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OVERVIEW OF THE REANALYSIS OF THE HARVARD SIX CITIES STUDY AND AMERICAN CANCER SOCIETY STUDY OF PARTICULATE AIR POLLUTION AND MORTALITY

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This article provides an overview of the Reanalysis Study of the Harvard Six Cities and the American Cancer Society (ACS) studies of particulate air pollution and mortality. The previous findings of the studies have been subject to debate. In response, a reanalysis team, comprised of

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Canadian and Amercian researchers, was invited to participate in an independent reanalysis project to address the concerns. Phase I of the reanalysis involved the design of data audits to determine whether each study conformed to the consistency and accuracy of their data. Phase II of the reanalysis involved conducting a series of comprehensive analyses using alternative statistical methods. Alternative models were also used to identify covariates that may confound or modify the association of particulate air pollution as well as identify sensitive population subgroups. The audit demonstrated that the data in the original analyses were of high quality, as were the risk estimates reported by the original investigators. The sensitivity analysis illustrated that the mortality risk estimates reported in both studies were found to be robust against alternative Cox models. Detailed investigation of the covariate effects found a significant modifying effect of education and a relative risk of mortality associated with fine particles and declining education levels. The study team applied spatial analytic methods to the ACS data, resulting in various levels of spatial autocorrelations supporting the reported association for fine particles mortality of the original investigators as well as demonstrating a significant association between sulfur dioxide and mortality. Collectively, our reanalysis suggest that mortality may be attributable to more than one component of the complex mixture of ambient air pollutants for U.S. urban areas.

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 United States (Ciocco & 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 emission-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 United States 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 (U.S. Environmental Protection Agency, 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 (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 & 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 & Brunekreef, 1993); (5) decrements in lung function (Hoek & Brunekreef, 1994); (6) restricted activities for adult workers; (7) increased absences of children from elementary school (Ransom & 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-h air quality standards for fine particles.

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 6000 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 the effects of these three pollutants. None of the pollutants demonstrated an association with cardiopulmonary mortality in either males or females.

The other two 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.

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	3,950,963[e]	2,112,239[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)
Sulfates[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 concentration for the most-polluted city and the least-polluted city with range in parentheses; given in $\mu g/m^3$.

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 U.S. 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 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 (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 yr 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 was restricted to a subcohort of 8111 Caucasian subjects (see Table 1 for a summary of population characteristics) who had been between 25 and 74 yr 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); 1430 deaths were uncovered, for which 1401 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, the investigators 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-yr 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.

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 United States (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 U.S. states, the District of Columbia, and Puerto Rico. Subjects were individuals 30 yr of age or older who were living in a household with at least one person who was 45 yr 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 U.S. 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 United States 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 U.S. 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 U.S. EPA 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 from the U.S. EPA high-volume samplers in metropolitan areas that did not meet the National Ambient Air Quality Standard. The arithmetic average of 24-h 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 the three first digits of their 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-yr 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 (e.g., sedentary lifestyle, active or passive cigarette smoke exposure) or ecologic risk factors (e.g., 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 (Lipfert & Wyzga, 1995; Gamble, 1998).

Because the U.S. 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 U.S. Congress, and other scientists urged the U.S. EPA, which 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 (HEI) 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.
- 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; 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 have been 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 the 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 yr 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 United States, 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 of the ecologic covariates that the reanalysis team considered in reanalyzing the ACS Study data, including mortality and particulate air pollution, demonstrated clear spatial patterns across the United States; 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.

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; 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 2 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 the 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 was 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; 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 original 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 (dichot) 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 sampled, 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 U.S. Environmental Protection Agency

(EPA) laboratory and records were not available at HSPH. The U.S. EPA laboratory responsible for data reduction in those study years, however, was the leading practitioner of these methods at that time. For the audited data set (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 data set 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 existed. 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 re-derive 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, the lack of contemporary documentation about inclusion and exclusion criteria and the 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, some minor discrepancies were noted. These included trivial differences in risk estimates owing to the order in which the reanalysis calculations were completed. The reanalysis team considered such differences to be immaterial. Also, 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 of 250 questionnaires and 250 death certificates were selected. 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 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 7706 female former smokers and 5421 female deaths occurring between 1 September 1988 and 31 December 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, however, had been 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, two-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 four-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 its own statistics for the metropolitan areas in this study using the U.S. 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 that 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 7706 female former smokers who met the selection criteria had been excluded from the original analysis, as discussed previously. In addition, we found that 5421 female deaths occurring between 1 September 1988 and 31 December 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 had 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 yr 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-yr 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 already 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), body mass index (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 Table 2 (Six Cities Study) and Table 3 (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

TABLE 2. Relative risk (RR) of mortality for the Six Cities Study associated with an increase in $PM_{2.5}$ of 18.6 μg/m^3, by time axis used in the survival model, underlying cause of death and covariate model specification. (95% confidence intervals given in parentheses, and percentage of deaths given in square brackets.)

