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Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality

Daniel Krewski, Michael Jerrett, Richard T. Burnett, Renjun Ma, Edward Hughes, Yuanli Shi, Michelle C. Turner, C. Arden Pope III, George Thurston, Eugenia E. Calle, and Michael J. Thun

with Bernie Beckerman, Pat DeLuca, Norm Finkelstein, Kaz Ito, D.K. Moore, K. Bruce Newbold, Tim Ramsay, Zev Ross, Hwashin Shin, and Barbara Tempalski

Includes a Commentary by the Institute's Health Review Committee

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ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI research and analyses to public and private decision makers.

HEI receives half of its core funds from the U.S. Environmental Protection Agency and half from the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or certain research programs. HEI has funded more than 280 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in the peer-reviewed literature and in more than 200 comprehensive reports published by HEI.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters, and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 140, *Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality,* presents a research project funded by the Health Effects Institute and conducted by Dr. Daniel Krewski of the McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, in Ottawa, Ontario, Canada, and his colleagues. This report contains three main sections.

The HEI Statement, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Health Review Committee's comments on the study.

The Investigators' Report, prepared by Krewski et al., describes the scientific background, aims, methods, results, and conclusions of the study.

The Commentary is prepared by members of the Health Review Committee with the assistance of HEI staff; it places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Health Review Committee, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

HEI STATEMENT

Synopsis of Research Report 140

Extended Analysis of the American Cancer Society Study of Particulate Air Pollution and Mortality

INTRODUCTION

The American Cancer Society (ACS) Cancer Prevention Study II (CPS-II), a large ongoing prospective study of mortality in adults initiated in 1982, was one of two U.S. cohort studies central to the 1997 debate on the National Ambient Air Quality Standard (NAAQS) for fine particulate air pollution in the United States. Because of the high importance of the original ACS study in formulating regulations and the controversy generated by the limitations of that study, the U.S. Environmental Protection Agency (U.S. EPA), the Congress, and industry requested that the Health Effects Institute conduct the Particle Epidemiology Reanalysis Project with the objective of independently and rigorously assessing the original data and findings. The results of the Reanalysis Project validated the quality of the original data (which included 7 years of follow-up), replicated the original results, and tested those results against alternative risk models and analytic approaches.

After the Reanalysis Project, Dr. Arden Pope and colleagues undertook an Updated Analysis of the ACS cohort using an additional 10 years of follow-up and exposure data. Recent advances in statistical modeling were incorporated into these analyses.

As described in Research Report 140, Dr. Daniel Krewski and colleagues, with HEI's support, conducted an Extended Analysis of the same cohort. This research increases the follow-up period for the ACS cohort to 18 years (1982 to 2000) — 11 years more than the original study. The investigators have produced national estimates of the risks of death from various causes and have extended the range of analyses to include refinements of statistical methods and incorporate sophisticated control of bias and confounding.

SUMMARY

The cohort for the current study consists of approximately 360,000 participants residing in areas of the country that have adequate monitoring information on levels of particulate matter with an aerodynamic diameter of 2.5 μm or smaller ($PM_{2.5}$) for 1980 and about 500,000 participants in areas with adequate information for 2000. The causes of death obtained from death certificates during follow-up that were analyzed included all causes, cardiopulmonary disease (CPD), ischemic heart disease (IHD, reduction of blood supply to the heart, potentially leading to heart attack), lung cancer, and all remaining causes. Data for 44 personal, individual-level covariates, based on participants' answers to a 1982 enrollment questionnaire, were also used for the analyses. Dr. Krewski's research team also collected data for seven ecologic (neighborhood-level) covariates, each of which represents local factors known or suspected to influence mortality, such as poverty level, level of education, and unemployment (at both Zip Code and city levels).

Long-term average exposure variables were constructed for $PM_{2.5}$ from monitoring data for two periods: 1979–1983 and 1999–2000. Similar variables were constructed for long-term exposure to other pollutants of interest from single-year (1980) averages, including total suspended particles, ozone (O_3), nitrogen dioxide, and sulfur dioxide (SO_2). Exposure was averaged for all monitors within a metropolitan statistical area (MSA) and assigned to participants according to their Zip Code area (ZCA) of residence.

Dr. Krewski's team chose the standard Cox proportional-hazards model (and a variation to allow for random effects) to calculate hazard ratios for various cause-of-death categories associated with

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Daniel Krewski at the McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, ON, Canada, and colleagues. Research Report 140 contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

the levels of air pollution exposure in the cohort. They extended the random effects Cox model to accommodate two levels of information for clustering and for ecologic covariates. Three main analyses were conducted: a Nationwide Analysis, Intra-Urban Analyses in the New York City (NYC) and Los Angeles (LA) regions, and an analysis designed to investigate whether critical time windows of exposure to pollutants might have affected mortality in the cohort.

Nationwide Analysis

For the Nationwide Analysis using the standard Cox model, the associations between average $PM_{2.5}$ concentrations in both 1979–1983 and 1999–2000 and mortality from all causes (except the category of "all other causes") were statistically significant. The hazard ratio (HR) for death was elevated by 3% to 15%, depending on the cause of death, for each increase of 10 $\mu g/m^3$ in $PM_{2.5}$. When the random effects Cox model was used with added control for ecologic covariates, the effect estimates increased slightly and remained significant; the strongest estimate was for IHD (HR = 1.24; 95% confidence interval [CI], 1.19–1.29). These effect estimates were, in general, higher than those found in some previous analyses of this cohort. The association of mortality with summer O_3 levels (calculated from concentrations measured from April to September 1980) was small, but significant, for deaths from all causes (HR = 1.02; 95% CI, 1.01–1.03) and from CPD (HR = 1.03; 95% CI, 1.02–1.04).

In earlier analyses of this cohort, investigators found that increasing education levels appeared to reduce the effect of $PM_{2.5}$ exposure on mortality. Results from the current study show a similar pattern, although with somewhat less certainty, for all causes of death except IHD, for which the pattern was reversed.

Intra-Urban Analyses

For the NYC Analysis, land-use regression (LUR) models were created to estimate exposure to $PM_{2.5}$ using concentrations averaged over 3 years or over the winter months only for 1 year. Annual average concentrations were calculated for each of 62 monitors from 3 years of daily monitoring data for 1999 through 2001. Those data were combined with land-use data collected from traffic-counting systems, roadway network maps, satellite photos of the study area, and local government planning and tax-assessment maps to assign estimated exposures to the ACS participants. As with the Nationwide Analysis, the team used the random effects Cox model to calculate HRs and incorporated the 44 individual-level covariates as well as the 7 ecologic covariates at the ZCA and MSA scales.

In the LA Analysis, the investigators used both LUR and kriging (a method of interpolating missing values) to estimate exposure concentrations for cohort members. The Cox models used to calculate associations between exposure and mortality included the same individual-level and ecologic covariates as in the NYC Analysis. The LA Analysis reported results separately for analyses that used exposure based on LUR and those based on kriging of monitored concentrations. The investigators assembled data from several sources for the LUR models, including the California EPA's 23 $PM_{2.5}$ monitors and the California Air Resources Board's database for 42 sites monitoring O_3.

Despite the common methodologic basis for the NYC and LA Analyses, the resulting LUR exposure models and associations between exposure and mortality were strikingly dissimilar. The LA results show much larger HRs than the NYC results, except for mortality due to IHD (LA: HR = 1.33; 95% CI, 1.08–1.63; NYC: HR = 1.47; 95% CI, 1.00–2.00; both per 10-$\mu g/m^3$ increase in $PM_{2.5}$). These differences may arise from the range of exposures derived for cohort members residing in each area, the relative uniformity of $PM_{2.5}$ exposure in the NYC region, and the differences between the land-use variables selected as the most appropriate for inclusion in the LUR models that were constructed for the two metropolitan areas.

