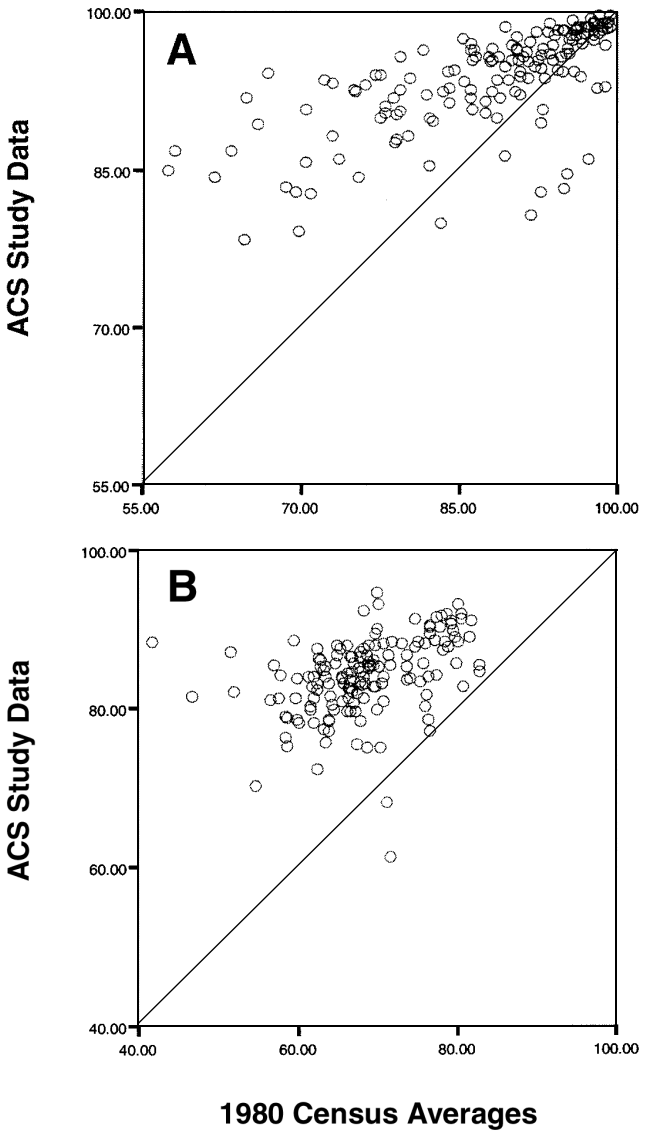



**Figure 23. Comparison between ACS Study data and 1980 Census averages for race and educational attainment.** A: Percentage of subjects (ACS Study) or residents (1980 US Census) in each MSA who defined themselves as being of white race. B: Percentage of subjects (ACS Study) or residents (1980 US Census) in each MSA who reported having completed high school.

from well-defined sampling frames. If different criteria and methods for enrollment had been used by the volunteers in different cities, it is conceivable that study participants in different cities varied substantially in their demographic, socioeconomic, and lifestyle characteristics. For example, volunteers in one city could have been, on average, more aggressive in persuading people to participate. As a result, the study participants in this city would comprise a broader psychological/social profile. In the city with less aggressive volunteers, the participants would be representative of the narrower, "easy to enroll", socially responsible segment. If these psychosocial characteristics were related to risk factors (such as education or occupation) and hence to mortality outcome, then intercity biases could ensue.

Because the ACS Study had no defined target population, response rates were also not defined, nor had any records been retained by ACS that could assist us in determining any city-specific biases. However, some evidence indicates that the ACS Study cohort is not representative. Figure 23a shows that the percentage of white persons enrolled in the ACS Study from each MSA is much higher than the census average for those same MSAs. Likewise, Figure 23b indicates that, according to 1988 Census Bureau data, the percentage of high school graduates was substantially higher among study participants than in the broader community of each MSA.

## CONCLUSIONS

Time-series studies that focus on the effects of short-term exposure to fine particles, as well as cohort studies that address the effects of long-term exposures, have demonstrated significant associations between fine particle air pollution and mortality. This report has focused on the Six Cities Study and the ACS Study because they played a pivotal role in the establishment of the first NAAQS for fine particles in the United States. The importance of these two studies to regulatory policy development in the United States led to our independent audit and reanalysis, conducted for the Health Effects Institute.

In Part I of the reanalysis, we focused on validating the data that had been used by the Original Investigators in these two studies, and on replicating their numerical results using the same analytic methods. The data quality audit established the integrity of most of the data in both studies, with the exception of the air pollution monitoring data used in the ACS Study that had been obtained from third party sources and could not be validated. Although some analytic errors and discrepancies were noted in each study, these did not have a marked impact on the original risk estimates and did not materially affect the conclusions that had been reached by the Original Investigators.

In Part II, the Reanalysis Team conducted a detailed sensitivity analysis to assess the robustness of the original findings to alternative analytic approaches. We applied a wide range of alternative analytic approaches, including new methods of analysis such as random effects survival models and spatial filtering techniques. We also examined the effects of additional covariates taken from the original questionnaires that had not been included in the original published analyses, as well as the effects of 20 ecologic covariates that we developed from available databases and the general scientific literature.

The risk estimates reported by the Original Investigators were remarkably robust to alternative specifications of the underlying risk models, thereby strengthening confidence in the original findings. Specifically, the inclusion of additional individual-level covariates beyond those considered by the Original Investigators had little impact on the original risk estimates. Similar risk estimates also were obtained regardless of whether age or calendar year was used as the time axis.

The Reanalysis Team did find evidence of variation in risk among population subgroups; the most important was that the relative risk of mortality associated with fine particle air pollution decreased with increasing educational attainment. We observed this modifying effect of education in both studies. Although the interpretation of this finding is unclear, it is possible that educational attainment is a marker for socioeconomic status, which in turn may be correlated with exposure to fine particle air pollution.

In order to evaluate the possibility that the association between fine particles and mortality might result in part from occupational exposures, the Reanalysis Team developed and applied two new exposure indicators that measured occupational dirtiness and exposure to known lung carcinogens. These aggregate indicators of occupational exposure are particularly appropriate for respiratory conditions, malignant and otherwise, associated with inhalation of a range of substances that represent the exposures of most importance in occupational health risk assessment. Although cardiovascular disease has been associated with few occupational exposures, our overall dirtiness index may be indicative of exposure to workplace substances as yet unrecognized as increasing the risk of cardiovascular disease, and thus may afford some degree of control for occupational confounding in the case of cardiovascular disease as well as respiratory disease mortality.

Generally we found little evidence of uncontrolled occupational confounding of the association between fine

particle air pollution and mortality, but we could not rule out the possibility of residual confounding by occupation in the ACS Study with respect to the association between lung cancer mortality and exposure to sulfate. Our ability to adjust for occupational confounding in the ACS Study also was limited by the quality of the available occupational data.

In the Six Cities Study, allowing for changes in BMI and smoking during the follow-up period had little effect on the relative risk of mortality associated with fine particle air pollution. However, the relative risk of mortality from all causes decreased slightly when we accounted for the general decline in fine particle air pollution during the follow-up period, which suggests that the relative risk may be changing with time. The flexible exposure-response models applied by the Reanalysis Team also provided some evidence that the effects on mortality of both fine particles and sulfate were not constant over time.

Our analysis of residential mobility in the Six Cities Study indicated that only 18.5% of subjects moved from their original city of residence during the follow-up period. The risk estimates for this stable subcohort of nonmovers were similar to those for the entire cohort. Risk declined with increasing educational attainment in both the nonmover and mover subcohorts, even though the much smaller subcohort of younger, better-educated people that moved out of their original city of residence had not demonstrated an excess relative risk overall. These analyses could only be conducted with the Six Cities Study data, because temporal information on covariates was not available for the ACS Study.

The original air pollution monitoring data used in the ACS Study also were not available for a detailed audit; thus the Reanalysis Team considered a number of alternative indicators of exposure to air pollution in the sensitivity analyses of that study. Our measures of fine particles and sulfate correlated highly with the measures that had been used by the Original Investigators, and led to comparable relative risks of mortality from all causes, cardiopulmonary disease, and lung cancer, further increasing confidence in the original analysis. However, adjustment for a known artifact in the sulfate measurements reduced the indicators of sulfate exposure by about 50%, leading to an increase in the relative risk of all-cause and cardiopulmonary disease mortality associated with sulfate, but not in the relative risk of lung cancer mortality.

The inclusion of additional ecologic covariates in the ACS Study led to a number of new findings. Although adjustment for most ecologic covariates, in the Extended Model using Cox proportional-hazards regression, did not markedly affect the relative risks of mortality associated with fine particle air pollution, the inclusion of certain sociodemographic covariates (population change, in particular) reduced the relative risks for both fine particles and sulfate. Whereas the gaseous copollutants nitrogen dioxide, ozone, and carbon monoxide were not associated with mortality, sulfur dioxide was a significant predictor of mortality. Furthermore, adjusting for sulfur dioxide greatly diminished the effect of sulfate, and also somewhat reduced the association between fine particles and mortality. The roles of both sulfate and sulfur dioxide as predictors of mortality in the ACS Study support the notion that mortality may be related to more than one component of the complex mixture of urban air pollution in the United States. (Whereas sulfate levels reflect broader regional exposure conditions, sulfur dioxide levels are determined more by local point sources of air pollution.) The absence of a plausible toxicological mechanism by which sulfur dioxide could lead to increased mortality further suggests that it might be acting as a marker for other mortality-associated pollutants.