	Time Axis	
Model	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 [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 [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 [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)[a]	1.42 (0.84–2.42)
Extended	1.29 (0.75,2.22)[a]	1.45 (0.85–2.47)
	Other Cancers [20%]	
Base	1.04 (0.73–1.47)	1.04 (0.73–1.47)
Original	1.02 (0.72–1.44)	1.02 (0.72–1.45)
Full	1.09 (0.77–1.54)	1.09 (0.77–1.55)
Final	1.08 (0.76–1.53)	1.08 (0.76–1.54)
	Other Causes [18%]	
Base	1.14 (0.77–1.67)	1.15 (0.78–1.70)
Original	1.10 (0.75–1.62)	1.12 (0.76–1.65)
Full	1.08 (0.73–1.59)	1.10 (0.74–1.63)
Extended	1.07 (0.73–1.58)	1.10 (0.74–1.62)

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

TABLE 3. Relative risk (RR) of mortality for the American Cancer Society Study due to selected causes associated with increases in sulfates (SO_4^{-2}) of 19.9 μg/m^3 and fine particulate matter ($PM_{2.5}$) of 24.4 μg/m^3 by covariate model specification, time axis and cause of death. (95% confidence intervals given in parentheses; percentage of deaths given in square brackets and is the same for $PM_{2.5}$ and SO_4^{-2})

	Time Axis			
	Calendar Year		Age	
Model	$PM_{2.5}$	SO_4^{-2}	$PM_{2.5}$	SO_4^{-2}
		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)	1.17 (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 (1.09–1.21)	1.17 (1.09–1.25)	1.14 (1.08–1.20)
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 [50%]		
Base	1.41 (1.27–1.56)	1.39 (1.28–1.50)	1.41 (1.27–1.60)	1.28 (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 [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)	1.35 (1.24–1.46)	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 [7%]		
Base	1.07 (0.80–1.42)	0.94 (0.75–1.17)	1.09 (0.82–1.45)	0.95 (0.76–1.18)
Original	0.98 (0.74–1.30)	0.84 (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 (0.74–1.32)	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	1.03 (0.81–1.31)	1.36 (1.13–1.66)	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 (1.02–1.37)	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 (0.81–1.07)	1.05 (0.88–1.26)	0.92 (0.80–1.06)
Original	1.01 (0.85–1.22)	0.88 (0.76–1.02)	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)

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 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 Table 4, 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 U.S. 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.

TABLE 4. 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)	1.35 (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)
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 (0.26–12.25)
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.

For both studies, 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. 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 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 on 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 yr 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 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. The original investigators had relied on air pollution data collected in 1980, whereas 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 U.S. EPA. The original investigators had reported fine particle data for 50 of the 154 cities they considered in the ACS Study, whereas 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 risks 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 Table 5. 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 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 artifact 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 ($PM_{152.5}$), or total suspended particles (TSP) in the approximately 60 cities for which such data were available in the IPMN. No associations with TSP were found in the 156 cities for which these data were available from AIRS.

Ecological Covariates

The reanalysis team also considered other unmeasured covariates at the metropolitan level that might affect the relation between fine particle or sulfate

TABLE 5. Relative risk for all cause mortality, cardiopulmonary and lung cancer mortality evaluated at 24.4 μg/m^3 for particulate matter measures and 19.9 μg/m^3 for sulfate measures, for the American Cancer Society Study by alternate measures of particulate-related pollution. (95% confidence intervals given in parenthesis)

		Underlying Cause of Death		
Pollutant[a]	Number of Cities	All Causes	Cardiopulmonary	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 (0.86–1.36)
$PM_{2.5}$ (DC)	63	1.12 (1.06–1.19)	1.26 (1.16–1.38)	1.08 (0.88–1.32)
SO_4 (OI)	151	1.15 (1.09–1.21)	1.25 (1.10–1.36)	1.33 (1.10–1.61)
SO_4 (cb-unadj)	144	1.14 (1.07–1.20)	1.24 (1.15–1.35)	1.33 (1.09–1.61)
SO_4 (cb-adj region)	144	1.23 (1.16–1.30)	1.34 (1.23–1.45)	1.25 (1.03–1.52)