Critical Periods of Exposure Analysis

Dr. Krewski's team performed an analysis designed to explore whether more recent exposures to air pollution are more or less strongly associated with mortality than exposures further in the past. Exposure profiles for this analysis were constructed from average $PM_{2.5}$ and SO_2 concentrations for periods 1 to 5 years, 6 to 10 years, and 11 to 15 years before death. As with other analyses, the investigators used the standard Cox model including individual-level covariates.

The investigators considered the time window with the best-fitting model (judged by the lowest Akaike information criterion [AIC] statistic, which is a measure of how well a model fits the available data) to be the period during which pollution had the

strongest influence on mortality. Overall, differences in model fit, HRs, and CIs among the three 5-year exposure periods were small and demonstrated no definitive patterns. High correlations between exposure levels in the three periods may have reduced the ability of this analysis to detect any differences in the relative importance of the time windows.

DISCUSSION

The basic Cox proportional-hazards model used for the mortality analyses has two major limitations that the investigators addressed in innovative ways developed specifically for this study: confounding by ecologic factors and spatial autocorrelation. Ecologic confounders are risk factors for mortality that are observed at the neighborhood level, rather than the individual level. In the current study, in contrast to the Reanalysis Project, ecologic information was collected at the ZCA level as well as the MSA level, although not all ecologic covariates considered previously were included in this analysis. Spatial autocorrelation arises from the way values for certain variables tend to be similar for people (or areas) that are geographically close. For example, people who live in the same household or neighborhood — or even in similar neighborhoods in the same city — tend to have similar health risks (diet, smoking habits, access to health care), as well as similar proximity to sources of exposure (e.g., freeways and industrial areas). The spatial models in this analysis differed from those used in the Reanalysis by including random effects at the ZCA, city, and state levels and by adjusting for correlation between adjacent ZCAs, cities, and states.

In its evaluation of the study by Krewski and colleagues, the Review Committee agreed with the investigators that key results were robust when adjusted for ecologic covariates and spatial autocorrelation in the statistical models. In a recently published follow-on study of O_3 and respiratory outcomes in the ACS data, including the same individual and ecologic covariates as the current study, Dr. Michael Jerrett and associates found no indication of important residual spatial autocorrelation in the association between O_3 and mortality.

Because the Reanalysis Project tested extensively for confounding by gaseous pollutants of the relationship between fine particles and mortality, the Krewski team instead focused the current study on an extensive exploration of spatial autocorrelation in a series of one-pollutant models. The Committee thought that the inclusion of some two-pollutant analyses would have strengthened the study. The authors note, however, that the available data for most gaseous pollutants were not sufficient for such analyses, since they came from only a few locations in each city and could not adequately represent the high degree of spatial variability of pollutant levels in a given metropolitan area.

The present report combines deaths from cardiovascular and respiratory causes—a decision that is important for continuity with earlier studies but one that makes the results more difficult to interpret biomedically. The report singled out the associations between $PM_{2.5}$ and IHD, consistent with previous investigations with this cohort, but the Committee felt it would be useful in the future to see the results for other categories of cardiovascular disease, such as stroke and heart failure, presented alongside those for IHD.

The fundamental difference in exposure between the two Intra-Urban Analyses lies in the different relative influence of regional background concentrations of $PM_{2.5}$. The intra-urban studies primarily investigated variability in local exposure within the regions that was driven by local sources such as traffic, industry, and residential or commercial emissions. Despite the substantial differences in how the LUR models were constructed and the likely quality of the data used, the LUR models for LA and NYC were both successful in explaining a moderate percentage of variability (60 to 65%) in $PM_{2.5}$ concentrations measured at the monitoring sites. The range of average annual monitored $PM_{2.5}$ concentrations considered in developing the models was not very different between LA (9.5 to 28 $\mu g/m^3$) and NYC (10 to 20 $\mu g/m^3$). However, the resulting ranges of exposure assigned by the LUR models in LA (< 10 to > 125 $\mu g/m^3$) and NYC (8 to 20 $\mu g/m^3$), by comparison, suggest that levels of $PM_{2.5}$ are regionally determined in NYC and highly locally variable in LA.

The intra-urban results for the two regions were very different, with a strong positive and significant association between $PM_{2.5}$ exposure and mortality from CPD in LA and no significant association in NYC. Both the LA and NYC results showed significant associations between $PM_{2.5}$ and mortality from IHD, consistent with the results of the Nationwide Analysis. The authors note that differences in the estimated HRs for LA and NYC were partially attributable to the different — and opposite — ways that

mortality that was not explained by the individual and ecologic variables in the Cox models was distributed relative to the varying $PM_{2.5}$ exposure levels in the two cities. The higher exposures in LA tended to occur in areas characterized by low socioeconomic status (and relatively high expected mortality), whereas the higher exposures in NYC were generally found in areas of high socioeconomic status (and relatively low expected mortality).

The Committee noted that the inconclusive results from the NYC Analysis (aside from that for IHD) were probably due to too little variation in $PM_{2.5}$ exposure across the NYC area, owing to the regional nature of $PM_{2.5}$ exposure in the Northeastern United States. Relatively uniform exposures would reduce the ability of the statistical models to detect patterns of mortality relative to exposure and to estimate HRs with precision. As for the LA results, the authors believe that the higher estimates are due to reduced error in the assignment of exposures. However, the Committee saw no persuasive argument that exposure measurement error would be expected to be less in the LA or NYC studies than in the Nationwide Analysis. Therefore, the Committee believes that the most likely explanation for the largely null results for the NYC Analysis and their divergence from the LA and Nationwide results was the low variability in $PM_{2.5}$ exposure levels across the NYC region.

The epidemiologic design used in the analysis of Critical Periods of Exposure was more complex than that of the full Nationwide Analysis because it used two distinct subcohorts of subjects from the main ACS cohort, rather than the whole cohort as in the Nationwide Analysis. For each deceased ACS participant in each subcohort, time windows of exposure were calculated as average exposures during successive five-year periods preceding the date of death.

The use of AIC to compare models including different five-year windows of past exposure is broadly reasonable, since the number of variables in each model being compared was the same. The Committee was somewhat disappointed that the investigators did not present results for "multi-window" models, in which the effects of exposure in one time window are controlled for the effects of exposure in another time window. Although it is important to know whether more recent exposure has a greater effect on risk than earlier exposure, the Committee considered that the evidence presented was not substantial enough to draw conclusions based on the extremely small differences in AIC values resulting from exchanging exposure in one time window with another.

CONCLUSIONS

The Extended Analysis represents a broadly sound and thorough analysis of an already important cohort study, with several innovative features. The results consolidate earlier findings by showing that the application of state-of-the-art statistical approaches to controlling confounders and spatial autocorrelation does not materially change risk estimates; important residual confounding (by climate and possibly other unmeasured determinants of large-scale spatial variation) cannot be excluded, however, particularly in the Nationwide Analysis. In analyzing the extended follow-up data from the ACS cohort for mortality, the report also provides new risk estimates, including — for the first time — an estimate for O_3 and premature mortality.

The Intra-Urban Analysis for LA suggests that mortality risks associated with $PM_{2.5}$ exposure may be elevated when there is a strong local component of exposure. When the NYC and LA Analyses are taken together, however, they underscore the important point that cities differ markedly in their local exposure conditions and emphasize the variable importance of the contributions of local sources to the overall risk of mortality associated with $PM_{2.5}$ exposure. These divergent results argue for caution in extrapolating from such studies in any one metropolitan area to other areas.