Because the original standard Cox model analyses of the ACS Study data had been predicated on the assumption that all observations are statistically independent, we conducted a number of analyses that allow for the spatial autocorrelation that was detected in the ACS Study data. These analyses employed two-stage random effects regression models that allowed for spatial clustering in mortality first at the city level, and then within seven broad airshed regions defined in the National Morbidity and Mortality Air Pollution Study (Samet et al 2000). Allowing for intracity or intraregional correlation in mortality resulted in slightly increased risk estimates that were subject to somewhat greater uncertainty than the original risk estimates.

We conducted additional spatial analyses after filtering out broader spatial patterns in mortality alone, or after filtering both the mortality and sulfate data, and obtained risk estimates comparable to or slightly lower than the risk estimates that had been reported by the Original Investigators. (Because of the limited number of cities for which measurements were available, spatial filtering could not be conducted for fine particle data.) The filtered risk estimates had wider confidence limits than the original risk estimates did, although the lower 95% confidence intervals for mortality from all causes and from cardiopulmonary disease were greater than the null value of unity.

Overall, these results, which allow for varying levels of spatial autocorrelation in the ACS Study data, support the association between fine particles and mortality that had been reported by the Original Investigators. However, the spatially adjusted risk estimates are subject to somewhat

greater uncertainty than the original risk estimates because of significant spatial autocorrelation in the ACS Study data.

The inclusion of ecologic covariates in our spatial adjustment models generally had somewhat less impact on the association between mortality and fine particles than did their inclusion in the original Cox regression model, which assumes no spatial autocorrelation in the data. In the Cox model, for example, the addition of population change, which demonstrated a high degree of spatial autocorrelation and a strong east-west gradient, notably reduced the relative risk of all-cause mortality associated with exposure to sulfate. In our spatial adjustment models, however, the sulfate-associated relative risk of all-cause mortality decreased only slightly when population change was included. In contrast, population change was a strong predictor of mortality in the standard Cox regression model, which assumes all individual observations are statistically independent.

Our spatial analyses also demonstrated a significant association between sulfur dioxide and mortality. Furthermore, this association appeared to be robust against adjustment for other ecologic covariates, including fine particles and sulfate, the covariates of primary interest here. In contrast, the inclusion of sulfur dioxide in our spatial regression methods resulted in a reduction in the mortality risk associated with exposure to both fine particles and sulfate. Nonetheless, even after adjustment for the effects of sulfur dioxide, both fine particles and sulfate demonstrated a positive association with mortality in our spatial regression methods.

Collectively, our reanalyses suggest that mortality may be associated with more than one component of the complex mix of ambient air pollutants in urban areas of the United States. Most of the individual pollutants that had been measured in the Six Cities Study demonstrated associations with mortality of similar magnitude, because the individual pollutants in these cities were highly correlated. Throughout the reanalysis of the ACS Study, both fine particles and sulfate demonstrated positive associations with mortality, as did sulfur dioxide.

Finally, it is important to bear in mind that the results of our reanalysis alone are insufficient to identify causal relations with mortality. Rather, we can conclude only that urban air pollution is associated with increased mortality in these two important epidemiologic investigations.

## REFERENCES

Abbey DE, Colome SD, Mills PK, Burchette R, Beeson WL, Tian Y. 1993. Chronic disease associated with long-term concentrations of nitrogen dioxide. J Expo Anal Environ Epidemiol 3:181–202.

Abbey DE, Mills PK, Petersen FF, and Beeson WL. 1991. Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-day Adventists. Environ Health Perspect 94:43–50.

Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Lawrence Beeson W, Yang JX. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159:373–82.

Abbey DE, Ostro BE, Petersen F, Burchette RJ. 1995. Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) and other air pollutants. J Expo Anal Environ Epidemiol 5:137–159.

Ahrens W, Merletti F. 1998. A standard tool for the analysis of occupational lung cancer in epidemiologic studies. Int J Occup Environ Health 4:236–240.

Alderson MR, Meade TW. 1967. Accuracy of diagnosis on death certificates compared with that in hospital records. Br J Prev Soc Med 21:22–29.

Amsel J, Waterbor JW, Oler J, Rosenwaike I, Marshall K. 1982. Relationship of site-specific cancer mortality rates to altitude. Carcinogenesis 5:461–465.

Bailey TC, Gatrell A. 1995. Interactive Spatial Data Analysis. Longman Scientific & Technical, Essex, England.

Boffetta P, Kogevinas M, Simonato L, Wilbourn J, Saracci R. 1995. Current perspectives on occupational cancer risks. Int J Occup Environ Health 1:315–325.

Brenner MH, Greeland S, Savitz DA. 1992a. The effects of nondifferential confounder misclassification in ecologic studies. Epidemiology 3:456–459.

Brenner MH, Savitz DA, Jockel KH, Greeland S. 1992b. Effects of nondifferential exposure misclassification in ecologic studies. Am J Epidemiol 135:85–95.

Breslow NE, Day NE. 1987. Statistical Methods in Cancer Research, Vol II, The Design and Analysis of Cohort Studies. Number 82. International Agency for Research on Cancer, Lyon, France.

Burnett R, Krewski D. 1994. Air pollution effects on hospital admission rates: A random effects modeling approach. Can J Stat 22:441–458.

Burnett RT, Brook JE, Philips O, Cakmak S, Raizenne M, Stieb D, Vincent R, Özkaynak H, Krewski D. 1998. The association between ambient concentrations of carbon monoxide

and daily mortality in Toronto, Canada. J Air Waste Manage Assoc 48:689–700.

Burnett RT, Dales R, Krewski D, Vincent R, Dann R, Brook JR. 1995. Associations between ambient particaulate sulfate and admission to Ontario hospitals for cardiac and respiratory diseases. Am J Epidemiol 142:15–22.

Carroll RJ, Ruppert D, Stefanski LA. 1995. Measurement Error in Nonlinear Models. Monographs on Statistics and Applied Probability 63. Chapman & Hall, London England.

Christiani DC, Wegman DH. 1995. Respiratory disorders. In: Occupational Health: Recognizing and Preventing Work-Related Disease (Levy BS, Wegman DH, eds) pp 427–454. Little, Brown, Toronto, Canada.

Clayton CA, Perritt RL, Pellizzari ED, Thomas KW, Whitmore RW, Wallace LA, Özkaynak H, Spengler JD. 1993. Particle total exposure assessment methodology (PTEAM) study: Distributions of aerosol and elemental concentrations in personal, indoor, and outdoor air samples in a Southern California community. J Expo Anal Environ Epidemiol 3:227–250.

Cleveland WS, Devlin SJ. 1988. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 74:829–836.

Cliff AD, Haggett P. 1988. Atlas of Disease Distributions: Analytical Approaches to Epidemiological Data. Basil Blackwell, Oxford, England.

Cook DG, Pocock SJ. 1983. Multiple regression in geographical mortality studies, with allowance for spatially correlated errors. Biometrics 39:361–371.

County and City Data Book. 1988. US Government Printing Office, Washington DC.

de Faire U, Friberg L, Lorich U, Lundman T. 1976. A validation of cause-of-death certification in 1,156 deaths. Acta Med Scand 20:223–228.

DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Control Clin Trials 7:177–188.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Dockery DW, Schwartz J, Spengler J. 1992. Air pollution and daily mortality: Associations with particulates and acid aerosols. Environ Res 59:362–373.

Dockery DW, Spengler JD. 1981a. Indoor-outdoor relationships of respirable sulfates and particles. Atmos Environ 15:335–343.

Dockery DW, Spengler JD. 1981b. Personal exposure to respirable particulates and sulfates. J Air Pollut Control Assoc 31:153–159.

Duncan C, Jones K. 1996. Health-related behaviour in context: A multi-level modeling approach. Soc Sci Med 42:817–830.

Easton DF, Peto J, Babiker AGA. 1991. Floating absolute risk: An alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Stat Med 10:1025–1035.

Environmental Systems Research Institute. 1999. US Places (24000+). Environmental Systems Research Institute, Redland CA.

Engel LW, Strauchen JA, Chiazze L, Heid M. 1980. Accuracy of death certification in an autopsied population with specific attention to malignant neoplasms and vascular diseases. Am J Epidemiol 111:99–112.

Evans RG, Stoddart GL. 1990. Producing health, consuming health care. Soc Sci Med 31:1347–1363.

Feinleib M, Kannel WB, Tedeschi CG, Landau TK, Garrison RJ. 1979. The relation of antemortem characteristics to cardiovascular findings at necropsy—The Framingham Study. Atherosclerosis 34:145–157.

Ferris BG Jr, Speizer FE, Spengler JD, Dockery W, Bishop YMM, Wolfson M, Humble C. 1979. Effects of sulfur oxides and respirable particles on human health. Am Rev Respir Dis 120:767–779.

Fung K, Krewski D. 1999a. Evaluation of quasi-likelihood, regression calibration, and SIMEX methods in logistic regression when one of the predictors is subject to additive measurement error. J Epidemiol Biostat 4:65–74.

Fung KY, Krewski D. 1999b. On measurement error adjustment methods in Poisson regression. Environmetrics 10:213–224.

Gamble JF. 1998. $PM_{2.5}$ and mortality in long-term prospective cohort studies: Cause-effect or statistical associations? Environ Health Perspect 106:535–549.

Geolytics Software. 1999. CensusCD 1980. Geolytics Inc, East Brunswick NJ.

Gérin M, Siemiatycki J, Desy M, Krewski D. 1998. Associations between several sites of cancer and occupational

exposure to benzene, toluene, xylene and styrene: Results of a case-control study in Montreal. Am J Ind Med 34:144–156.

Gérin M, Siemiatycki J, Kemper H, Begin D. 1985. Obtaining occupational exposure histories in epidemiologic case-control studies. J Occup Med 27:420–426.

Getis A, Ord C. 1996. Local spatial statistics: An overview. In: Spatial Analysis: Modeling in a GIS Environment (Longley P, Batty M, eds). GeoInformation International, Cambridge MA.

