

## MORTALITY AND LONG-TERM EXPOSURE TO AMBIENT AIR POLLUTION: ONGOING ANALYSES BASED ON THE AMERICAN CANCER SOCIETY COHORT

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*This article provides an overview of previous analysis and reanalysis of the American Cancer Society (ACS) cohort, along with an indication of current ongoing analyses of the cohort with additional follow-up information through to 2000. Results of the first analysis conducted by Pope et al. (1995) showed that higher average sulfate levels were associated with increased mortality, particularly from cardiopulmonary disease. A reanalysis of the ACS cohort, undertaken by Krewski et al. (2000), found the original risk estimates for fine-particle and sulfate air pollution to be highly robust against alternative statistical techniques and spatial modeling approaches. A detailed investigation of covariate effects found a significant modifying effect of education with risk of mortality associated with fine particles declining with increasing educational attainment. Pope et al. (2002) subsequently reported results of a subsequent study using an additional 10 yr of follow-up of the ACS cohort. This updated analysis included gaseous copollutant and new fine-particle measurements, more comprehensive information on occupational exposures, dietary variables, and the most recent developments in statistical modeling integrating random effects and nonparametric spatial smoothing into the Cox proportional hazards model. Robust associations between ambient fine particulate air pollution and elevated risks of cardiopulmonary and lung cancer mortality were clearly evident, providing the strongest evidence to date that long-term exposure to fine particles is an important health risk. Current ongoing analysis using the extended follow-up information will explore the role of ecologic, economic, and, demographic covariates in the particulate air pollution and mortality*

The reanalysis of the American Cancer Society Study of the association between particulate air pollution and mortality is supported through a contract with the Health Effects Institute, a nonprofit organization in Cambridge, MA, established to conduct independent research on health issues of concern to both federal government and industry in the United States. The reanalysis team is coordinated by the R. Samuel McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa where the first author (D. Krewski) holds the NSERC/SSHRC/McLaughlin Chair.

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association. This analysis will also provide insight into the role of spatial autocorrelation at multiple geographic scales, and whether critical instances in time of exposure to fine particles influence the risk of mortality from cardiopulmonary and lung cancer. Information on the influence of covariates at multiple scales and of critical exposure time windows can assist policymakers in establishing timelines for regulatory interventions that maximize population health benefits.

In 1997, the U.S. Environmental Protection Agency (EPA) promulgated the first national ambient air quality objectives for fine particulate matter (PM<sub>2.5</sub>) less than 2.5  $\mu\text{m}$  in aerodynamic diameter (Greenbaum et al., 2001). Although short-term exposure to particulate air pollution has been associated with increased morbidity and mortality in the general population (Burnett et al., 2000; Lin et al., 2002; Villeneuve et al., 2003), a major contributor to the PM<sub>2.5</sub> standard was evidence derived from two cohort studies demonstrating that long-term exposure to particulate air pollution resulted in increased mortality in U.S. cities: Dockery et al. (1993) conducted a 20-yr prospective cohort study starting in 1974 based on 6 cities comprising the Harvard Six Cities Study, while Pope et al. (1995) conducted a retrospective cohort study involving 156 cities involved in a large cohort followed by the American Cancer Society (ACS) since 1982. Although current evidence suggests that both short-term and long-term exposure to particulate air pollution increases mortality in the general population (Burnett et al., 2001, 2003; Coyle et al., 2003; Fung et al., 2005), long-term exposures demonstrate stronger associations with mortality and greater relative risks. Because the findings of the two cohort mortality studies played a pivotal role in the establishment of the PM<sub>2.5</sub> standard, Krewski et al. (2000) conducted an independent reanalysis of the data from these two important studies to (1) validate the original findings and (2) test the robustness of the findings to alternative analytic approaches.

Abbey and associates (1999) also 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 3 California air basins. From 1973 through 1992, the researchers estimated monthly ambient concentrations of PM<sub>10</sub>, ozone, sulfur dioxide, and nitrogen dioxide (NO<sub>2</sub>) using 348 fixed-site monitoring stations, and gathered mortality data from 1977 through 1992. This study focused on PM<sub>10</sub> rather than PM<sub>2.5</sub>, and was not included in the reanalysis project.