[a] Based on Inhalable Particulate Network, 1979–1983: $PM_{2.5}$(OI, MD) – median fine particle mass from Original Investigators; $PM_{2.5}$(DC, MD) – median fine particulate mass from $PM_{2.5}$ (DC) (fine fraction). All values are in means unless indicated by MD (median). Based on National Aerometric Database, 1980–1981: SO_4(OI) – sulfates from Original Investigators; SO_4(unadj) – sulfates from both Inhalable Particulate Network and National Aerometric Database with no adjustment for SO_2 artifact; SO_4(adj) – sulfates from both Inhalable Particulate Network and National Aerometric Database with adjustment for SO_2 artifact.

air pollution and mortality. This examination was restricted to the ACS Study because the Six Cities Study involved, at most, five degrees of freedom 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. 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 (Table 6). 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 Table 6. 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 ($p < .05$).

TABLE 6. Ecologic Covariates Used in the Sensitivity Analysis of the American Cancer Society Study

Ecologic Covariate	Number of Cities		Description	Relative Risk for All-Cause Mortality in the Sulfate Cohort
	Sulfates	Fine Particles		
Demographic Data				
Population Change	139	48	Percent net change in number of residents between 1980 and 1986.	0.85 (0.81–0.89)
Race				
Whites	151	50	Percent of persons in 1980 who classify themselves as Caucasian.	1.02 (0.98–1.06)
African Americans	151	50	Percent of persons who classify themselves as African American (1980)	1.01 (0.96–1.06)
Socio-economic Data				
Income	151	50	Per capita income for 1979.	0.93 (0.88–0.97)
Unemployment	151	50	Percent of total civilian labor force who were unemployed in 1986.	1.12 (1.06–1.19)
Poverty	151	50	Percent of individuals living below the poverty level in 1979.	0.95 (0.89, 1.01)
Education	151	50	Percentage of persons 25 years of age or older who indicated that they had completed 4 years of high school or some years of college.	0.91 (0.86–0.96)
Income disparity	151	50	Gini coefficient, based on income distribution in 1979.	0.88 (0.84, 0.93)
Health Services Data				
Physicians	138	48	Number of professionally active, non-federal physicians with known addresses per 100,000 resident population as of July 1, 1985.	0.95 (0.89–1.01)
Hospital beds	139	48	Number of hospital beds per 100,000 resident population as of July 1, 1985.	1.13 (1.06–1.21)
Climate Data				
Temperature	135	46	Average maximum daily temperature in Fahrenheit for the years 1980 to 1989 inclusive.	0.88 (0.85–0.92)
Temperature variation	135	46	Average monthly variance in maximum daily temperature in Fahrenheit for the years 1980 to 1989 inclusive.	1.18 (1.11–1.24)
Ecological Covariate				
Relative humidity	95	37	Average minimum daily relative humidity in whole percent for the years 1984 to 1989 inclusive was averaged by month.	1.05 (0.99–1.12)
Variation relative humidity	95	37	Average monthly variance in minimum daily relative humidity for the years 1984 to 1989 inclusive.	0.96 (0.90–1.02)

TABLE 6. Ecologic Covariates Used in the Sensitivity Analysis of the American Cancer Society Study (*Continued*)

Physical Environment				
Data				
Altitude	110	38	Measured as metres above sea-level.	1.05 (0.99–1.12)
Water hardness	109	49	Concentration of $CaCO_3$ (ppm) in drinking water, ca. 1970.	1.08 (1.02–1.13)
Gaseous				
Co-pollutants				
Carbon monoxide	107	44	All gaseous co-pollutants were	0.98 (0.92–1.03)
Nitrogen dioxide	74	33	measured as annual average of	0.93 (0.87–0.99)
Ozone	117	45	daily average concentrations for	0.93 (0.87–0.99)
Sulfur dioxide	113	38	1980 from residential, commercial or mobile monitors, except for ozone in which daily one-hour maximum concentrations were used	1.30 (1.23–1.38)

However, income disparity among the population and nitrogen dioxide levels was 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