Grambsch PM, Therneau TM. 1994. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81:515–526.

Greenland S, Morgenstern H. 1989. Ecologic bias, confounding, and effect modification. Int J Epidemiol 18:269–274.

Greenland S, Robbins J. 1994. Invited commentary: Ecologic studies—Biases, misconceptions, and counterexamples. Am J Epidemiol 139:747–760.

Griffith DA, Doyle PG, Wheeler DC, Johnson DL. 1998. A tale of two swaths: Urban childhood blood-lead levels across Syracuse, New York. Ann Assoc Am Geogr 88:640–645.

Hamilton JT. 1995. Testing for environmental racism: Prejudice, profits, political power? J Policy Anal Manage 14:107–32.

Institute of Medicine, Committee on Environmental Justice. 1998. Toward Environmental Justice: Research, Education, and Health Policy Needs. National Academy Press, Washington DC

Janssen NA, Hoek G, Brunekreef B, Harssema H, Mensink I, Zuidhof A. 1998. Personal sampling of particles in adults: Relation among personal, indoor, and outdoor air concentrations. Am J Epidemiol 147:537–547.

Jerrett M. 1997. Environmental equity in Canada: An empirical investigation into the income distribution of pollution in Ontario. Environ Planning A29: 1777–1800.

Jerrett M. 1999. A GIS-spatial equity analysis of particulate air pollution in Hamilton. Presentation to the Canadian Geographers Association. Lethbridge, Alberta, Canada.

Judge K, Mulligan JA, Benzeval M. 1998. Income inequality and population health. Soc Sci Med 46:567–579.

Kaplan GA. 1996. People and places: Contrasting perspectives on the association between social class and health. Int J Health Serv 263:507–519.

Kaplan GA, Pamuk ER, Lynch JW, Cohen RD, Balfour JL. 1996. Inequality in income and mortality in the United States: Analysis of mortality and potential pathways Br Med J 7037:999–1003.

Kawachi I, Kennedy BP. 1997. The Relationship of income inequality to mortality: Does the choice of indicator matter? Soc Sci Med 45:1121–1127.

Koenig JQ, Larson TV, Norris G, Claiborn C, Finn D, Zweidinger R, Lewtas J, Schwartz J. 1998. A Fine Particulate Composition Variability and Exacerbation of Asthma. HEI Particulate Matter Research Inventory. Health Effects Institute, Cambridge MA.

Koenig JQ, Larson TV, Hanley QS, Rebolledo V, Dumler K, Checkoway H, Wang SZ, Lin D, Pierson WE. 1993. Pulmonary function changes in children associated with fine particulate matter. Environ Res 63:26–38.

Kotchmar DJ, McMullen T, Hasselblad V. 1987. Adequacy of a single monitoring site for defining mean outdoor concentrations of fine particles in a demarcated residential community. J Air Pollut Control Assoc 37:377–381.

Krewski D, Burnett RT, Goldberg MS, Siemiatycki J. 1998. Analytic Plan for the Re-analysis of the Harvard Six Cities Study and the American Cancer Society Study of Air Pollution and Mortality. Institute of Population Health, University of Ottawa, Ottawa, Canada.

Langbein LI, Lichtman AJ. 1978. Ecological Inference. Sage Publications, Beverley Hills CA.

Leaderer BP, Naeher L, Jankun T, Balenger K, Holford TR, Toth C, Sillivan J, Wolfson JM, Kountrakis P. 1999. Indoor, outdoor, and regional summer and winter concentrations of $PM_{10}$, $PM_{2.5}$, $SO_4^{2-}$, $H^+$, $NH_4^+$, $NO_3^-$, $NH_3$, and nitrous acid in homes with and without kerosene space heaters. Environ Health Perspect 107:223–231.

Leech JA, Wilby K, McMullen E, Laporte K. 1996. The Canadian Human Activity Pattern Survey: Report of methods and population surveyed. Chronic Dis Can 17:118–123.

Link BG, Phelan JC. 1996. Understanding sociodemographic differences in health—The role of fundamental social causes. Am J Public Health 4:471–473.

Lipfert FW, Malone RG, Daum ML, Mendell NR, Yang CC. 1988. A Statistical Study of the Macroepidemiology of Air Pollution and Total Mortality. BNL 52122 US-404. US Department of Energy, Brookhaven National Laboratory, Upton NY.

Lippmann M, Thurston GD. 1996. Sulfate concentrations as an indicator of ambient particulate matter air pollution for health risk evaluations. J Expo Anal Environ Epidemiol 6:123–146.

Massey DS, Denton NA. 1993. American apartheid: Segregation and the making of the underclass. Harvard University Press, Cambridge MA.

Miron J. 1984. Spatial autocorrelation in regression analysis: A beginner's guide. In: Spatial Statistics and Models (Gaile GL, Willmott CJ, eds) pp 201–222. D Reidel Publishing, Boston MA.

Moolgavkar SH, Luebeck EG. 1996. A critical review of the evidence on particulate air pollution and mortality. Epidemiology 7:420–428.

Murdoch DJ, Krewski D, Wargo J. 1992. Cancer risk assessment with intermittent exposure. Risk Anal 12:569–577.

National Research Council. 1998. Research Priorities for Airborne Particulate Matter I: Immediate Priorities and a Long-Term Research Portfolio. National Academy Press, Washington DC.

National Research Council. 1999a. Health Effects of Exposure to Radon, BEIR VI. National Academy Press, Washington DC.

National Research Council. 1999. Research Priorities for Airborne Particulate Matter II: Evaluating Research Progress and Updating the Portfolio. National Academy Press, Washington DC.

Odland J. 1988. Spatial Autocorrelation. Sage Publications, Beverly Hills CA.

Özkaynak H, Thurston G. 1987. Associations between 1980 US mortality rates and alternative measures of airborne particle concentration. Risk Anal 7:449–460.

Percy C, Stanek E, Gloeckler L. 1981. Accuracy of cancer death certificates and its effect on cancer mortality statistics. Am J Public Health 71:242–250.

Piantadosi S, Byar DP, Green SB. 1988. The ecological fallacy. Am J Epidemiol 127:893–904.

Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151:669–674.

Preston DL, Lubin JH, Pierce DA, McConney ME. 1993. Epicure. Hirosoft International Corporation, Seattle WA.

Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW, Schwarz J, Zanobetti A. 2000. The National Morbidity and Mortality Air Pollution Study, Part II: Morbidity and Mortality from Air Pollution in United States. Research Report 94. Health Effects Institute, Cambridge MA.

Sawada M. 1999. Global spatial autocorrelation indices–Moran's I, Geary's C and the general cross-product statistic. University of Ottawa website www.uottawa.ca/academic/arts/geographie/lpcweb/sections1/reports/moransi/moran.htm.

Schrijvers CT, Stronks K, van de Mheen HD, Mackenbach JP. 1999. Explaining educational differences in mortality: The role of behavioral and material factors. Am J Public Health 89:535–540.

Schwartz J, Dockery DW, Neas LM. 1996. Is daily mortality associated specifically with fine particles? J Air Waste Manage Assoc 46:927–939.

Schwartz J. 1991. Particulate air pollution and daily mortality: A synthesis. Public Health Rev 19:39–60.

Schwartz J. 1994a. What are people dying of on high air pollution days? Environ Res 64:26–35.

Schwartz S. 1994b. The fallacy of the ecological fallacy: The potential misuse of a concept and the consequences. Am J Public Health 5:819–824.

Shyrock HS. 1976. The Methods and Materials of Demography. Academic Press, New York NY.

Siemiatycki J, Nadon L, Lakhani R, Béégin, D, Géérin M. 1991. Exposure assessment. In: Risk Factors for Cancer in the Workplace (Siemiatycki J, ed) pp 45–114. CRC Press, Baton Rouge LA.

Spengler JD, Brauer M, Koutrakis P. 1990. Acid air and health. Environ Sci Technol 24:946–956.

Spengler JD, Dockery DW, Turner W, Wolfson M, Ferris BG. 1981. Long-term measurements of respirable sulfates and particles inside and outside homes. Atmos Environ 15:23–30.

Spengler JD, Sexton K. 1983. Indoor air pollution: A public health perspective. Science 221:9–17.

US Bureau of the Census. 1988. County and City Data Book. US Government Printing Office, Washington DC.

US Environmental Protection Agency. 1996. Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information. OAQPS Staff Paper. EPA/452/R-96-013. Office of Air Quality Planning and Standards, Research Triangle Park NC.

Vedal S. 1997. Ambient particles and health: Lines that divide. J Air Waste Manag Assoc 5:551–581.

Wallace L. 1996. Indoor particles: A review. J Air Waste Manage Assoc 46:98–126.

Wilkinson RG. 1996. Unhealthy Societies: The Afflictions of Inequality. Routledge, London, England.

World Health Organization. 1975. *International Classification of Diseases, Ninth Revision*, Vol 1. World Health Organization, Geneva, Switzerland.

Zidek JV, Wong H, Le HD, Burnett R. 1996. Causality, measurement error and multicollinearity in epidemiology. Environmetrics 7:441–451.

## PART II APPENDICES AVAILABLE ON REQUEST

The following appendices may be downloaded in PDF format from the Health Effects Institute Web site (*www.healtheffects.org*). Hard copies may be requested by contacting HEI at 955 Massachusetts Avenue, Cambridge MA 02139 (phone, 617-876-6700; fax, 617-876-6709; email, pubs@healtheffects.org). Please give the full title of the Special Report, the Part II title, and the titles of the appendices you wish to request.