Since the completion of the reanalysis project, Pope et al. (2002) reported new results on the association between fine particulate matter and mortality based on further follow-up of the ACS cohort through to 1998. This article provides an overview of previous analysis of the ACS cohort, as well as an indication of ongoing analyses of the cohort that are currently underway by our research team, with additional follow-up through to 2000.

## THE AMERICAN CANCER SOCIETY COHORT

The original ACS prospective cohort CPS-II, which was first initiated in 1982, included approximately 1.2 million men and women for all 50 U.S. states, the District of Columbia, and Puerto Rico. Study participants, who were 30 yr of age or older and living in a household with at least 1 person who was 45 yr or older, 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 behaviours. Vital status of participants was assessed by the volunteers, who made inquiries directly to participants or their families in 1984, 1986, and 1988, and 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).

Epidemiologic analysis was restricted to two subset of adults, who had completed questionnaires, for whom descendent death certificates were available, and who lived in areas of the United States for which data on sulfate or fine-particle air pollution were available. The study 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). In total, 38,963 and 20,765 deaths were recorded for these 2 groups, respectively. Loss to follow-up between 1982 and 1988 was approximately 2% of participants, and death certificates were obtained for approximately 96% of deaths. Fine particles for 50 metropolitan areas had been measured by the U.S. EPA Inhalable Particle Monitoring Network (IPMN), which operated between 1979 and 1983 (Lipfert et al., 1988). Average median fine particle concentration across the 50 metropolitan areas was  $18.2 \mu\text{g}/\text{m}^3$  (range:  $9.0\text{--}33.5 \mu\text{g}/\text{m}^3$ ). Sulfate concentrations in the 151 metropolitan areas were assembled from multiple sources most of which was derived from Özkaynak and Thurston (1987). The average daily sulfate concentrations for the year 1980 were  $11 \mu\text{g}/\text{m}^3$  (range:  $3.6\text{--}23.5 \mu\text{g}/\text{m}^3$ ). (This study is hereafter referred to as the ACS Study and is the subject of the Reanalysis Project.)

## ANALYSIS OF THE ORIGINAL ACS COHORT

Pope et al. (1995) conducted the first analysis of the ACS cohort focusing specifically on the association between particulate air pollution and mortality, with follow-up through to 1989. Subjects were assigned to metropolitan areas according to their three-digit ZIP code at the time they completed the initial questionnaire. The mean concentration of sulfate (for 1980) and the median

concentration of fine particles (for 1979–1983) in each metropolitan area, just before the cohort was enrolled, were used as the indices of air pollution. Using Cox proportional-hazards models stratified by sex, race and 5-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 in climate conditions among metropolitan areas.

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.

### REANALYSIS OF THE ACS COHORT

The findings of both 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).

In response to these concerns, an independent reanalysis of these two studies was commissioned by the Health Effects Institute, an independent research organization representing both the U.S. Environmental Protection Agency and the automobile industry. Following a competitive process, a multi-institutional team led by the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa was selected to undertake the reanalysis.

The objectives of the reanalysis were twofold. The first objective was to validate the data used by the Six Cities Study and the ACS Study and to replicate the original results. The second objective was to evaluate the sensitivity of the original findings to alternative analytic methods, which included a detailed examination of covariate effects and the inclusion of spatial analysis. An overview of the reanalysis of the ACS cohort is given by Krewski et al. (2003). Using the same data and methods of analysis, it was possible to reproduce the risk

estimates reported by the original investigators. Although the audit did identify that some subjects had been omitted from follow up, correction of these errors did not materially affect the original risk estimates (Hoover et al., 2003).