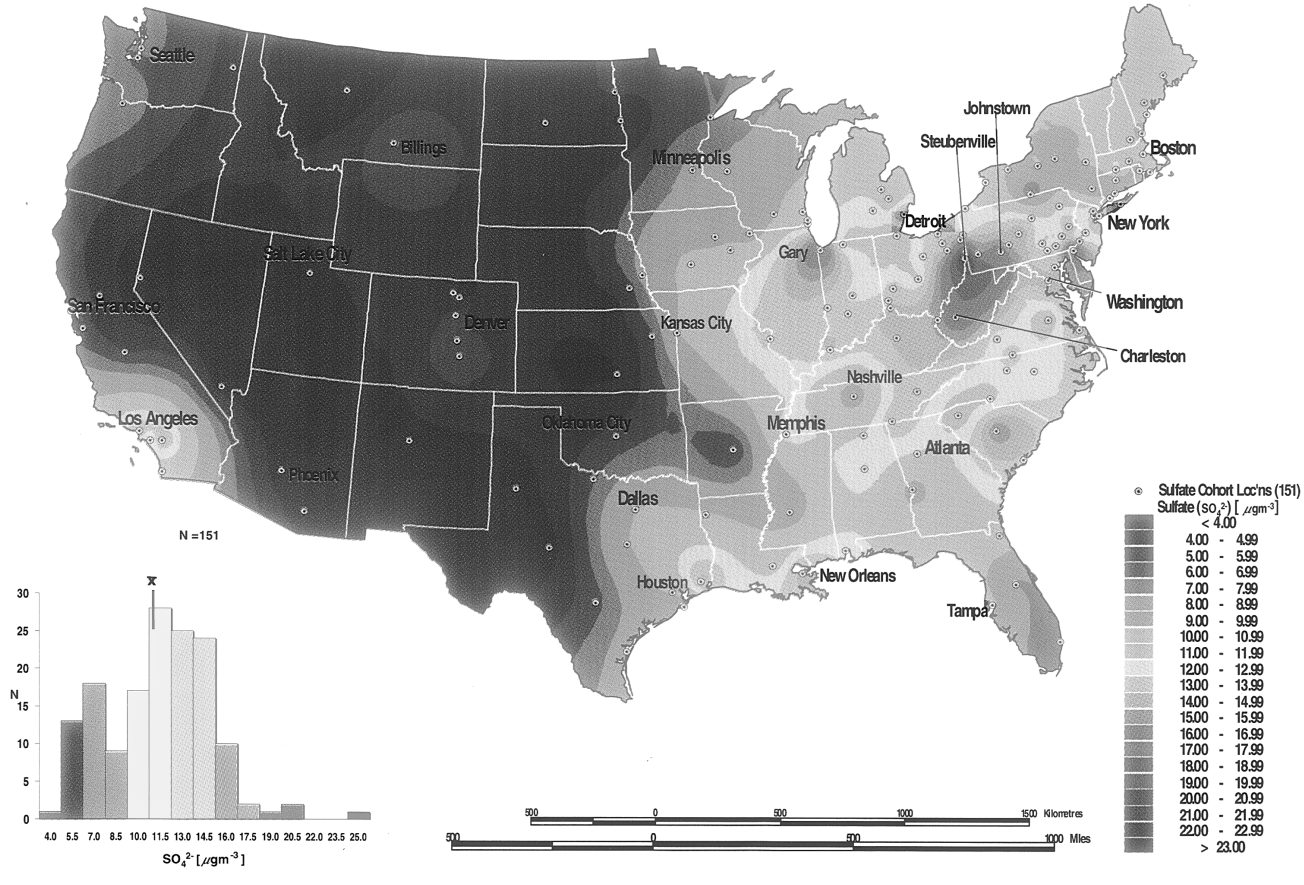

FIGURE 1. Spatial distribution of sulfate.