No single study can be the basis for accepting the existence of a causal relationship between air pollution and mortality. With this in mind, the Review Committee thought that — with the emergence of new cohort evidence from the United States and Europe — the similarities and differences among the results of the various studies need to be examined closely. Nevertheless, the size and character of the ACS cohort makes it likely that it will remain preeminent.

INVESTIGATORS' REPORT

Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality

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with Bernie Beckerman, Pat DeLuca, Norm Finkelstein, Kaz Ito, D.K. Moore, K. Bruce Newbold, Tim Ramsay, Zev Ross, Hwashin Shin, and Barbara Tempalski

McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa (D.K., R.T.B., Y.S., M.C.T.); Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa (D.K., R.T.B); Division of Environmental Health Sciences, School of Public Health, University of California–Berkeley (M.J.); Healthy Environments and Consumer Safety Branch, Health Canada (R.T.B); Department of Mathematics and Statistics, University of New Brunswick, Fredericton (R.M.); Edward Hughes Consulting (E.H.); Department of Economics, Brigham Young University (C.A.P.); Nelson Institute of Environmental Medicine, New York University School of Medicine (G.T.); Department of Epidemiology and Surveillance Research, American Cancer Society (E.E.C., M.J.T.)

ABSTRACT

We conducted an extended follow-up and spatial analysis of the American Cancer Society (ACS)* Cancer Prevention Study II (CPS-II) cohort in order to further examine associations between long-term exposure to particulate air pollution and mortality in large U.S. cities. The current study sought to clarify outstanding scientific issues that arose from our earlier HEI-sponsored Reanalysis of the original ACS study data (the Particle Epidemiology Reanalysis Project). Specifically, we examined (1) how ecologic covariates at the community and neighborhood levels might confound and modify the air pollution–mortality association; (2) how spatial autocorrelation and multiple levels of data (e.g., individual and neighborhood) can be taken into account within the random effects Cox model; (3) how using land-use regression to refine measurements of air pollution exposure to the within-city (or intra-urban) scale might affect the size and significance of health effects in the Los Angeles and New York City regions; and (4) what exposure time windows may be most critical to the air pollution–mortality association.

The 18 years of follow-up (extended from 7 years in the original study [Pope et al. 1995]) included vital status data for the CPS-II cohort (approximately 1.2 million participants) with multiple cause-of-death codes through December 31, 2000 and more recent exposure data from air pollution monitoring sites for the metropolitan areas.

In the Nationwide Analysis, the influence of ecologic covariate data (such as education attainment, housing characteristics, and level of income; data obtained from the 1980 U.S. Census; see Ecologic Covariates sidebar on page 14) on the air pollution–mortality association were examined at the Zip Code area (ZCA) scale, the metropolitan statistical area (MSA) scale, and by the difference between each ZCA value and the MSA value (DIFF). In contrast to previous analyses that did not directly include ecologic covariates at the ZCA scale, risk estimates increased when ecologic covariates were included at all scales. The ecologic covariates exerted their greatest effect on mortality from ischemic heart disease (IHD), which was also the health outcome most strongly related with exposure to $PM_{2.5}$ (particles 2.5 μm or smaller in aerodynamic diameter), sulfate (SO_4^{2-}), and sulfur dioxide (SO_2), and the only outcome significantly associated with exposure to nitrogen dioxide (NO_2). When ecologic covariates were simultaneously included at both the MSA and DIFF levels, the

This Investigators' Report is one part of Health Effects Institute Research Report 140, which also includes a Commentary by the Health Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Daniel Krewski, McLaughlin Centre for Population Health Risk Assessment, Room 320, University of Ottawa, One Stewart Street, Ottawa, ON K1N 6N5, Canada. E-mail: cphra@uottawa.ca.

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

hazard ratio (HR) for mortality from IHD associated with $PM_{2.5}$ exposure (average concentration for 1999–2000) increased by 7.5% and that associated with SO_4^{2-} exposure (average concentration for 1990) increased by 12.8%. The two covariates found to exert the greatest confounding influence on the $PM_{2.5}$–mortality association were the percentage of the population with a grade 12 education and the median household income.

Also in the Nationwide Analysis, complex spatial patterns in the CPS-II data were explored with an extended random effects Cox model (see Glossary of Statistical Terms at end of report) that is capable of clustering up to two geographic levels of data. Using this model tended to increase the HR estimate for exposure to air pollution and also to inflate the uncertainty in the estimates. Including ecologic covariates decreased the variance of the results at both the MSA and ZCA scales; the largest decrease was in residual variation based on models in which the MSA and DIFF levels of data were included together, which suggests that partitioning the ecologic covariates into between-MSA and within-MSA values more completely captures the sources of variation in the relationship between air pollution, ecologic covariates, and mortality.

Intra-Urban Analyses were conducted for the New York City and Los Angeles regions. The results of the Los Angeles spatial analysis, where we found high exposure contrasts within the Los Angeles region, showed that air pollution–mortality risks were nearly 3 times greater than those reported from earlier analyses. This suggests that chronic health effects associated with intra-urban gradients in exposure to $PM_{2.5}$ may be even larger between ZCAs within an MSA than the associations between MSAs that have been previously reported. However, in the New York City spatial analysis, where we found very little exposure contrast between ZCAs within the New York region, mortality from all causes, cardiopulmonary disease (CPD), and lung cancer was not elevated. A positive association was seen for $PM_{2.5}$ exposure and IHD, which provides evidence of a specific association with a cause of death that has high biologic plausibility. These results were robust when analyses controlled (1) the 44 individual-level covariates (from the ACS enrollment questionnaire in 1982; see 44 Individual-Level Covariates sidebar on page 22) and (2) spatial clustering using the random effects Cox model. Effects were mildly lower when unemployment at the ZCA scale was included.

To examine whether there is a critical exposure time window that is primarily responsible for the increased mortality associated with ambient air pollution, we constructed individual time-dependent exposure profiles for particulate and gaseous air pollutants ($PM_{2.5}$ and SO_2) for a subset of the ACS CPS-II participants for whom residence histories were available. The relevance of the three exposure time windows we considered was gauged using the magnitude of the relative risk (HR) of mortality as well as the Akaike information criterion (AIC), which measures the goodness of fit of the model to the data. For $PM_{2.5}$, no one exposure time window stood out as demonstrating the greatest HR; nor was there any clear pattern of a trend in HR going from recent to more distant windows or vice versa. Differences in AIC values among the three exposure time windows were also small. The HRs for mortality associated with exposure to SO_2 were highest in the most recent time window (1 to 5 years), although none of these HRs were significantly elevated. Identifying critical exposure time windows remains a challenge that warrants further work with other relevant data sets.

This study provides additional support toward developing cost-effective air quality management policies and strategies. The epidemiologic results reported here are consistent with those from other population-based studies, which collectively have strongly supported the hypothesis that long-term exposure to $PM_{2.5}$ increases mortality in the general population. Future research using the extended Cox–Poisson random effects methods, advanced geostatistical modeling techniques, and newer exposure assessment techniques will provide additional insight.

INTRODUCTION

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

Epidemiologic studies conducted over several decades have provided evidence to suggest that long-term exposure to elevated ambient levels of particulate air pollution is associated with increased mortality. Two U.S. cohort studies, the Harvard Six Cities Study (Dockery et al. 1993), a 20-year prospective cohort study, and the ACS Study (Pope et al. 1995), a larger retrospective cohort study, reported that mortality from all causes increased in association with an increase in the concentration of $PM_{2.5}$.