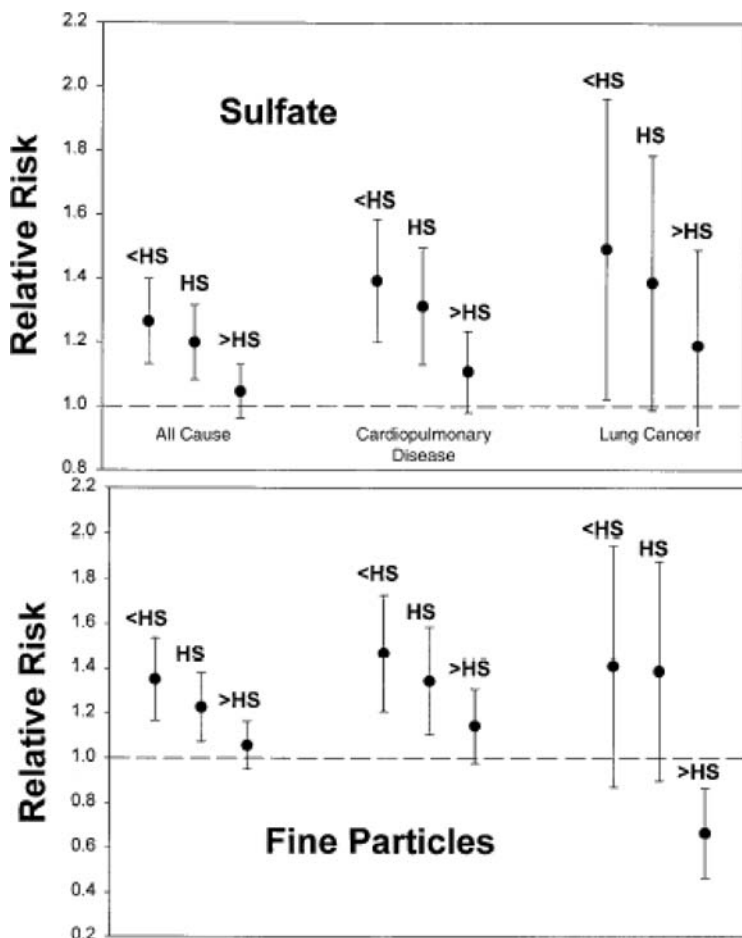
Sensitivity analyses showed the mortality risk estimates for fine particle and sulfate air pollution reported by the original investigators in the ACS Study to be highly robust against alternative risk models of the Cox proportional-hazards family, including models with additional covariates from the original questionnaires not included in the original published analyses.

Our detailed investigation of covariate effects (Willis et al., 2003a) revealed a significant modifying effect of education, 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 the ACS Study.

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 (Krewski et al., 2000). Extensive control for occupational exposures also did not alter the original risk estimates (Siemiatycki et al., 2003). 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. The general effects of including exposure covariates in the Cox model have been investigated further by Abrahamowicz et al. (2004).

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 (Burnett et al., 2001; Ma et al., 2003). 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. Issues in the analysis of spatial data of this type are discussed further by Ramsay et al. (2003a, 2003b) and Jerrett et al. (2003b).

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 ( $\text{NO}_2$ ,  $\text{O}_3$ , and  $\text{CO}$ ) that we examined.



**FIGURE 1.** Relative risks of mortality by cause of death and educational attainment associated with sulfate or fine particles in the reanalysis of the ACS Study. HS, high school. Error bars represent  $\pm 2$  SE.

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 reanalysis suggests 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. 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.

## REANALYSIS WITH EXTENDED FOLLOW-UP

Based on the original reanalysis, Pope et al. (2002) performed a subsequent study using an additional 10 yr of data, which doubles the follow-up time to more than 16 yr and triples the number of deaths. Exposure data were expanded to include gaseous copollutant data and new PM<sub>2.5</sub> data, which have been collected since the promulgation of the new air quality standards. The improved follow-up data improve control of occupational exposures and incorporate dietary variables that account for total fat consumption as well as the consumption of vegetables, citrus, and high-fiber grains. Moreover, the study incorporates the most recent advances in statistical modeling, including the integration of random effects and nonparametric spatial smoothing components in the Cox proportional hazards model.

Vital status of study participants was ascertained by ACS volunteers in September of 1984, 1986, and 1988. Reported deaths were verified with death certificates and vital status was ascertained through to 1998 using automated linkage to the CPS-II study population with the National Death Index (Calle & Terrell, 1993). Death certificates or codes for cause of death (ICD-9) were obtained for more than 98% of all known deaths. Although the CPS-II cohort included approximately 1.2 million participants with adequate questionnaire and cause-of-death data, our analysis was restricted to those participants who resided in U.S. metropolitan areas with available pollution data. The actual size of the analytic cohort varied depending on the number of metropolitan areas for which pollution data were available.