A. Quality Assurance Audit of the Data
B. Occupational Exposures
C. Flexible Modeling of the Effects of Fine Particles and Sulfate on Mortality
D. Alternate Air Pollution Data in the ACS Study
E. Selection of Ecologic Covariates for the ACS Study
F. Definition of Metropolitan Areas in the ACS Study
G. Values of the Ecologic Covariates
H. Spatial Analyses
I. Random Effects Cox Models

# Acknowledgments

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

This reanalysis of the Six Cities and ACS Studies of the association between particulate air pollution and mortality was a complex undertaking, involving a large number of scientists representing a range of disciplines. The Reanalysis Team itself comprised 31 individuals from 13 institutions in Canada and the United States; the new Centre for Population Health Risk Assessment in the Institute of Population Health at the University of Ottawa served as the focal point for the project.

All members of the Reanalysis Team made unique contributions to this multidisciplinary effort and are acknowledged elsewhere by name. Although all team members made outstanding contributions, Alette Willis deserves special recognition not only for her painstaking technical work in reconstructing the 1980 boundaries of the metropolitan areas included in the ACS Study and assembling additional socioeconomic, demographic, and environmental data for use by the Reanalysis Team, but also for serving as technical editor and coordinator for various report drafts. Kate Keating and Paula Carty also assisted with technical editing of report drafts, all of which were prepared under tight timelines. Additional contributions were made by Kimberly Zartolas and Ashley Wong, who spent the summer of 1999 at Harvard University coding the residence histories for all subjects included in the Six Cities Study, and by Sylvie Mauviel, who provided secretarial and administrative services to team members.

The Reanalysis Team gratefully acknowledges the cooperation of the Original Investigators in both the Six Cities Study and the ACS Study. Dr Douglas W Dockery, Dr Frank E Speizer, and Martha Fay answered many questions from the Reanalysis Team about the Six Cities Study, as did Drs C Arden Pope III, Michael J Thun, and Eugenia Calle about the ACS Study. Site visits with both sets of Original Investigators early in the Reanalysis Project were also of great value. We could not have asked for more patience and cooperation throughout the two-year period during which the reanalysis was conducted.

The Reanalysis Team met with the HEI Expert Panel four times during the course of the project to review interim results and to discuss methodologic approaches to specific issues. Discussions with the Expert Panel were extremely valuable and served to clarify a number of critical analytic issues. The Reanalysis Team also benefitted greatly from formal comments provided by the Special Panel of the HEI Health Review Committee on drafts of our reports submitted to HEI. Although the Advisory Board did not have the same opportunities to review the work in progress, their comments on major analytic issues were of great value to the Reanalysis Team.

The important role of HEI staff members also needs to be acknowledged. Dr Aaron J Cohen was the research project manager at HEI and skillfully facilitated interactions among the Reanalysis Team, Expert Panel, and Advisory Board. We were pleased to work with such an experienced and knowledgeable research manager. Daniel S Greenbaum, President of HEI, made the Reanalysis Project a personal priority and was actively engaged throughout the process. Dr JoAnn Ten Brinke was the review project manager and oversaw the production of the final report at HEI, coordinating the efforts of the HEI Review Panel and the editorial staff in the final stages of the project. This was a complex undertaking, given the intensive level of review to which the draft and revised reports were subjected as well as the length and scope of the final report. The editorial staff at HEI, led by Virgi Hepner for this project, did an outstanding job of editing and preparing the final manuscript for publication.

A project of this magnitude could not have been completed in a timely manner without excellent administrative support. Howard E Garsh at HEI and Gilles Morier at the University of Ottawa handled the detailed administrative arrangements, permitting the Reanalysis Team to focus on the task at hand, knowing that budgets and schedules were being carefully monitored. Mariella Peca and Hélène l'Abbée worked closely with Gilles on administrative and financial project matters at the University of Ottawa.

A number of individuals less directly involved with the Reanalysis Project also need to be acknowledged. Bob Bilgrad at the National Death Index provided guidance on procedures to be followed in securing the approvals needed to work with data on the vital status of individual subjects. Drs John Bachman and John Vandenberg directed questions from the Reanalysis Team about monitoring data collected by the US Environmental Protection Agency to

the right scientists at EPA. We specifically acknowledge Jacob G Summers, who provided the Reanalysis Team with data from the Aerometric Information Retrieval System, and Jose M Sune, who provided us with data from the Inhalable Particle Monitoring Network.

# About the Primary Authors

**Daniel Krewski** is currently professor of medicine and professor of epidemiology and community medicine at the University of Ottawa, where he is involved in a number of activities in population health risk assessment within the new Insitute of Population Health. Dr Krewski has also served as adjunt research professor of statistics in the Department of Mathematics and Statistics at Carleton University since 1984. Prior to joining the Faculty of Medicine at the University of Ottawa in 1998, he was director of Risk Management in the Health Protection Branch of Health Canada. While with Health Canada, he also served as acting director of the Bureau of Chemical Hazards and as chief of the Biostatistics Division in the Environmental Health Directorate. Dr Krewski obtained his PhD in statistics from Carleton University and subsequently completed an MHA at the University of Ottawa. His professional interests include epidemiology, biostatistics, risk assessment, and risk management. Dr Krewski is a Fellow of the American Statistical Association and the Society for Risk Analysis. He currently serves as a member of the US National Academy of Sciences' Board on Environmental Studies and Toxicology and as a member of the Academy's Committee on Research Priorities for Airborne Particulate Matter.

**Richard T Burnett** received his PhD from Queen's University in 1982 in mathematical statistics. He is now a senior research scientist with the Environmental Health Directorate of Health Canada, where he has been working since 1983 on issues relating to the health effects of outdoor air pollution. Dr Burnett's work has focused on the use of administrative health and environmental information to determine the public health impacts of combustion-related pollution using nonlinear random-effects models, time series and spatial analysis techniques.

**Mark S Goldberg** is an associate professor with the National Institute of Scientific Research at the University of Quebec in Laval and is adjunct professor at McGill University in Montreal. Dr Goldberg obtained degrees in physics (BS 1975) and epidemiology and biostatistics (MS 1985, PhD 1992) from McGill. He is currently investigating the short-term effects of air pollution on mortality and identifying susceptible subgroups. His research interests include occupational risk factors for female breast cancer, and delivery of treatment and other health services for breast cancer.

**Kristin Hoover** started Hoover Consultants in 1989 after a request for quality assurance consulting on the Natural Resources Damage Assessment for the *Valdez* oil spill. During the past 11 years, she has worked on many audits in toxicology, analytic chemistry, regulatory review, and quality assurance, especially the potential health effects of particulate and gaseous air pollution. Prior to consulting, Ms Hoover was corporate product safety manager for Pennwalt Corporation and a senior toxicologist at Arco Chemical Company. She holds degrees in natural resources and environmental biology and is senior author of the book Managing Conduct and Data Quality of Toxicology Studies, which was the culmination of a conference sponsored jointly by government and industry. Ms Hoover was a founding board member of the Society of Quality Assurance, which now counts over a thousand members.

**Jack Siemiatycki** is professor of epidemiology at the University of Quebec with a concurrent appointment at McGill University. His 150 publications and reports cover many methodologic and substantive issues, including health survey methodology, juvenile diabetes epidemiology, health effects of asbestos, and occupational causes of cancer. He is recognezed for the development of novel methods of exposure assessment for investigation of environmental/occupational causes of cancer. Dr Siemiatycki is a Distinguished Scientist of the Medical Research Council of Canada.

**Michael Jerrett** is assistant professor in the School of Geography and Geology, the Health Studies Program, and the Environmental Health Program at McMaster University, Hamilton, Ontario, Canada. He earned his PhD in geography from the University of Toronto. He specializes in spatial analysis of environment–health relationships. Dr Jerrett has designed and analyzed local, provincial and national level health and environment databases in Canada, the United States, Mexico, and Vietnam.

**Michal Abrahamowicz** is associate professor of biostatistics in the Department of Epidemiology and Biostatistics at McGill University and medical scientist in the Division of Clinical Epidemiology at Montreal General Hospital. His research interests include survival analyses, nonparametric regression, epidemiology of cancer, cardiovascular and rheumatologic diseases, cohort studies, and randomized clinical trials.

**Warren H White** is a senior research associate in the Chemistry Department at Washington University in St Louis. Educated as a mathematician at the California Institute of Technology and University of Wisconsin, Dr White spent several years teaching and researching in the area that has since become known as *chaos theory*. He returned to California Institute of Technology to work on the 1972–73 Aerosol Characterization Experiment (ACHEX), an early multiinvestigator field study of particulate air pollution in Los Angeles. Dr White has since continued to study ambient aerosols, their effects on radiative transfer and visibility, and their relationship to particle and precursor gas emissions. Dr White is a member of the EPA's Clean Air Science Advisory Committee and serves on National Academy of Science panels assessing research priorities for airborne particulate matter and tropospheric ozone.