Both studies came under intense scrutiny in 1997 when the results were used by the U.S. Environmental Protection Agency (U.S. EPA) to support new National Ambient Air Quality Standards for $PM_{2.5}$ and to maintain the standards for PM_{10} that were already in effect. The findings of these two studies were 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., education, unemployment, poverty); 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 (Gamble 1998; Lipfert and Wyzga 1995). To address growing public controversy concerning the studies' methods and their results, Harvard University and the ACS requested that the Health Effects Institute organize an independent Reanalysis of these studies.

Through a competitive process, a Reanalysis Team led by Dr. Daniel Krewski of the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa was selected by an independent Expert Panel appointed by the HEI Board of Directors, with support from the U.S. EPA, industry, Congress, and other stakeholders. The Reanalysis Project was overseen by the Expert Panel, which was chaired by Dr. Arthur Upton from the University of Medicine and Dentistry of New Jersey and former Director of the National Cancer Institute, with assistance by a broad-based Advisory Board of stakeholders and scientists. The findings of the Reanalysis (Phase I and Phase II) were published in an HEI Special Report in 2000 (Krewski et al. 2000a,b). The final results were extensively peer reviewed by an independent Special Panel of the HEI Review Committee, which was chaired by Dr. Millicent Higgins of the University of Michigan.

THE PARTICLE EPIDEMIOLOGY REANALYSIS PROJECT: OBJECTIVES AND FINDINGS

The overall objective of the Reanalysis Project was to conduct a rigorous and independent assessment of the findings of the Harvard Six Cities and ACS Studies of air pollution and mortality. *Phase I: Replication and Validation* involved a quality assurance (QA) audit of a sample of the original data and validation of the original numeric results. *Phase II: Sensitivity Analyses* tested the robustness of the original analyses to alternate risk models and analytic methods.

In Phase I, the Reanalysis assured the quality of the original data, replicated the original results, and tested those results against alternative risk models of the Cox proportional-hazards family and other analytic approaches without substantively altering the original findings of an association between indicators of PM air pollution and mortality (Krewski et al. 2000a, 2003a).

Phase II of the Reanalysis made innovative contributions to understanding the air pollution–mortality association by developing new methods of spatial analysis for cohort studies that involve both individual-level and ecologic covariates. Most of the Phase II analysis used the standard Cox model, which assumes that the probability of death is independent among subjects. We challenged this assumption in a number of ways by introducing largely ad hoc statistical approaches that were developed for this specific dataset. (In the current Extended Analysis, we have formalized these statistical models that include extensions of the standard Cox model to include random effects at multiple levels of clustering, such as MSA and ZCA. In addition, we have developed models and estimation methods to allow the random effects to have spatial structure such that clusters of data that are geographically close are assumed to be more correlated than those more spatially distant.)

Key findings from the Reanalysis indicated that (1) educational status significantly modifies the risk of mortality associated with exposure to $PM_{2.5}$ in that the risk declines as education attainment rises; (2) SO_2 may exert a more robust effect on mortality than SO_4^{2-}; (3) other possible ecologic confounders have no significant effect in models that control for spatial autocorrelation; and (4) spatial risk models attenuate the air pollution effect, both in terms of size and certainty.

The implications of the findings for air quality risk management were significant and pointed to the vital need for further study of the role that ecologic covariates have in the association between air pollution and mortality. Although the methods 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 $PM_{2.5}$, further work was required to determine how robust the results would be to more sophisticated spatial models.

GEOGRAPHIC SCALE OF ANALYSIS

As an initial step toward understanding the effects of ecologic covariates in confounding or modifying the relationship between particulate air pollution and mortality, the Reanalysis Team first used data at the MSA (city) scale in order to match the work by the original investigators (Pope et al. 1995). The Reanalysis demonstrated that several ecologic covariates significantly influenced health outcomes when incorporated into the standard Cox model (Krewski et al. 2000a,b). One of the more surprising results was the lack of confounding effect that ecologic covariates exerted on the air pollution–mortality relationship in models that controlled for spatial autocorrelation. For example, when SO_4^{2-} and SO_2 were included as ecologic variables in spatial regression models with $PM_{2.5}$ as the

main exposure variable, they were the only ecologic covariates that showed a significant impact at the MSA scale.

The Reanalysis Team next relied on multi-level data (individual-level and MSA-level covariates) in a two-stage analysis with a random effects Cox model. The extensive battery of individual-level variables included in the first stage may have removed most of the possible confounding effects before the ecologic covariates were tested in the second stage. This seems unlikely, however, because of other compelling studies that point to the importance of contextual or community-level variables in assessing mortality (Duncan et al. 1996; Curtis and Taket 1996; Macintyre and Ellaway 2000).

Other methodologic limitations in the Reanalysis Project probably also contributed to the unexpected lack of statistical effect when the ecologic covariates were incorporated in the models. At the MSA scale of aggregation, for example, many ecologic covariates may be too dissimilar across the city for a mean value to represent the socioeconomic or environmental phenomenon of interest (e.g., income level) without large measurement error. A growing number of studies implicate neighborhood-scale ecologic covariates as confounders of health outcomes (Macintyre et al. 1993; Macintyre and Ellaway 1998, 2000; Eyles 1999). In many analyses, data gathered on county and census-tract scales vary within a large MSA more widely than they do between MSAs (Jerrett et al. 1997, 2001).

Another aggregation issue, referred to as the modifiable areal unit problem (MAUP), emphasizes the need for choosing the correct scale because the size and boundaries of the zones influence the reported values. For example, if the boundary of an ecologic unit—such as a census block or a ZCA—includes a neighborhood with a high poverty level, changing the boundary to exclude that neighborhood would substantially lower the mean poverty level for the ecologic unit. (This is referred to as the zoning effect.) An observed spatial pattern might reflect the zone boundaries chosen for analysis rather than a true underlying spatial pattern. Spatially aggregated data are more uncertain than the individual data on which the aggregations are based; and an observed pattern may result from artifacts of aggregation (Fotheringham et al. 2000). Even variables measured at the same scale may display different spatial patterns because of the zones chosen for analysis.

Aggregation of data can also produce changes in the statistical values computed on the variables because information is lost when individual data are aggregated into ecologic zones and fewer data are in the model (Amrhein and Reynolds 1997). (This is referred to as the scale effect.) The scale effect also suggests that some changes in statistical results occur because the aggregated data refer to different levels in the geographic hierarchy (e.g, states, metropolitan areas, cities, ZCAs) and each level contains different information about the geographic variable of interest (Steel and Holt 1996). Each scale can have a different spatial pattern for mortality as well as for the ecologic covariates that influence mortality.

To minimize these aggregation problems, some researchers suggest that the smallest available unit of analysis should be used unless earlier evidence indicates that larger units will reveal more about the effect in question (Bailey and Gatrell 1995). In related studies of environmental justice that have investigated whether disadvantaged and minority groups suffer greater pollution exposure than wealthier and majority groups, empirical evidence and compelling conceptual arguments suggest that geographic scale affects the outcome of the analysis (Greenberg 1993; Cutter et al. 1996; Jerrett et al. 1997; McMaster et al. 1997). Likewise, some of the observed relationships between air pollution and health may be reduced or modified by the context of ecologic covariates measured at scales finer than metropolitan areas or measured at many scales. Further analyses of ecologic covariates in the ACS study at multiple scales would answer lingering questions about whether these variables exert a significant influence and would provide important guidance for location-specific air quality management policies.