In general, fine-particulate air pollution declined in the United States during the follow-up period of the reanalysis. The fine particle mortality relative risk (RR) ratios from a variety of alternative modeling approaches and assumptions are offered in Table 1. The final model included covariates for smoking,

**TABLE 1.** Relative Risks of Mortality by Cause of Death Associated With an Increase in Fine Particles or Sulfate in Risk Models With Alternative Time Axes in the Reanalysis of the ACS Study

	Fine particles <sup>a</sup>	Sulfate
All causes	1.18 (1.10–1.27)	1.16 (1.10–1.23)
Cardiopulmonary disease	1.30 (1.18–1.45)	1.27 (1.17–1.38)
Cardiovascular disease	1.36 (1.22–1.52)	1.36 (1.25–1.48)
Respiratory disease	1.00 (0.76–1.33)	0.83 (0.67–1.04)
Lung cancer	1.02 (0.80–1.29)	1.36 (1.13–1.65)
Other cancers	1.14 (0.99–1.30)	1.10 (0.99–1.23)
Other causes	1.01 (0.84–1.21)	0.88 (0.76–1.01)

*Note.* 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 (24.5 µg/m<sup>3</sup> for fine particles and 19.9 µg/m<sup>3</sup> for sulfate). Data are RRs with 95% CIs.

<sup>a</sup>Fine particles are ≤2.5 µm in diameter.

education, and marital status, and the inclusion of additional covariates had little effect on the estimated associations with fine-particulate air pollution on cardiopulmonary and lung cancer mortality. All three indices of fine-particulate air pollution were associated with all-cause, cardiopulmonary, and lung cancer mortality, but not mortality from all other causes combined.

Cigarette smoking was highly significantly associated with elevated risk of all-cause, cardiopulmonary, and lung cancer mortality. For example, estimated RRs for an average current smoker (men and women combined, 22 cigarettes/d for 33.5 yr, with initiation before 18 yr) were equal to 2.58, 2.89, and 14.80 for all-cause, cardiopulmonary, and lung cancer mortality, respectively. Statistically significant but substantially smaller and less robust associations were also observed for education, marital status, BMI, alcohol consumption, occupational exposure, and diet variables. Risk of mortality was also estimated for coarser ( $\geq\text{PM}_{10}$ ) particle fractions and for gaseous air pollution. Weaker, less consistent mortality associations were observed with an increase in particle size. Of the gaseous pollutants, only sulfur dioxide was associated with elevated mortality risk, including mortality from causes not related to cardiopulmonary and lung cancer deaths.

The introduction of the random-effects component to the model resulted in larger standard errors of the estimates and therefore somewhat wider 95% confidence intervals. There was no evidence of statistically significant spatial autocorrelation in the survival data after controlling for fine particulate air pollution and the various individual risk factors. Graphical examination of the correlations of the residual mortality with distance between metropolitan areas revealed no significant spatial autocorrelation. Nevertheless, the inclusion of spatial smoothing was included to further investigate the robustness of the estimated particulate pollution effect.

The extended follow-up study established robust associations between ambient fine particulate air pollution and elevated risks of both cardiopulmonary and lung cancer mortality (Table 2). Each  $10\text{-}\mu\text{g}/\text{m}^3$  increase in long-term average  $\text{PM}_{2.5}$  ambient concentrations was associated with approximately a 4%, 6%, and

**TABLE 2.** Adjusted Mortality Relative Risk (RR) Associated With a  $10\text{-}\mu\text{g}/\text{m}^3$  Change in Fine Particles Measuring Less than  $2.5\ \mu\text{m}$  Diameter

Cause of mortality	Adjusted RR (95% CI) <sup>a</sup>		
	1979–1983	1999–2000	Average
All causes	1.04 (1.01–1.08)	1.06 (1.02–1.10)	1.06 (1.02–1.11)
Cardiopulmonary	1.06 (1.02–1.10)	1.08 (1.02–1.14)	1.09 (1.03–1.16)
Lung cancer	1.08 (1.01–1.16)	1.13 (1.04–1.22)	1.14 (1.04–1.23)
All other causes	1.01 (0.97–1.05)	1.01 (0.97–1.06)	1.01 (0.95–1.06)

<sup>a</sup>Estimated and adjusted based on the baseline random-effects Cox proportional hazards model, controlling for age, sex, race, smoking, education, marital status, body mass, alcohol consumption, occupational exposure, and diet. CI indicates confidence interval.