# Abbreviations and Other Terms

**MEASURES OF PARTICLES AND SULFATE**

| | |
|---|---|
| $PM_{2.5}$ | particulate matter 2.5 μm or smaller in aerodynamic diameter |
| $PM_{2.5}$(DC) | **mean** fine particle fraction from dichotomous samplers |
| $PM_{2.5}$(DC MD) | **median** fine particle mass concentration from dichotomous samplers |
| $PM_{2.5}$(OI MD) | **median** fine particle concentration used by the Original Investigators |
| $PM_{10}$ | particulate matter 10 μm or smaller in aerodynamic diameter |
| $PM_{15}$ | particulate matter 15 μm or smaller in aerodynamic diameter |
| $PM_{15}$(DC) | **mean** inhalable particle fraction from dichotomous samplers |
| $PM_{15}$(SSI) | **mean** inhalable particle fraction from high-volume SSI samplers |
| $PM_{15-2.5}$ | the coarse particle fraction of particulate matter [15-μm particles minus 2.5-μm particles] |
| $PM_{15-2.5}$(DC) | **mean** coarse particle fraction from dichotomous samplers |
| $SO_4^{2-}$ | sulfate |
| $SO_4^{2-}_{(\text{cb-adj region})}$ | sulfate data for 1980–1981 inclusive, with region-specific adjustment for artifactual sulfate |
| $SO_4^{2-}_{(\text{cb-adj season})}$ | sulfate data for 1980–1981 inclusive, with season-specific adjustment for artifactual sulfate |
| $SO_4^{2-}_{(\text{cb-adj US})}$ | sulfate data for 1980–1981 inclusive, with US-specific adjustment for artifactual sulfate |
| $SO_4^{2-}_{(\text{cb-unadj})}$ | sulfate data for 1980–1981 inclusive, unadjusted for artifactual sulfate |
| $SO_4^{2-}$(DC) | sulfate data from $PM_{15}$(DC) |
| $SO_4^{2-}$(OI) | sulfate data used by the Original Investigators |
| TSP | total suspended particles |
| TSP(IPMN) | **mean** TSP mass concentrations based on IPMN data |

**OTHER TERMS**

| | |
|---|---|
| ACS Study | the American Cancer Society Study |
| AIRS | Aerometric Information Retrieval System |
| ARRCCM | *American Review of Respiratory and Critical Care Medicine* |
| BMI | body mass index |
| $CaCO_3$ | calcium carbonate |
| CAPITA | Center for Air Pollution Impact and Trend Analysis |
| CASAC | Clean Air Science Advisory Committee |
| CI | confidence interval |
| CO | carbon monoxide |
| CPS-II | American Cancer Society's Cancer Prevention Study II |
| DC | measurement from a dichotomous sampler |
| *df* | degrees of freedom |
| EPA | US Environmental Protection Agency |
| FP+CP | fine particles + coarse particles |
| FVC | forced vital capacity |
| $H^+$ | aerosol acidity |
| HSPH | Harvard School of Public Health |
| IARC | International Agency for Research on Cancer |
| ICD-9 | *International Classification of Diseases, Ninth Revision* |
| IP | inhalable particles |
| IPMN | Inhalable Particle Monitoring Network |
| JAWMA | *Journal of the Air and Waste Management Association* |
| MA | metropolitan area |
| MD | median |
| MSA | metropolitan statistical area |
| NAAQS | National Ambient Air Quality Standard |
| NAD | National Aerometric Database |
| NDI | National Death Index |
| NEJM | *New England Journal of Medicine* |
| $NO_2$ | nitrogen dioxide |

| | |
|---|---|
| NOAA | US National Oceanic and Atmospheric Administration |
| $O_3$ | ozone |
| OSI | Office of Scientific Integrity |
| *r* | bivariate correlation coefficient |
| range | the difference in mean concentrations between the most-polluted city and the least-polluted city |
| RR | relative risk |
| SAS | Statistical Application Software |
| SID | subject identification number |
| Six Cities Study | the Harvard Six Cities Study |
| $SO_2$ | sulfur dioxide |
| SSI | high-volume sampler with size-selective inlet |
| SSN | Social Security Number |

HEALTH
EFFECTS
INSTITUTE

# COMMENTARY

## Health Review Committee

Milicent Higgins, John C Bailar III, Michael Brauer, Bert Brunekreef, David Clayton, Manning Feinleib, Brian Leaderer, and Richard L Smith.

# COMMENTARY

HEALTH EFFECTS INSTITUTE

## Health Review Committee



*Continued*

HEALTH EFFECTS INSTITUTE

# COMMENTARY

## Health Review Committee

### 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 $\tau^2$ 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 ($\rho$) 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 $\tau^2$. 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 $\tau^2$ 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.

## REFERENCES

Abbey D, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Beeson WL, Yang JE. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159:373–382.

Briggs SLK, Thurston GD, Dumyahn TS, Evans JS, Spengler JD, Turner WA. 1982. The effectiveness of dichotomous sampler quality assurance procedures. Proceedings of the Air Pollution Control Association Annual Meeting, New Orleans. Air Pollution Control Association, Pittsburgh, PA.

Brown PJ, Le ND, Zidek JV. 1994. Multivariate spatial interpolation and exposure to air pollutants. Can J Stat 22:489–509.

Cressie N. 1993. Statistics for Spatial Data, 2nd ed. John Wiley & Sons, New York NY.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Dominici F, Samet JM, Zeger SL. 2000. Combining evidence on air pollution and daily mortality from the 20 largest US cities: A hierarchical modelling strategy (with discussion). J R Stat Soc 163(3):in press.

Easton DF, Peto J, and Babiker AG. 1991. Floating absolute risk: An alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Stat Med 10:1025–1035.

Gamble JF. 1998. Fine particles and mortality in long-term prospective cohort studies: Cause-effect or statistical associations? Environ Health Perspect 106:535–549.

Guttorp P, Meiring W, Sampson P. 1994. A space-time analysis of ground-level ozone data. Environmetrics 5:241–254.

Higgins MW, Thom T. 1989. Incidence, prevalence, and mortality: Intra- and intercounty differences. In: Clinical Epidemiology of Chromic Obstructive Pulmonary Disease (Hensey MJ, Saunders NA, eds) pp 23–43. Marcel Dekker, New York NY.

Holland DM, De Oliveira V, Cox LH, Smith RL. 2000. Estimation of regional trends in sulfur dioxide over the eastern United States. Environmetrics 11:373–393.

Holland DM, Saltzman N, Cox LH, Nychka D. 1999. Spatial prediction of sulfur dioxide in the eastern United States. In: geoENV II, Geostatistics for Environmental Applications (Gomez-Hernandez J, Soares A, Froidevaux R, eds) pp 65–76. Kluwer, Dordrecht, Germany.

Moolgavkar SH, Luebeck EG. 1996. A critical review of the evidence on particulate air pollution and mortality. Epidemiology 7:420–428.

National Center for Health Statistics. 1998, Health, United States, 1998 with Socioeconomic Status and Health Chartbook. National Center for Health Statistics, Hyattsville, MD. DHHS Publication (PHS) 98–1232

National Heart, Lung and Blood Institute; the National Lung Health Education Program Executive Committee. 1998. Strategies in Preserving Lung Health and Preventing COPD and Associated Diseases. Supplement 136S–141S.

Nyberg F, Gustavsson P, Järup L, Bellander T, Berglind N, Jakobsson R, Pershagen G. 2000. Urban air pollution and lung cancer in Stockholm. Epidemiology 11:487–495.

Nychka D, Saltzman N. 1998. Design of air quality networks. In Case Studies in Environmental Statistics (Nychka D, Piegorsch W, Cox LH, eds) pp 51–76. Lecture Notes in Statistics, Number 132. Springer-Verlag, New York NY.

Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151:669–674.

Raizenne M, Neas LM, Damokosh AI, Dockery DW, Spengler JD, Koutrakis P, Ware JH, Speizer FE. 199. Health effects of acid aerosols in North American children: Pulmonary function. Environ Health Perspect 104(5):506–514.

Samet JM, Dominici F, Zeger SL, Schwartz J, Dockery DW. 2000. National Morbidity, Mortality, and Air Pollution Study: Part I. Methods and Methodologic Issues. Research Report 94. Health Effects Institute, Cambridge MA.

Sampson PD, Guttorp P. 1992. Nonparametric estimation of nonstationary spatial covariance structure. J Am Stat Assoc 87:108–119.

Speizer FE, Samet JM. 1994. Air pollution and lung cancer. In: Epidemiology of Lung Cancer (Samet JM, ed) pp 131–150. Marcel Dekker, New York NY.

van der Lende R, Kok TJ, Reig RP, Quanjer PH, Schouten JP, Orie NG. 1981. Decreases in VC and $FEV_1$ with time: Indicators for the effect of smoking and air pollution. Bull Eur Physiopathol Respir 17:775–792.

Vedal S. 1997. Ambient particles and health: Lines that divide. J Air Waste Manage Assoc 47:551–581.

HEALTH
EFFECTS
INSTITUTE

# 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.

Although this document was produced with partial funding by the United States Environmental Protection 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.

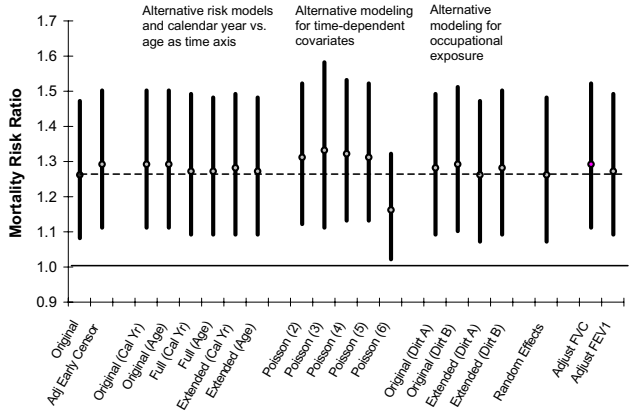



**Figure 1. Estimated risk ratios for mortality from all causes calculated for each increase of 18.6 μg/m$^3$ in $PM_{2.5}$ in the Six Cities Study.** Values reported in the original publication are represented by the dashed line; values (and 95% CIs) are shown for alternative models considered in the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

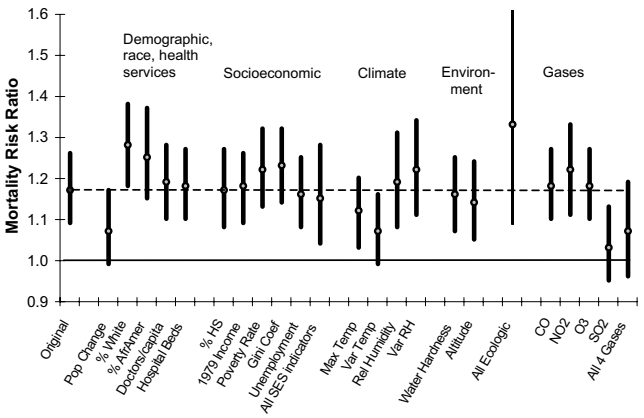



**Figure 3. Estimated risk ratios for mortality from all causes in the ACS Study after inclusion of possible confounders in the reanalyses.** Values reported in the original publication are represented by the dashed line; values (and 95% CIs) are shown for the Extended Model used in the reanalyses. Labels 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