REFINEMENT OF EXPOSURE ESTIMATES

Previous studies using the ACS database have relied on comparing between communities the central monitor estimates that assign the same level of exposure to an entire MSA. Recent studies have recognized that exposure to air pollution may vary spatially within a city (Briggs et al. 2000a; Jerrett et al. 2001; Brunekreef and Holgate 2002; Zhu et al. 2002; Brauer et al. 2003), and these variations may follow social gradients that influence susceptibility to environmental exposures (Jerrett et al. 2003). For example, residents of poorer neighborhoods may live closer to point sources of industrial pollutants or roadways with higher traffic density (O'Neil et al. 2003). Health effects may be higher around such sources, and these effects are diminished when using average pollutant concentrations for the entire community.

Recent studies of $PM_{2.5}$ have shown that intra-urban exposure gradients can be associated with atherosclerosis (Künzli et al. 2005) and a high risk of reduced life expectancy (Jerrett et al. 2005a). Those studies have used geostatistical interpolation models that capture regional patterns of pollution well, but often fail to account for the near-source impact from local traffic and industry. Given the large health effects reported in these and in European studies

(Hoek et al. 2002; Nafstad et al. 2003), estimates of intra-urban exposure need to be refined to reduce uncertainties associated with the modeling processes.

Several recent studies have demonstrated that land-use regression (LUR) has the potential to supply accurate, small-area estimates of air pollutant concentrations without the data entry and monetary expense of dispersion or exposure modeling (Brauer et al. 2003; Briggs et al. 2000b). The goal of LUR is to explain, to the extent possible, the variation in existing air quality data for a given pollutant using data on nearby traffic, land use, and population variables. In most cases, multiple linear regression is used to develop a model with data from existing monitors that can be applied to unmonitored locations if the appropriate geographic data are available.

Ross and colleagues (2006) developed LUR models using traffic data, distance to the coast, and road length measurements to predict NO_2 levels in San Diego, California. When the predicted concentrations were compared with measured concentrations at validation locations—data from sites that were not included in creating the model—the values matched to within, on average, 2.1 ppb. The model explained nearly 80% of the variation in NO_2 levels in San Diego. LUR models used to predict NO_2 levels using traffic and other variables in Montréal and in several European cities also produced accurate predictions (Jerrett et al. 2005b).

In contrast to localized gases such as NO_2, PM mass has a significant regional component that includes smaller contributions from local sources (Bari et al. 2003). This complicates the estimation of intra-urban exposure with LUR. LUR models have been used with some success to predict $PM_{2.5}$ concentrations in Europe as part of the Traffic Related Air Pollution and Childhood Asthma Study (TRAPCA) (Brauer et al. 2003). However, North American cities have vastly different transportation and land-use patterns and the applicability of LUR to predict $PM_{2.5}$ concentrations is unknown (Gilbert et al. 2005).

LIMITATIONS OF THE RANDOM EFFECTS COX MODEL

Although the Reanalysis made progress toward understanding the influence of spatial autocorrelation on the health effects of SO_4^{2-} exposure, the methods used were criticized on a number of grounds (HEI Health Review Committee 2000). In particular, all methods assumed that the relationship between exposure and health outcome was fixed over space. For example, our spatial filtering method used a 600-km buffer to remove significant spatial autocorrelation before we used weighted-least-squares methods to estimate effects. Even after applying this filter, though, the relationship between air pollution and mortality may still differ depending on the location within the United States (known as nonstationarity behavior over space). A more flexible modeling strategy was needed to address such nonstationarity.

Furthermore, reliance on one autocorrelation parameter may have effectively removed variables that operate at the broad regional scale, such as SO_4^{2-} concentrations, but it may not have controlled autocorrelation from pollutants that have a more spatially concentrated or local distribution, such as SO_2 (HEI Health Review Committee 2000; Krewski et al. 2000a,b). 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: The effect of SO_2 exposure changed less than the effect of SO_4^{2-} exposure when spatial autocorrelation and the ecologic covariates were accounted for in the model (HEI Health Review Committee 2000). Models capable of adapting to the available data and accounting for spatial autocorrelation may alter these results and show that the effects of SO_2 and of SO_4^{2-} exposure are equally robust to adjustment; or such models may further confirm the results from the Reanalysis.

In either case, the implications for policy formulation and regulatory intervention are considerable. In the Phase II Reanalysis we developed an approach for Cox models with two levels of nested random effects (referred to as the random effects Cox model; Ma et al. 2003). This method allowed us to characterize the clustering of spatial effects at two geographic levels. In the Extended Analysis described in this report, our random effects Cox model needed to be expanded to fully describe complex spatial patterns in the ACS data in order to accommodate more than two levels of geographic nesting (e.g., neighborhood within county, county within MSA, MSA within state).

POST-REANALYSIS STUDIES OF THE ACS COHORT

After the Reanalysis, Pope and associates (2002) undertook a subsequent analysis using an additional 10 years of data, which doubled the follow-up time to more than 16 years and tripled the number of deaths (referred to as the Updated Analysis). Exposure data were expanded to include gaseous copollutants and new $PM_{2.5}$ data that had been collected since 1999 as a result of the NAAQS for $PM_{2.5}$ enacted in 1997. Recent advances in statistical modeling were incorporated in the analyses, especially the use of random effects (relaxation of the assumption of independent observations) and control for spatial autocorrelation.

Results from that Updated Analysis provided the strongest evidence to date that long-term exposure to $PM_{2.5}$ air

pollution common to many metropolitan areas is an important risk factor for death from lung cancer and CPD. For each 10-μg/m^3 increase in long-term average $PM_{2.5}$ ambient concentrations, the associated risk of death from all causes, CPD, and lung cancer increased by approximately 4%, 6%, or 8%, respectively. No evidence of statistically significant spatial autocorrelation was found in the survival data after $PM_{2.5}$ air pollution and the various individual risk factors were controlled. Graphical examination of the correlations of the residual mortality with distance between metropolitan areas also revealed no significant spatial autocorrelation after controlling residual spatial patterns in mortality using a smoothed function of latitude and longitude.

Pope and colleagues (2004) examined pathways by which inhaled particles may increase CPD deaths in the ACS cohort, although it is difficult to make empirical observations from epidemiologic data about possible mechanistic pathways of disease. The results of that analysis are largely consistent with others: Pathways that link long-term PM exposure with risk of death from CPD include pulmonary and systemic inflammation, accelerated atherosclerosis, and altered cardiac autonomic function. Künzli and associates (2005) have published the first epidemiologic evidence to support the suggestion that the systemic effects of PM exposure result in a chronic vascular response.

EXPOSURE TIME WINDOWS

Although the Harvard Six Cities Study and the ACS Study have demonstrated an association between long-term exposure to PM air pollution and mortality (Dockery et al. 1993, Pope et al. 1995, 2002), none of those studies provided an indication of whether there may be a critical time period of exposure responsible for the observed association (Goddard et al. 1995). Investigations by Zeger and associates (1999) and by 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 conditions (Brunekreef 1997; Goldberg et al. 2000, 2001a, b). During the Reanalysis, we developed individual temporal exposure profiles for some subjects in the Harvard Six Cities Study by coding their residence histories; however, limited data about population mobility and limited variation in individual time-dependent exposure profiles precluded identifying critical exposure time windows (Villeneuve et al. 2002).

Identifying these time windows has important implications for establishing time lines for policy interventions that will maximize public health benefits. Doing so requires information on temporal patterns of exposure at the individual level. Given the regulatory importance of the results, further work to develop individual time-dependent exposure profiles for ACS cohort participants is needed.