8% increased risk of all-cause, cardiopulmonary, and lung cancer mortality, respectively. The analysis utilized additional follow-up data doubling the follow-up time to more than 16 yr, resulting in approximately triple the number of deaths. Overall, the findings using the extended follow-up data provide the strongest evidence to date that long-term exposure to fine particulate air pollution common to many metropolitan areas is an important risk factor for lung cancer and cardiopulmonary mortality. Pathways by which particles may increase cardiopulmonary mortality in the ACS cohort are examined by Pope et al. (2003).

### ONGOING ANALYSIS

During the course of a subsequent three year research program, the research team proposed to conduct further analyses of the association between particulate air pollution and mortality in large U.S. cities, based on the American Cancer Society Cancer Prevention Survey with the most recent follow-up through to 2000. This research intends to further extend the reanalysis using the extended follow-up done on the American Cancer Society (ACS) cohort by the research team, using alternative spatial models to further examine association between particulates and mortality.

Although the new methods of spatial analysis developed in the reanalysis were useful for exploring the spatial structure of the data and the impact of spatial autocorrelation on estimates of risk associated with exposure to particulate air pollution, further work is required to test how robust the results are to more sophisticated spatial models. Preliminary work with more advanced spatial models has been conducted by members of our research team (Cakmak et al., 2003; Burnett et al., 2001), yet many other questions remain on how alternative spatial models will influence the risk estimates from air pollution exposure.

For example, the geographic scale of analysis may influence modeled estimates of risk from air pollution exposure. All previous analyses were conducted at the metropolitan area (MA) scale. Preliminary work by our team using smaller county units suggests the risk estimates increase significantly when using county rather than MA analytic units (Willis et al., 2003b). This analysis may be subject to bias, since air pollution data was available for counties in which air pollution levels may be expected to be highest. Likewise, the effect of ecologic confounders differs in analyses using smaller geographic units. Our ongoing reanalysis is vital since many important questions about the ACS Study data could not be answered in the reanalysis and the reanalysis using extended follow-up.

Our current research program will address three research questions:

1. Do social, economic, and demographic ecologic variables confound or modify the relationship between particulate air pollution and mortality?

As an initial step toward understanding the effects of ecologic variables in confounding or modifying the relationship between particulate air pollution

and mortality, we relied on the MA scale to match the one used by the original investigators (cf. Krewski et al., 2000; Pope et al., 1995). The original reanalysis demonstrated that several ecologic covariates were significant when incorporated into the standard Cox regression model, assuming independent observations. One of the more surprising results was the lack of confounding effect ecologic covariates exerted on the air pollution–mortality relationship in models that controlled for spatial autocorrelation. Sulfate and sulfur dioxide were the only significant ecologic variables in the spatial regression models.

The reanalysis relied on cross-level or multilevel data, and the extensive battery of individual variables used in the first stage of the random effects model may have removed most of the potential confounding effects before the ecologic variables were tested in the second stage. Yet this seems unlikely because of compelling literature that points to the importance of “contextual” or community-level effects (Duncan & Jones, 1996; Curtis & Taket, 1996; Macintyre & Ellaway, 2000). Other methodological limitations probably contributed to the unexpected results. At the MA scale of aggregation, many ecologic variables may display too much intraurban variation to represent the socioeconomic or environmental phenomenon of interest without large measurement error. A growing literature points to neighborhood scale ecologic effects (Macintyre et al., 1993; Macintyre & Ellaway, 1998, 2000; Eyles, 1999). In many cases, variation within large metropolitan areas is greater than variation between these areas (cf. Jerrett et al., 1997, 2001, for comparable analyses at the county and Census-tract scales). For such variables, measures derived at the MA scale lack validity when their construction fails to represent the intended socioeconomic or environmental process. Variables measured at finer scales may provide more valid estimates of the ecologic processes at work and therefore may show different relationships with the mortality experience in the ACS cohort than those measured at the MA scale.

The need for correct scale is emphasized by another aggregation issue, referred to as the “modifiable aerial unit problem” (MAUP). This problem arises due to the uncertainty induced by the aggregation process. Observed spatial patterns might be a function of the zones chosen for analysis rather than the underlying spatial pattern in attribute values. Spatially aggregated data display higher levels of uncertainty than the individual data on which those aggregations are based, and observed patterns may result from artifacts of aggregation (Fotheringham et al., 2000).