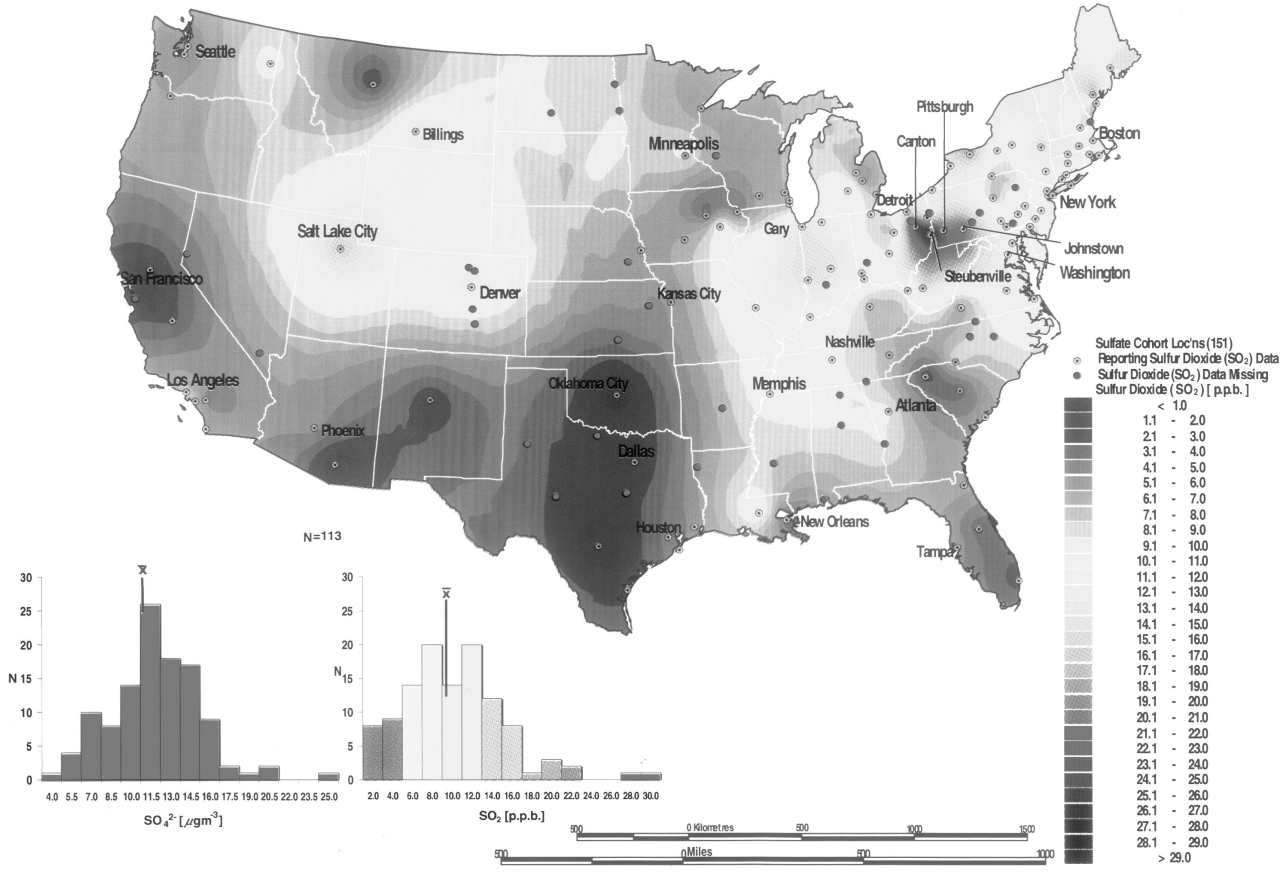

FIGURE 2. Spatial distribution of sulfur dioxide.