SPECIFIC AIMS OF THE CURRENT EXTENDED ANALYSIS

A Phase III study was launched by the Reanalysis Team in 2002 to conduct an Extended Analysis of the association between particulate air pollution and mortality in large U.S. cities using alternative spatial models and extended follow-up data from the ACS CPS-II database. For the original study (Pope et al. 1995) and the Reanalysis (Krewski et al. 2000a,b), vital status data were only available for approximately 7 years of follow-up (through December 31, 1989). The Extended Analysis included vital status data with multiple cause-of-death codes for approximately 18 years (through December 31, 2000). In addition, more recent exposure data were compiled based on mean concentrations of air pollutants from various monitoring sites for the metropolitan areas (Krewski et al. 2000a,b).

The Phase III Extended Analysis program addressed the following four key questions (the fourth aim was added in year 2 with supplementary funding):

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

The analysis of ecologic covariates at multiple scales would provide greater understanding of the potential confounding and modifying effects of these variables. Although the Reanalysis suggested that these variables are unlikely to exert a significant confounding influence when the analysis is also controlled for spatial autocorrelation, we planned to directly address several unresolved issues: (a) the scale and spatial boundaries for ecologic covariate data; (b) nested spatial effects (neighborhood effects within MSA effects) and (c) operational variables that represent the separate and combined effects of many ecologic confounders at once. (This aim was pursued in the Nationwide Analysis.)

2. How can spatial autocorrelation and multiple levels of data be taken into account within the random effects Cox model?

The standard Cox regression model commonly used to analyze cohort mortality data is based on the assumption that individual data are independent. However, in Phase II of the Reanalysis, spatial autocorrelation (data for neighboring ACS cohort participants are not independent due to complex spatial patterns) showed that this assumption was not true. Ignoring such spatial autocorrelation —

applying statistical models that assume all data are independently measured and are not correlated — has important implications about bias and the precision of model-based estimates of risk. In Phase II, a random effects Cox model was developed to take into account spatial patterns in the data that could be described at either one (e.g., city) or two (e.g., city and county) levels of clustering. Computer software capable of efficiently fitting the random effects Cox model was also developed. In Phase III, the random effects model would be extended to include spatial autocorrelation of the random effects at two levels of clustering. This extended random effects Cox model would permit us to explore much more complex spatial patterns in the ACS data and may lead to improved estimates of risk. (This aim was pursued in the Nationwide Analysis.)

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

The overall objective was to develop individual time-dependent exposure profiles for a subset of the ACS cohort in order to determine which exposure time windows may be most critical to the association between air pollution and mortality from all causes, CPD, and lung cancer. Whereas almost no information on population mobility was available for Phase II of the Reanalysis, the additional follow-up data available for this Extended Analysis included information on residence changes within the CPS-II Nutrition Cohort (n = 184,194), which was established in 1992 as a subgroup of the larger CPS-II cohort. As in the Harvard Six Cities Study (Dockery et al. 1993), residence histories would be used to develop time-dependent exposure profiles by matching residences to particulate air pollution monitors at the MSA level. The construction of the time-dependent exposure profiles would make use of national exposure data (Lall et al. 2004). (This aim was pursued in the Critical Exposure Time Windows Analysis.)

4. How would refining the exposure gradient to the intra-urban level affect the size and significance of health effects?

A growing body of evidence suggests that refining the scale of exposure estimates and assigning them to cohort members, especially at the intra-urban scale (within cities), will elevate estimates of pollutant-related health effects. For example, Hoek and associates (2002) demonstrated that CPD mortality risk was nearly twice as high for subjects living near major roads than for those living farther away; and Nafstad and colleagues (2004) reported an estimated increase in male mortality risk of over 18% across the gradient of plausible modeled exposures to NO_2. These and similar findings summarized elsewhere (Jerrett et al. 2005b) have demonstrated a need to investigate exposures at the intra-urban scale within the ACS cohort. (This aim was pursued in Intra-Urban Analyses for the New York City and Los Angeles regions.)

NATIONWIDE ANALYSIS

In the Reanalysis (Krewski et al. 2000a,b), we determined values of the ecologic covariates only at the MSA level and did not consider the spatial distribution of ACS cohort members within each MSA. In the current analyses, we determined ecologic covariate values at the ZCA level, which is much smaller geographically than the MSA and thus may be more representative of the economic and social environment of the cohort members.

The cohort follow-up is from 1982 to 2000, thus adding 11 additional years of follow-up to our previous analyses of these data for which we examined follow-up from 1982 to 1989 (Krewski et al. 2000a,b).

Finally, we extended our random effects Cox model, which we had introduced in the Reanalysis (Krewski et al. 2000a,b), to include spatial autocorrelation on the random effects themselves. This more realistic stochastic model specification allowed us to examine the spatial correlation structure of mortality within the cohort and to assess the sensitivity of the association between air pollution and mortality to the spatial structure of the data.

MATERIALS AND METHODS

Study Population

The original ACS study (Pope et al. 1995), the HEI-sponsored Reanalysis (Krewski et al. 2000a,b), and the Extended Analysis reported here all have relied on data from the ACS CPS-II database, an ongoing prospective mortality study of approximately 1.2 million adults.

Cohort participants were enrolled by ACS volunteers beginning in the fall of 1982; most were friends, neighbors, or acquaintances of the volunteers. Enrollment was restricted to persons who were at least 30 years of age and who were members of households with at least one individual 45 years of age or older. Participants completed a confidential questionnaire that included questions about several demographic characteristics, including lifestyle factors such as smoking history and alcohol use, occupational exposures, and level of education.

Participants resided in all 50 states, the District of Columbia, and Puerto Rico. For all analyses, however, the cohort has been restricted to include only those who resided in U.S. metropolitan areas within the 48 contiguous states (including the District of Columbia) for which

air pollution data were available. The number of metropolitan areas to be analyzed differs depending on the pollutant of interest, available data, time period, and the quality control criteria used to compile the data.

Mortality of the participants was ascertained by volunteers in 1984, 1986, 1988, and biannually thereafter using the National Death Index (Calle and Terrell 1993). At each time point, death certificates or multiple cause-of-death codes were obtained for participants known to have died. This Extended Analysis, with an additional 11 years of follow-up, contributes substantially more data on deaths and thereby enhance the statistical power of the analyses.

Air Pollution Exposure Data

For Phase II of the Reanalysis and this Extended Analysis in Phase III, several air pollution variables were examined; data were obtained from these sources (Krewski et al. 2000a,b).

- $PM_{2.5}$ (1979–1983) average concentrations from the Inhalable Particle Monitoring Network (IPMN) between 1979 and 1983;
- $PM_{2.5}$ (1999–2000) average concentrations from the Aerometric Information Retrieval System (AIRS) network from 1999 to 2000;
- PM_{15} (1979–1983) average concentrations from the IPMN between 1979 and 1983;
- TSP (1980) (total suspended particulate) mass from the National Aerometric Database (NAD) for 1980;
- SO_4^{2-} (1980–1981) concentrations from the IPMN and NAD (adjusted for a sampling artifact) for 1980 and 1981;
- SO_4^{2-} (1990) concentrations computed by part of our team at NYU for 1990;
- SO_2 (1980) concentrations from AIRS for 1980;
- NO_2 (1980) concentrations from AIRS for 1980;
- CO (1980) concentrations from AIRS for 1980;
- O_3 (1980) concentrations from AIRS for 1980; and
- O_3 (1980 summer) concentrations from AIRS for April–September, 1980.

Having estimates of $PM_{2.5}$ concentrations for both 1979–1983 and 1999–2000 allowed us to compare exposure at the start and end of the follow-up years. Both annual and summertime O_3 (ozone) levels were estimated because O_3 is generally higher in warm months when people spend more time outdoors or with windows open and thus have higher exposure. Furthermore, in many cities O_3 is monitored only from April to September.

For any pollutant, the average concentration calculated from all available monitoring data within each MSA was used as a summary measure of exposure and assigned to each subject within the MSA. Thus all subjects residing in an MSA were assigned the same exposure value.