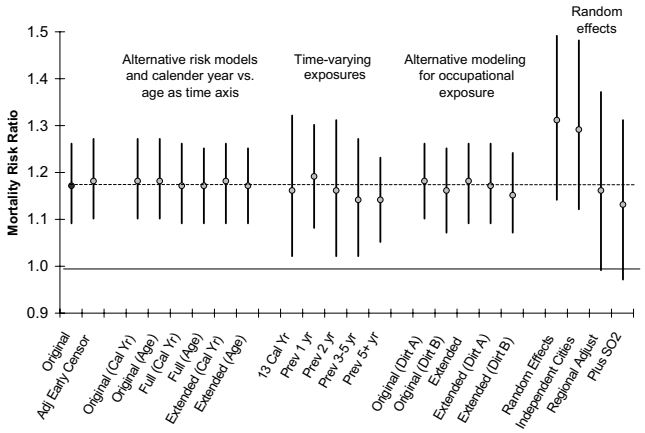



**Figure 2. Estimated risk ratios for mortality from all causes calculated for each increase of 24.5 μg/m$^3$ in $PM_{2.5}$ in the ACS Study.** Values reported in the original publication are represented by the dashed line; values (and 95% CIs) are shown for alternative models considered in the reanalyses.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

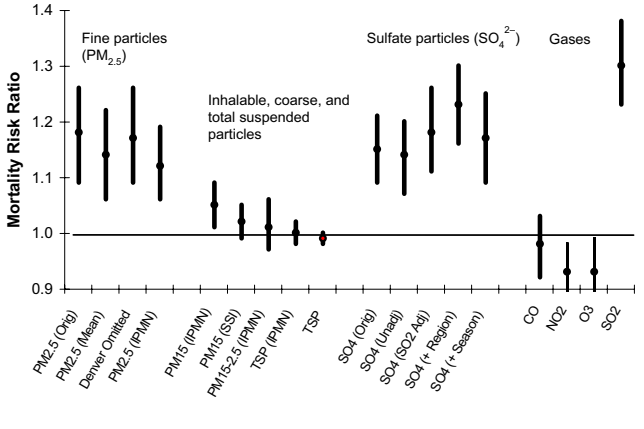



**Figure 4. Estimated risk ratios for mortality from all causes calculated for the original fine particle and sulfate data used in the ACS Study and for the alternative fine particle, sulfate, particulate matter, and gaseous pollutant data used in the reanalyses.**

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 $\mu$m.[13] Fine-particulate air pollution includes particles with an aerodynamic diameter equal to or below 2.5 $\mu$m. 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.

Supported in part by grants (ES-01108 and ES-00002) from the National Institute of Environmental Health Sciences, by cooperative agreements (CR-811650 and CR-818090) with the Environmental Protection Agency, and by a contract (RP-1001) with the Electric Power Research Institute.

Presented in part at the annual meeting of the American Thoracic Society, San Francisco, May 19, 1992, and at the Aerosols in Medicine Congress of the International Society for Aerosols in Medicine, Garmisch-Partenkirchen, Germany, April 1, 1993.

Reprinted from the *New England Journal of Medicine*
**329:**1753-1759 (December 9), 1993

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 $<2.5$ $\mu$m) and inhalable particles (aerodynamic diameter, $<15$ $\mu$m before 1984 and $<10$ $\mu$m 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 $\mu$g per cubic meter), fine particles (range, 11.0 to 29.6 $\mu$g per cubic meter), and sulfate particles (range, 4.8 to 12.8 $\mu$g 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,

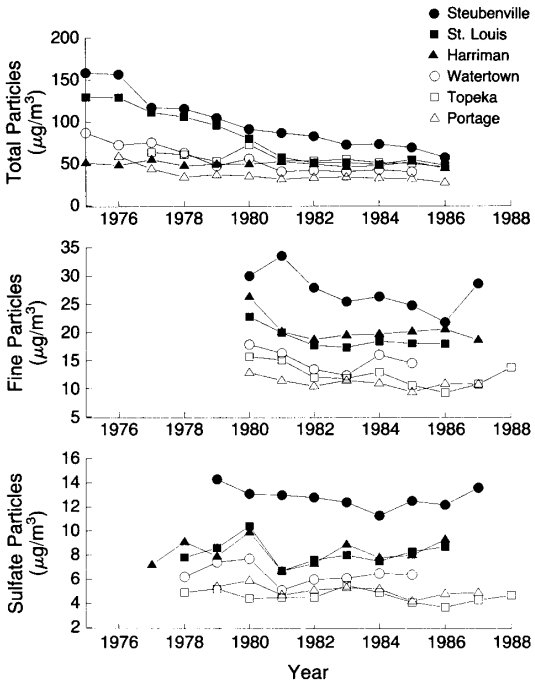



Figure 1. Annual Average Concentrations of Total Particles, Fine Particles, and Sulfate Particles in the Six Cities.

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-

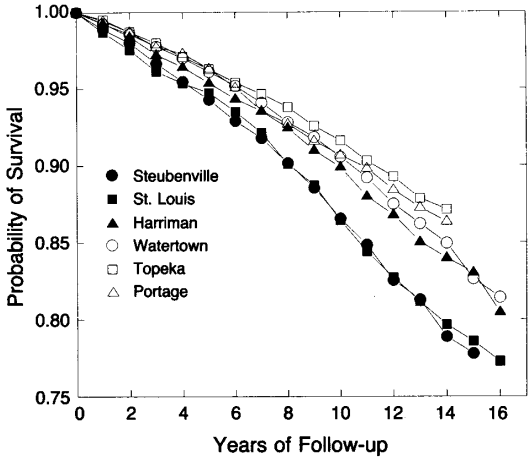



Figure 2. Crude Probability of Survival in the Six Cities, According to Years of Follow-up.

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.

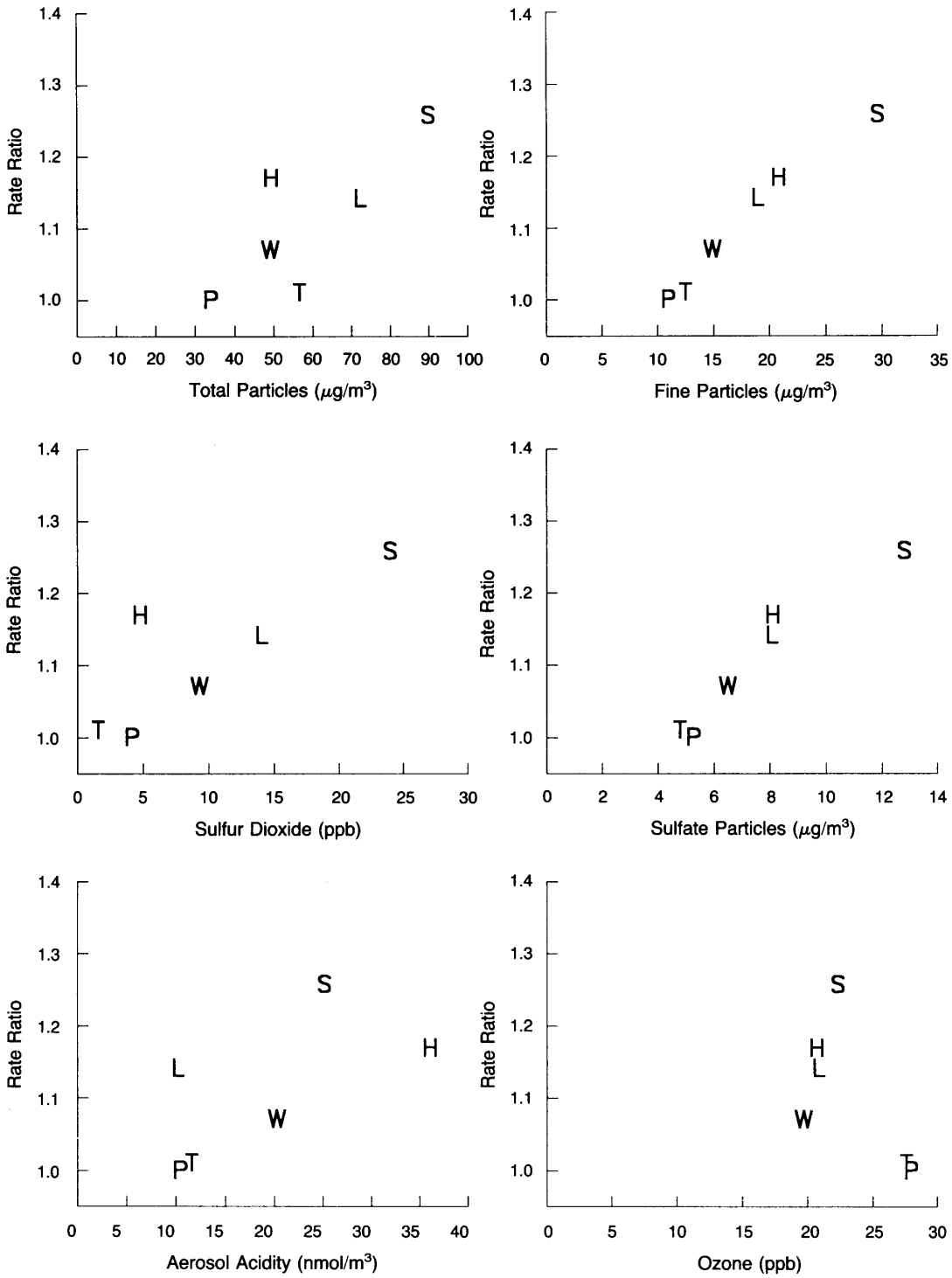



Figure 3. Estimated Adjusted Mortality-Rate Ratios and Pollution Levels in the Six Cities.
Mean values are shown for the measures of air pollution. P denotes Portage, Wisconsin; T Topeka, Kansas; W Watertown, Massachusetts; L St. Louis; H Harriman, Tennessee; and S Steubenville, Ohio.