Aggregation produces changes in values of statistics computed on the variables in two ways. First, there is the “scale effect” that results from a loss of information that occurs when individual data are aggregated to ecologic zones and fewer observations exist in the model (Amrhein & Reynolds, 1997). The scale effect also suggests that some changes in statistical results occur because the aggregate data refer to different levels in the geographic hierarchy (e.g., states, metropolitan areas, cities, ZIP code areas) and each of these contains

different information about the geographic process of interest (Steel & Holt, 1996). Each scale can have a different spatial pattern in both mortality experience and the ecologic variables that influence mortality.

Second, the MAUP occurs when the boundaries of the unit of analysis affect variation in statistical values derived from these units. This is referred to as the "zoning effect." Even variables measured at the same scale may display different spatial patterns because of the zonal boundaries chosen for analysis rather than the underlying spatial pattern. For example, if the boundary of an ecologic unit includes a neighborhood with high poverty, changes to this boundary that exclude the poor neighborhood would reduce the poverty rate for the entire ecologic unit.

To minimize these aggregation problems, some researchers suggest that the smallest available unit of analysis should be used unless prior evidence indicates larger units will reveal more about the effect in question (Bailey & Gatrell, 1995). Testing ecologic variables either at the scale that previous studies have shown to be important or at the smallest available scale could alter the results of the reanalysis and show that ecologic variables confound the air pollution–mortality relationship. In related literature on environmental justice that investigates whether disadvantaged and minority groups suffer greater pollution exposure than wealthier groups and whites, empirical evidence and compelling conceptual arguments suggest geographic scale affects the outcome of the analysis (Greenberg, 1993; Cutter, 1996; McMaster et al., 1997; Jerrett et al., 1997). Likewise, some of the observed air pollution–health relationship may be reduced or modified by the contextual effects of ecologic variables measured at finer scales than metropolitan areas or at multiple scales.

## 2. How can spatial autocorrelation and multiple levels be taken into account within the random effects Cox models?

While the reanalysis made progress toward understanding the influence of spatial autocorrelation on the sulfate effect, the methods utilized were criticized on a number of grounds (Higgins et al., 2000). In particular, all methods relied on a fixed relationship over space. For example, the filtering method used a 600-km buffer to remove significant spatial autocorrelation prior to estimation with weighted least squares. Yet the relationship between air pollution and mortality may display nonstationarity over space, meaning the air pollution effect differs depending on the location within the United States. We intend to follow a more flexible modeling strategy to assess nonstationary relationships.

Reliance on one autocorrelation parameter may have effectively filtered variables that operate at the broad regional scale such as sulfate, but it may not have controlled autocorrelation from pollutants such as sulfur dioxide (Higgins et al., 2000), which has a more spatially concentrated or local distribution (Krewski et al., 2000). The inability of the spatial regression methods to deal simultaneously with variables that exhibit different spatial patterns may have contributed to the second key finding of the reanalysis, namely, that the effect

of sulfur dioxide was more robust to control for spatial autocorrelation and other ecologic covariates than the sulfate effect (Higgins et al., 2000). Models capable of adapting to the available data and observed empirical relationships may alter the results and show that sulfur dioxide is no more robust to adjustment for autocorrelation than sulfate, or it may further confirm the original findings of the reanalysis. In either case, the implications for policy formulation and regulatory intervention are considerable.

### 3. What critical exposure time windows affect the association between air pollution and mortality?

While the cohort mortality studies conducted by Dockery et al. (1993) and Pope et al. (1995, 2002) demonstrated an association between particulate air pollution and mortality, neither of these investigations provided an indication of the critical period of exposure (Goddard et al., 1995) responsible for this association. Recent investigations by Zeger et al. (1999) and Schwartz (2000) have shown that mortality cannot be attributed entirely to the effects of short-term peak exposures, which may affect sensitive individuals with preexisting cardiorespiratory disease (Brunekreef, 1997; Goldberg et al., 2000, 2001a, 2001b). Although Krewski et al. (2000) developed individual temporal exposure profiles for subjects in the Harvard Six Cities Study by coding the residence histories of those subjects, limited population mobility and limited variation in individual time-dependent exposure profiles precluded identification of critical exposure-time windows (Villeneuve et al., 2002).