Ecologic Covariates

Data Collection and Assembly A major component of this research dealt with improving analytic control of confounding variables over time and across space, particularly at the intra-urban scale. We obtained information about ecologic covariates at the neighborhood scale for approximately 12,000 ZCAs listed in the 1980 U.S. Census database to amass one of the largest sets of ecologic covariates data ever assembled for an air pollution or population health study. These ZCAs covered our MSAs of interest — the 156 cities used for the Reanalysis Project (Krewski et al. 2000a,b) and in the Updated Analysis by Pope and associates (2002).

Compilation of these data for ecologic covariates required that we completely recheck the coverages used for the Updated Analysis by Pope and colleagues in 2002 using the ArcView 9 (2004) Geographic Information System (GIS) software because some census definitions have changed during intervening years.

Identifying ZCAs To collect intra-urban ecologic covariate data, we purchased the complete 1980 census database from the U.S. Census Bureau (USCB), which includes Zip Code tabulation. This census contains data that have not been colleced in subsequent census years. Of particular interest were variables such as the proportion of housing units with air conditioning. These two variables may influence indoor exposures (especially particle penetration) and may confound the air pollution–mortality association if left uncontrolled. Moreover, because the lowest level of geographic identity available for ACS respondents was the Zip Code of residence, we had to rely on aggregating data at the ZCA level for neighborhood analyses. None of the commercial vendors who process historic census data could provide data by Zip Code.

To facilitate finding and extracting data from the USCB database, we developed a relational database management system format and a program that would convert the flat-text USCB file into a relational database. The program was developed using Microsoft Visual Basic to load the USCB file, store it in a logical format analogous to the schema of the database, and output the data of each logical table to the appropriate table in a Microsoft Access database. From this *convertedUSCB.file*, we extracted data for most of the ecologic covariates for approximately 12,000 ZCAs that

cover the 156 MSAs for which we had both pollution and ACS data.

Extracting the ecologic data presented considerable challenges. The most significant obstacle was the incongruity of spatial designations between the United States Postal Service (USPS) and Census Bureau. Zip Codes are defined by the USPS for delivering mail, not for collecting and analyzing the socioeconomic data the census requires. Zip Codes lack definitive boundaries and change frequently at the discretion of postal officials. They do not conform to boundaries of standard geographies such as counties, cities, or census units. Likewise, the Census Bureau does not have maps or digital files that show the boundaries of Zip Codes and they have no file that relates MSAs to Zip Codes for any time period.

We needed to find maps to integrate both sets of boundaries so we could compare the positions of each Zip Code's exact geographic center; we preferred to use maps from 1980, close to the inception of the ACS study (in 1982) when participants' residences were registered with Zip Codes. We contacted, without success, at least six organizations to obtain digital maps of the 1980 Zip Code boundaries: the U.S. Postmaster General, the USCB, Quick Data, Environmental Systems Research Institute (ESRI), the U.S. Geological Survey (USGS) time-series database for watersheds, and the University of Michigan census Web site. We also contacted colleagues at George Washington University who have direct access to the USCB.

Various companies have created maps by interpolating boundaries between Zip Codes. However, the companies we contacted could not provide what we needed: GDT (Lebanon, NH) did not have data available for 1980 (personal communication with Norm Finkelstein, March, 2003); and GeoLytics Inc. (East Brunswick, NJ) produced a 1980 Census CD but without the data we needed (personal communication with Pat Deluca, June, 2003). Neither the USPS Web site nor the ESRI Web site had maps; and the map librarians at McMaster University and the University of Waterloo (both in Ontario, Canada) had nothing we could use. (McMaster University does have a 1980 U.S. Gazetteer book, but the resolution is not very good.)

Despite so many obstacles, out of about 12,000 Zip Codes in which CPS-II participants lived, we were ultimately successful in matching about 10,000 with spatial boundaries consistent with USCB data.

We used a similar process for the Los Angeles area; the ACS data showed that participants resided in 373 ZCAs. When we compared the ACS ZCAs with the USCB Zip Code data, we found that only 275 of them appeared in our USCB file for California (*convertedUSCBforCA.file*). To identify the discrepancies between the ACS and USCB lists, and to consider any impact on the validity of the data, we created a computer query to match the 373 ZCAs in the ACS table with the Zip Codes in census records contained in *convertedUSCBforCA.file*. This query produced a data set that lists the 373 ACS ZCAs along with the corresponding Zip Codes from *convertedUSCBforCA.file*.

This analysis showed that 98 of the 373 ACS ZCAs do not appear in the *convertedUSCBforCA.file.* To assess how excluding participants in these 98 Zip Codes would affect the validity of further analyses based on *converted USCB .file*, we used the USPS "Zip Code Lookup" tool online. By checking the status of each of the missing 98 Zip Codes, we found the following:

- 50 could not be found in the USPS database.
- 36 were described as Post Office [PO] Boxes.
- 3 were described as UNIQUE (serving a discrete building or installation).
- 9 were described as STANDARD (serving a collection of buildings or homes found in the network of streets the Zip Code represents).

We excluded most of these missing ZCAs because we surmised they probably did not contain residential addresses. If the missing ZCAs are randomly distributed, excluding any or all of the cohort members who live in the 98 missing Zip Codes should not adversely affect our results because we are already using a non-random sample that has been arbitrarily cut down to half its original size due to the availability of pollution data. Using the ACS participants residing in 80% or more of the original ACS Zip Codes, we still had ample data to detect effects and, as shown in our subsequent analyses, we did not lose many ACS subjects.

A further complication in reconciling ZCAs with census data was the imperfect correspondence between where people live and where they get their mail. Some people live in rural areas where there is no mail delivery and they collect mail at a post office in a nearby town. The boundaries of such PO Box Zip Codes (about 5,000 of them) are not formally defined. Some urban residents pick up mail at a PO Box, perhaps near their work place, and reside in one Zip Code but receive mail in another.

Extracting Ecologic Covariate Data by ZCA Next we focused on compiling data for the ecologic covariates for analysis. For this study we limited the ecologic covariates to those that had been found to be important as predictors in the Reanalysis (Krewski et al. 2000a,b; also see Ecologic Covariates sidebar):

- median household income;
- poverty: percentage of people with < 125% of poverty-level income;
- unemployment: percentage of persons over the age of 16 years who are unemployed;
- education: percentage of adults with less than a grade 12 education;
- percentage of homes with air conditioning;
- income disparity as evaluated by the Gini coefficient; and
- percentage of the population who are not white (according to self-reported information).

Because we were concerned that comparing ZCA characteristics between cities does not fully control for ecologic confounding, we also created two other variables to include in the Cox models. The first was to aggregate, within an MSA, all the ZCAs in which ACS subjects lived to obtain an average estimate of the ecologic covariates of interest as the MSA value. The second was to differentiate the MSA value from the respective ZCA-specific values. The difference value (DIFF) for a ZCA is the specific value in each ZCA minus the MSA value. This DIFF value ensured that comparisons could be made for local communities, where the ecologic covariates were most likely to be interpretable because local factors that affect the comparisons (such as cost of living, housing conditions, economic opportunities) may be similar.

STATISTICAL METHODS AND DATA ANALYSIS

To examine the association between ambient concentrations of air pollutants and mortality on a national scale, we initially used the standard Cox model to link pollution levels to survival, and adjusted for potentially confounding risk factors. We included data from the CPS-II cohort questionnaires for 44 individual-level covariates:

- eight variables to represent active smoking habits including nonlinear terms for cigarettes per day and number of years smoked;

ECOLOGIC COVARIATES

Ecologic covariates are variables or factors known or suspected to influence mortality that represent the social, economic, and environmental settings (contextual conditions) at community and neighborhood levels where individuals live, work, or spend time.