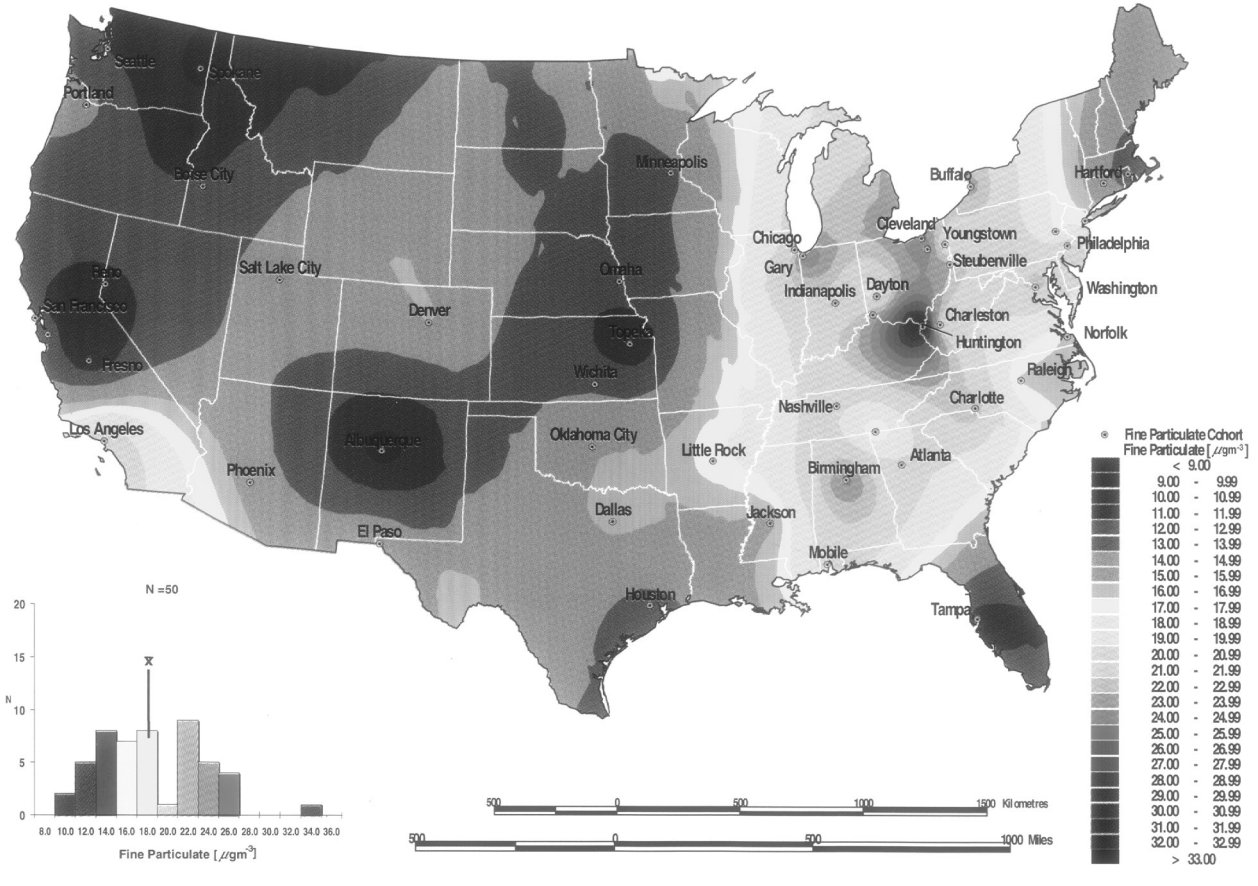

FIGURE 3. Spatial distribution of fine particles.

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 autocorrelated. Second, although we adjusted for 20 different ecologic covariates, spatial autocorrelation may be present as a result of some missing, unmeasured variable.

Spatial Analysis Models

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 Figure 1 and Figure 2, respectively. Note that the majority of the cities fall in the eastern United States, 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 (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 (Table 7).

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, 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

TABLE 7. Impact of Selected Ecologic Covariates on the Realitve 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 Filtering[c]	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 (1.05–1.49)	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)

TABLE 7. Impact of Selected Ecologic Covariates on the Realitve 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] (*Continued*)

	Sulfate				Fine Particles		
		Random Effects				Random Effects	
Ecologic Covariate[b]	Independent Observations	Independent Cities	Regional Adjustment	Spatial Filtering[c]	Independent Observations	Independent Cities	Regional Adjustment
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 HEI, 2000.

[c] Used Filtered Both Sides Model.

[d] See Tables 40 and 41 for sulfates; and Tables 46 and 47 for fine particles in the Health Effects Institute (HEI) Special Report entitled "Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality" (Krewski et al., 2000).

[e] See Tables 42 and 43 for sulfates, and Tables 48 and 49 for fine particles in the HEI Special Report (Krewski et al., 2000).

[f] See Tables 44 and 45 of the HEI Special Report (Krewski et al., 2000).

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.

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 United States developed for use in the 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 Table 7 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 Table 7. 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 Table 7). 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.

DISCUSSION

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 U.S. 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 United States 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 reanalysis project through the use of alternative air pollution data derived from original sources, described in Part II of the original 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.

CONCLUSIONS

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

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The present report provides an overview of the full set of analyses conducted by the reanalysis team. A more detailed report is available online at http:/www.healtheffects.org. Hard copies can also be obtained by writing to Dr. Jane Warren, Director of Research, Health Effects Institute, 955 Massachusetts Avenue, Cambridge, MA 02139, USA.

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.

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 methodological 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.

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