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.

## References


1. Lave LB, Seskin EP. Air pollution and human health. Baltimore: Johns Hopkins University Press, 1977.
2. Evans JS, Tosteson T, Kinney PL. Cross-sectional mortality studies and air pollution risk assessment. Environ Int 1984;10:55-83.
3. Ozkaynak H, Thurston GD. Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. Risk Anal 1987;7:449-61.
4. Bobak M, Leon DA. Air pollution and infant mortality in the Czech Republic, 1986–88. Lancet 1992;340:1010-4.
5. Schwartz J, Marcus A. Mortality and air pollution in London: a time series analysis. Am J Epidemiol 1990;131:185-94.
6. Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. Am Rev Respir Dis 1992;145:600-4.
7. Kinney PL, Ozkaynak H. Associations of daily mortality and air pollution in Los Angeles County. Environ Res 1991;54:99-120.
8. Dockery DW, Schwartz J, Spengler JD. Air pollution and daily mortality: associations with particulates and acid aerosols. Environ Res 1992;59:362-73.
9. Schwartz J. Particulate air pollution and daily mortality in Detroit. Environ Res 1991;56:204-13.
10. Fairley D. The relationship of daily mortality to suspended particulates in Santa Clara County, 1980–1986. Environ Health Perspect 1990;89:159-68.
11. Pope CA III, Schwartz J, Ransom MR. Daily mortality and $PM_{10}$ pollution in Utah Valley. Arch Environ Health 1992;47:211-7.
12. Schwartz J, Dockery DW. Particulate air pollution and daily mortality in Steubenville, Ohio. Am J Epidemiol 1992;135:12-9.
13. Environmental Protection Agency. Revisions to the National Ambient Air Quality Standards for particulate matter. Fed Regist 1987;52:24634-69.
14. Miller FJ, Gardner DE, Graham JA, Lee RE Jr, Wilson WE, Bachmann JD. Size considerations for establishing a standard for inhalable particles. J Air Poll Control Assoc 1979;29:610-5.
15. Ferris BG Jr, Speizer FE, Spengler JD, et al. Effects of sulfur oxides and respirable particles on human health: methodology and demography of populations in study. Am Rev Respir Dis 1979;120:767-79.
16. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837-9.
17. Koutrakis P, Wolfson JM, Spengler JD. An improved method for measuring aerosol strong acidity: results from a nine-month study in St. Louis, Missouri and Kingston, Tennessee. Atmos Environ 1988;22:157-62.
18. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall, 1984.
19. Fleming TR, Harrington DP. Counting processes and survival analysis. New York: John Wiley, 1991.
20. SAS/STAT user's guide, version 6. 4th ed. Cary, N.C.: SAS Institute, 1989.
21. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.
22. SAS technical report P-217, SAS/STAT software: the PHREG procedure, version 6. Cary, N.C.: SAS Institute, 1991.
23. Wilson R, Colome SD, Spengler JD, Wilson DG. Health effects of fossil fuel burning: assessment and mitigation. Cambridge, Mass.: Ballinger, 1980.
24. Dockery DW, Spengler JD. Indoor–outdoor relationships of respirable sulfates and particles. Atmos Environ 1981;15:335-43.
25. Suh HH, Spengler JD, Koutrakis P. Personal exposures to acid aerosols and ammonia. Environ Sci Tech 1992;26:2507-17.
26. Wallace LA, Pellizzari E, Sheldon L, et al. The TEAM study of inhalable particles ($PM_{10}$): study design, sampler performance, and preliminary results. Presented at the Annual Meeting of the Air & Waste Management Association, Vancouver, British Columbia, June 16–21, 1991. (Paper 91-171.3.)
27. Braun-Fahrlander C, Ackermann-Liebrich U, Schwartz J, Gnehm HP, Rutishauser M, Wanner HU. Air pollution and respiratory symptoms in preschool children. Am Rev Respir Dis 1992;145:42-7.
28. Dockery DW, Ware JH, Ferris BG Jr, Speizer FE, Cook NR, Herman SM. Change in pulmonary function in children associated with air pollution episodes. J Air Pollut Control Assoc 1982;32:937-42.
29. Ostro BD, Lipsett MJ, Wiener MB, Selner JC. Asthmatic responses to airborne acid aerosols. Am J Public Health 1991;81:694-702.
30. Pope CA III, Dockery DW. Acute health effects of $PM_{10}$ pollution on symptomatic and asymptomatic children. Am Rev Respir Dis 1992;145:1123-8.
31. Pope CA III, Dockery DW, Spengler JD, Raizenne ME. Respiratory health and $PM_{10}$ pollution: a daily time series analysis. Am Rev Respir Dis 1991;144:668-74.
32. Chestnut LG, Schwartz J, Savitz DA, Burchfiel CM. Pulmonary function and ambient particulate matter: epidemiological evidence from NHANES I. Arch Environ Health 1991;46:135-44.
33. Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, Ferris BG Jr. Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis 1989;139:587-94.
34. Schwartz J. Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. Environ Res 1989;50:309-21.
35. Ware JH, Ferris BG Jr, Dockery DW, Spengler JD, Stram DO, Speizer FE. Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am Rev Respir Dis 1986;133:834-42.
36. Xu XP, Dockery DW, Wang LH. Effects of air pollution on adult pulmonary function. Arch Environ Health 1991;46:198-206.
37. Bates DV, Sizto R. Air pollution and hospital admissions in southern Ontario: the acid summer haze effect. Environ Res 1987;43:317-31.
38. Bates DV, Baker-Anderson M, Sizto R. Asthma attack periodicity: a study of hospital emergency visits in Vancouver. Environ Res 1990;51:51-70.
39. Ponka A. Asthma and low level air pollution in Helsinki. Arch Environ Health 1991;46:262-70.
40. Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am J Public Health 1989;79:623-8.
41. *Idem*. Respiratory hospital admissions associated with $PM_{10}$ pollution in Utah, Salt Lake, and Cache Valleys. Arch Environ Health 1991;46:90-7.
42. Euler GL, Abbey DE, Magie AR, Hodgkin JE. Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total suspended particulates and sulfur dioxide in California Seventh-Day Adventist residents. Arch Environ Health 1987;42:213-22.
43. Ostro BD. Associations between morbidity and alternative measures of particulate matter. Risk Anal 1990;10:421-7.
44. Ransom MR, Pope CA III. Elementary school absences and $PM_{10}$ pollution in Utah Valley. Environ Res 1992;58:204-19.

# 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

*(Received in original form June 3, 1994 and in revised form October 5, 1994)*

Supported in part by National Institute of Environmental Health Sciences Grants ES-00002 and ES-01108 and by Environmental Protection Agency Cooperative Agreements CR-811650 and CR-818090.

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

Am J Respir Crit Care Med Vol 151. pp 669–674, 1995

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.

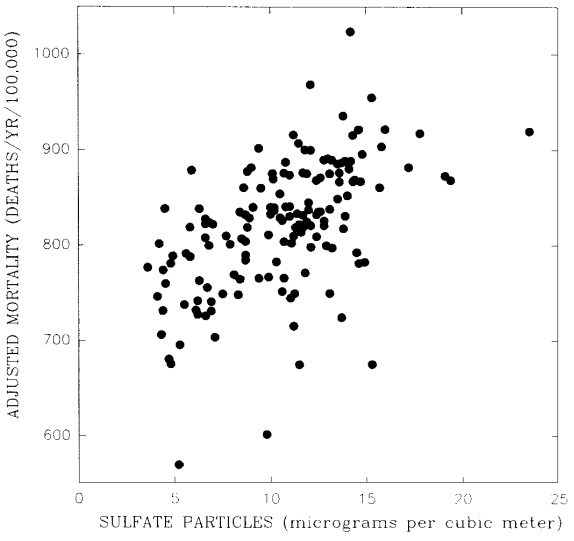



*Figure 1.* Age-, sex-, and race-adjusted population-based mortality rates for 1980 plotted against mean sulfate air pollution levels for 1980. Data from metropolitan areas that correspond approximately to areas used in prospective cohort analysis.

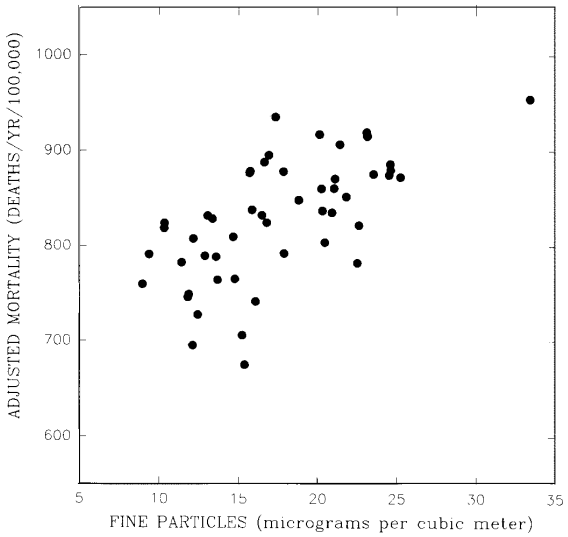



*Figure 2.* Age-, sex-, and race-adjusted population-based mortality rates for 1980 plotted against mean fine particulate air pollution levels for 1979 to 1983. Data from metropolitan areas that correspond approximately to areas used in prospective cohort analysis.