Due to this robust association and a lack of other studies on the long-term effects, the ACS studies have formed the cornerstone for government regulatory interventions such as the U.S. Environmental Protection Agency National Fine Particle Standard and have been used as a basis for estimating the attributable burden of mortality from air pollution by the World Health Organization. Furthermore, none of the past studies have decomposed the follow-up period into distinct time windows to address the question of whether health effects remain constant over time, are concentrated in earlier periods due to harvesting susceptible subjects, or have increased over time due to cumulative exposures. In this research we employ two-stage multilevel models with new imputed exposure data for different periods of follow up in the ACS cohort.

## EXPECTED FUTURE CONTRIBUTIONS

Subsequent analyses will be conducted using new, more powerful data from the ACS cohort with extended follow-up through to 1998, providing an additional 9 yr of data. There will also be more recent and complete exposure data drawn from ongoing complementary research by members of our team.

This research will make significant contributions to current policy and scientific debates surrounding the association between air pollution and mortality. By extending the spatial analytic methods used in the reanalysis, we will be

able to describe more complex spatial features of the ACS data, thereby providing better estimates of the mortality risk associated with particulate air pollution. This work will require the extension of the random effects Cox regression model to more than two levels of random effects. This extension will result in a powerful new analytic tool that will be of value to other investigators engaged in the study of spatial health data. The opportunity to develop individual time-dependent exposure profiles for a large subcohort of the ACS study will further afford an opportunity to identify the critical period of exposure to particulate air pollution associated with elevated mortality rates.

Our proposed analysis of ecologic covariates at multiple scales will lead to a greater understanding of the potential confounding and modifying effect of these variables on the air pollution–mortality association. While the reanalysis suggested these variables probably do not exert a significant confounding influence, lingering questions about scale and the construct validity of the variables used will be addressed directly with our ongoing analysis that focuses on multiple scales, hierarchies of effects, and operational variables (derived from the principal components) that measure the combined effect of many ecologic confounders at once. The investigation of ecologic effect modification could also have important implications for control policies. If ecologic effect modification is significant, this finding would suggest policies aimed at reducing pollution in areas of low social status rather than seeking average reductions.

The standard Cox regression model commonly used in the analysis of cohort mortality data is based on the assumption that individual observations are independent. Due to the presence of spatial autocorrelation induced by complex spatial patterns in the ACS data, this assumption was shown not to hold in the reanalysis. Ignoring such spatial autocorrelation has important implications with respect to bias and precision of model-based estimates of risk.

In the reanalysis we developed a random effects Cox regression model to take into account spatial patterns in the data that could be described at either one (e.g., city) or two (e.g., county and city) levels of clustering. Computer software capable of efficiently fitting the random effects Cox model was also developed.

We have now developed a multilevel random effects Cox model capable of handling more than two levels of clustering. This extended random effects Cox model will permit the reanalysis team to explore much more complex spatial patterns in the ACS data, leading to improved estimates of risk. This model will have applications not only in subsequent analysis of the ACS data, but will be a valuable analytic tool for other investigators involved in spatial analyses.

On the issue of accounting for spatial autocorrelation in the models, the combination of the nonlinear random effects model with spatial surfaces will meaningfully advance past efforts. The incorporation of nonparametric models into the random effects models will allow for flexible modeling of autocorrelation and subsequent visualization of how the effects vary over space. All of these expansions to and advancements on existing spatial risk models will

reduce scientific uncertainty on the air pollution–mortality association that results from violation of the independence assumption in the Cox models.

Particulate air pollution has been associated with both acute and chronic health outcomes. In the reanalysis, we attempted to identify periods of exposure that were most strongly associated with mortality. The identification of such critical “exposure-time windows” requires information on temporal patterns of exposure at the individual level. By coding the residence histories for subjects in the Harvard Six Cities Study, time-dependent exposure profiles were developed for all individuals in the study. Limited mobility among the study participants resulted in little interindividual temporal variation in exposure, precluding identification of the critical period of exposure.

Although virtually no information on population mobility in the ACS cohort was available to the team for the reanalysis, an additional follow-up of the ACS cohort includes information on residence changes within a nutritional subcohort. Preliminary analysis of mobility within this subcohort indicates greater mobility than in the Harvard Six Cities Study. This additional mobility, coupled with the broader geographic base spanned by the ACS cohort, affords more opportunity to explore temporal patterns of exposure and risk than was possible in the reanalysis. Information on critical exposure time windows can assist policymakers with establishing timelines for regulatory interventions that maximize public health benefits based on the age structure of the population, their duration and place of residence, and their mobility.

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