## 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.

## References


1. Lipfert, F. W. 1994. Air Pollution and Community Health: A Critical Review and Data Sourcebook. Van Nostrand Reinhold, New York.
2. Schwartz, J., and D. W. Dockery. 1992. Increased mortality in Philadelphia associated with daily air pollution concentrations. *Am. Rev. Respir. Dis.* 145:600–604.
3. Pope, C. A., III, J. Schwartz, and M. R. Ransom. 1992. Daily mortality and $PM_{10}$ pollution in Utah Valley. *Arch. Environ. Health* 47:211–217.
4. Schwartz, J. 1994. Air pollution and daily mortality: a review and meta-analysis. *Environ. Res.* 64:36–52.
5. Ostro, B. D. 1993. The association of air pollution and mortality: examining the case for inference. *Arch. Environ. Health* 48:336–342.
6. Dockery, D. W., and C. A. Pope, III. 1994. Acute respiratory effects of particulate air pollution. *Annu. Rev. Public Health* 15:107–132.
7. Pope, C. A., III, and R. E. Kanner. 1993. Acute effects of $PM_{10}$ pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 147:1336–1340.
8. Pope, C. A., III, and D. W. Dockery. 1992. Acute health effects of $PM_{10}$ pollution on symptomatic and asymptomatic children. *Am. Rev. Respir. Dis.* 145:1123–1128.
9. Hoek, G., and B. Brunekreef. 1993. Acute effects of a winter air pollution episode on pulmonary function and respiratory symptoms of children. *Arch. Environ. Health* 48:328–335.
10. Braun-Fahrlander, C., U. Ackermann-Liebrich, J. Schwartz, H. P. Gnehm,

M. Rutishauser, and H. U. Wanner. 1992. Air pollution and respiratory symptoms in preschool children. *Am. Rev. Respir. Dis.* 145:42–47.
11. Dockery, D. W., F. E. Speizer, D. O. Stram, J. H. Ware, J. D. Spengler, and B. G. Ferris, Jr. 1989. Effects of inhalable particles on respiratory health of children. *Am. Rev. Respir. Dis.* 139:587–594.
12. Pope, C. A., III. 1991. Respiratory hospital admissions associated with $PM_{10}$ pollution in Utah, Salt Lake, and Cache Valleys. *Arch. Environ. Health* 46:90–97.
13. Thurston, G. D., K. Ito, P. L. Kinney, and M. Lippmann. 1992. A multi-year study of air pollution and respiratory hospital admissions in three New York state metropolitan areas: results for 1988 and 1989 summers. *J. Expos. Anal. Environ. Epidemiol.* 2:429–450.
14. Ostro, B. D. 1990. Associations between morbidity and alternative measures of particulate matter. *Risk Analysis* 10:421–427.
15. Ransom, M. R., and C. A. Pope, III. 1992. Elementary school absences and $PM_{10}$ pollution in Utah Valley. *Environ. Res.* 58:204–219.
16. Lave, L. B., and E. P. Seskin. 1970. Air pollution and human health. *Science* 169:723–733.
17. Lipfert, F. W., R. G. Malone, M. L. Daum, N. R. Mendell, and C. C. Yang. 1988, April. A Statistical Study of the Macroepidemiology of Air Pollution and Total Mortality. Brookhaven National Laboratory, Upton, NY. Report No. BNL 52122.
18. Ozkaynak, H., and G. D. Thurston. 1987. Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. *Risk Analysis* 7:449–461.
19. Bobak, M., and D. A. Leon. 1992. Air pollution and infant mortality in the Czech Republic, 1986–88. *Lancet* 340:1010–1014.
20. Dockery, D. W., C. A. Pope, III, X. Xu, *et al.* 1993. An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med.* 329:1753–1759.
21. Thun, M. J., M. M. Namboodiri, and C. W. Heath, Jr. 1991. Aspirin use and reduced risk of fatal colon cancer. *N. Engl. J. Med.* 325:1593–1596.
22. Calle, E. E., and D. D. Terrell. 1993. Utility of the National Death Index for ascertainment of mortality among Cancer Prevention Study II participants. *Am. J. Epidemiol.* 137:235–241.
23. World Health Organization. 1977. International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Vol. 1. 9th revision. WHO, Geneva.
24. U.S. Postal Service. 1989. 1989 National Five Digit Zip Code & Post Office Directory. National Information Data Center, Washington, DC.
25. Fleming, T. R., and D. P. Harrington. 1991. Counting Processes and Survival Analysis. John Wiley, New York.
26. SAS Technical Report P-217. 1991. SAS/STAT Software: The PHREG Procedure. Version 6. SAS Institute Inc., Cary, NC.
27. National Center for Health Statistics. 1985. Vital Statistics of the United States, 1980, Volume II, Annual Mortality, Part B. U.S. Government Printing Office, Washington, DC.
28. U.S. Bureau of the Census. 1983. 1980 Census of Population. U.S. Department of Commerce, Washington, DC.
29. Wilson, R., S. D. Colome, J. D. Spengler, and D. G. Wilson. 1980. Health Effects of Fossil Fuel Burning. Ballinger, Cambridge, MA.
30. Dockery, D. W., and J. D. Spengler. 1981. Indoor-outdoor relationships of respirable sulfates and particulates. *Atmos. Environ.* 15:335–343.
31. Suh, H. H., J. D. Spengler, and P. Koutrakis. 1992. Personal exposures to acid aerosols and ammonia. *Environ. Sci. Tech.* 26:2507–2517.
32. Wallace, L. A., E. Pellizzari, L. Sheldon, *et al.* 1991. The TEAM study of inhalable particles ($PM_{10}$): study design, sampler performance, and preliminary results. Paper 91-171.3, 84th annual meeting of the Air & Waste Management Association, June 16–21, 1991.
33. Kircher, T., J. Nelson, and H. Burdo. 1985. The autopsy as a measure of accuracy of the death certificate. *N. Engl. J. Med.* 313:1263–1269.
34. Marcus, E. B., A. S. Buist, C. J. Maclean, and K. Yano. 1989. Twenty-year trends in mortality from chronic obstructive pulmonary disease: the Honolulu heart program. *Am. Rev. Respir. Dis.* 140:S64–S68.
35. Camilli, A. E., D. R. Robbins, and M. D. Lebowitz. 1991. Death certificate reporting of confirmed airways obstructive disease. *Am. J. Epidemiol.* 133:795–800.

# RELATED HEI PUBLICATIONS

## PARTICULATE MATTER

| Report Number | Title | Principal Investigator | Publication Date* |
|---|---|---|---|
| **Research Reports** | | | |
| 75 | Ozone Exposure and Daily Mortality in Mexico City: A Time-Series Analysis | DP Loomis | 1996 |
| 81 | Methods Development for Epidemiologic Investigations of the Health Effects of Prolonged Ozone Exposure | IB Tager | 1998 |
| 82 | Acute Effects of Ambient Ozone on Asthmatic, Wheezy, and Healthy Children | JM Peters | 1998 |
| 83 | Daily Changes in Oxygen Saturation and Pulse Rate Associated with Particulate Air Pollution and Barometric Pressure | DW Dockery | 1999 |
| 86 | Statistical Methods for Epidemiologic Studies of the Health Effects of Air Pollution | W Navidi | 1999 |
| 91 | Mechanisms of Morbidity and Mortality from Exposure to Ambient Air Particles | JJ Godleski | 2000 |
| 93 | Effects of Concentrated Ambient Particles in Rats and Hamsters: An Exploratory Study | T Gordon | 2000 |
| 94 | The National Morbidity, Mortality, and Air Pollution Study<br>*Part I.* Methods and Methodologic Issues<br>*Part II.* Morbidity, Mortality, and Air Pollution in the United States | JM Samet | 2000 |
| 95 | Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations | M Lippmann | 2000 |
| 96 | Acute Pulmonary Effects of Ultrafine Particles in Rats and Mice | G Oberdörster | 2000 |
| … | Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany<br>*Part I.* Role of Particle Number and Particle Mass (in Press) | H-E Wichmann | 2000 |
| … | Identifying Subgroups of the General Population that May Be Susceptible to Short-Term Increases in Particulate Air Pollution: A Time-Series Study in Montreal, Quebec (in Press) | MS Goldberg | 2000 |
| … | A Case-Crossover Analysis of Fine Particulate Matter Air Pollution and Out-of-Hospital Sudden Cardiac Arrest (in Press) | H Checkoway | 2000 |
| **Special Reports** | | | |
| | Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects | | 1995 |
| | Particulate Air Pollution and Daily Mortality: The Phase I Report of the Particle Epidemiology Evaluation Project | | |
| | *Phase I.A.* Replication and Validation of Selected Studies | | 1995 |
| | *Phase I.B.* Analyses of the Effects of Weather and Multiple Air Pollutants | | 1997 |
| **HEI Communications** | | | |
| 5 | Formation and Characterization of Particles: Report of the 1996 HEI Workshop | | 1997 |
| 8 | The Health Effects of Fine Particles: Key Questions and the 2003 Review | | 1999 |
| **HEI Program Summaries** | | | |
| | Research on Particulate Matter | | 1999 |

** Reports published since 1990.*
*Copies of these reports can be obtained by writing or calling the Health Effects Institute, 955 Massachusetts Avenue, Cambridge MA 02139. Phone (617) 876-6700 FAX (617) 876-6709 E-mail pubs@healtheffects.org www.healtheffects.org*

HEALTH
EFFECTS
INSTITUTE

955 Massachusetts Avenue
Cambridge MA 02139 USA
+1-617-876-6700

**SPECIAL REPORT**

July 2000