These data are typically collected for the United States Census and were extracted from the U.S. Census Bureau 1980 database for the Zip Code areas in which participants lived.

Air Conditioning

Percentage of homes with air conditioning

Availability of air conditioning is a good proxy for type of home construction; buildings with air conditioning typically have a relatively low level of infiltration of outdoor air into the structure.

Grade 12 Education

Percentage of adults with less than a grade 12 education

Nationwide Analysis — three stages: less than high school, finished high school, high school plus more

New York and Los Angeles Analyses — two stages: grade 12 completed or not

Ethnic/Racial Identification

Self-reported identification of ethnic/racial group

Nationwide Analysis — percentage not white

New York Analysis — percentage white

Los Angeles Analysis — percentages for white, black, and Hispanic

Unemployment

Percentage of persons over the age of 16 years who are unemployed

Household Income

Median household income

Reported as $000s (U.S. dollars)

Income Disparity

A measure of the inequality of income or wealth distribution within neighborhoods and cities

Reported as the Gini coefficient

Poverty

Percentage of people with income < 125% of the poverty level

(The Los Angeles Analysis included total population instead of poverty.)

- seven variables to characterize former smoking habits;
- one variable for exposure to passive smoke;
- two variables to represent marital status;
- two variables to represent linear and squared terms for body mass index;
- six variables to characterize consumption of beer, wine, and other alcohol;
- seven variables to characterize the subject's main lifetime occupation and his or her possible exposure to PM in the workplace;
- one variable to represent self-reported exposure to dust and fumes in the workplace;
- eight variables to represent diet; and
- two variables to characterize level of education.

The baseline HR was stratified by 1-year age groups, gender, and race. This standard Cox model assumes that all observations are statistically independent, an assumption that was relaxed in subsequent analyses.

However, it is possible that survival may cluster by community or neighborhood. That is, longevity among subjects within the same community or neighborhood may be more similar than longevity between these subjects and those in different geographic locales; this would remain true even after controlling for all known and available personal risk factor information, such as smoking habits, diet, education, and occupation. Furthermore, subjects who live close together typically share similar longevity patterns. Lack of statistical control for these factors can bias both the estimate of air pollution's effect on health and the associated standard errors.

To characterize the statistical error structure of survival data, statistical methods and computer software that incorporate two levels of spatial clustering (e.g., MSA, and ZCA within MSA) have been developed. At each of the two clustering levels we incorporated a spatial autocorrelation structure such that the correlation in survival after adjusting for known risk factors is dependent on the distance between clusters. This distance can be defined in ordinary units (kilometers or miles) or as adjacency, or it can be based on other notions of distance in economic or social terms. The association between concentrations of ambient air pollutants and survival can be examined at the spatial scales both between MSAs and between ZCAs within an MSA, thus permitting a simultaneous exposure assessment of health effects at the macro and micro level.

The Random Effects Cox Model

The standard Cox model, proposed by Sir David Cox (1972), assumes that the survival times for individuals are statistically independent. In our earlier Reanalysis of the ACS cohort, we found evidence of spatial autocorrelation in the data (Krewski et al. 2000a,b) that needed to be considered in the current Extended Analysis. Ma and coworkers (2003) developed a modification of the standard Cox model that incorporates random effects to represent spatial patterns in the data (the random effects Cox model), and established large-sample properties of the maximum likelihood estimates of the model parameters.

Here, we consider a Cox model with two levels of spatially correlated random effects (e.g., MSA, and ZCA within MSA). Suppose that the cohort of interest is composed of m spatially correlated clusters indexed by i. Within the ith cluster, there are J_i spatially correlated subclusters indexed by (i,j). Specifically, we assume that the cluster-level random effects $U_1, ..., U_m$ are positive random effects with expectation and covariance

$$\mathrm{E}(U_i) = 1 \quad \text{and} \quad \mathrm{Cov}(U_s, U_i) = \sigma^2 \rho_1^{\,d(s,i)}, \tag{1}$$

where σ^2 is the MSA-level variance of the random effects, $0 < \rho_1 < 1$, and $d(s,i)$ indicates the distance between clusters indexed by s and i. This distance between two independent clusters is defined as $d(s,i) = \infty$. Negative ρ_1 can be estimated if the distances are integers.

We further assume that, given the cluster-level random effects $U_* = u_* = (u_1, \ldots, u_m)$, the subcluster-level random effects $U_{11}, ..., U_{mJm}$ are positive and spatially dependent with

$$\begin{aligned} &\mathrm{E}(U_{ij} | U_*) = U_i \quad \text{and} \\ &\mathrm{Cov}(U_{st}, U_{ij} | U_*) = \delta(s,i) \nu^2 \rho_2^{\,r[(s,t),(i,j)]}, \end{aligned} \tag{2}$$

where ν^2 is the ZCA-level variance of the random effects, $0 < \rho_2 < 1$, and $r[(s,t),(i,j)]$ indicates the distance between subclusters indexed by (s,t) and (i,j). The Kronecker notation $\delta(s,i)$ is 1 if $s = i$, and 0 otherwise. In addition, the conditional distribution of U_{ij}, given $U_* = u_*$, is assumed to depend on u_i only.

Furthermore, within each subcluster (i,j) there are n_{ij} individuals. Suppose that the cohort is stratified on the basis of one or more relevant covariates and these strata are indexed by $s = 1, 2, ..., a$. The (i,j,k) denotes the kth subject within the jth subcluster within the ith cluster. The (i,j,k)

and s notations do not imply any fixed relationship between strata and clusters; for example, males and females could correspond to different strata, whereas clusters and subclusters could be communities and families that include both males and females. Let the hazard function for individual (i,j,k) from stratum s at time t be denoted by $\lambda_{ijk}^{(s)}(t)$. Given the random effects, we assume that the individual hazard functions are conditionally independent, with

$$\lambda_{ijk}^{(s)}(t) = \lambda_0^{(s)}(t) u_{ij} \exp(\beta^T x_{ijk}^{(s)}). \tag{3}$$

The survival times, either observed or censored, are spatially correlated. The distribution of random effects is assumed to not depend on the regression parameter β. Without loss of generality, we assume that the design matrix $X = (x_{111}^{(1)}, \ldots, x^{(a)}_{mJmnmJm})^T$ is of full rank. A random effects Cox model with a single level of spatially correlated random effects is obtained as a special case of the Cox model with two levels of random effects by setting $v^2 = 0$ and $J_i = 1$ for all i.

Our assumptions (1) and (2) on random effects concern the spatial dependence and the first two moments only. This is desirable since the mechanism by which the unobserved random effects were generated is usually not completely known (Ma et al. 2003).

Auxiliary Random Effects Poisson Models

As in Ma and associates (2003), we make inferences on the random effects Cox models by fitting random effects Poisson models. Let $\tau_{s1}, \ldots, \tau_{sq_s}$ denote the distinct failure times in the sth stratum, with m_{sh} $(s = 1, \ldots, a;\ h = 1, \ldots, q_s)$ indicating the multiplicity of failures occurring at time $\tau_{sh}(s = 1, \ldots, \alpha;\ h = 1, \ldots, q_s)$. The risk set at time τ_{sh} is a subset of stratum s: $\Re(\tau_{sh}) = [(i,j,k) : t_{ijk} \le \tau_{sh}]$, where t_{ijk} is the observed survival time for individual (i,j,k) from the sth stratum. In addition, let $Y_{ijk,h}^{(s)}$ be 1 if a failure occurs for individual (i,j,k) from the sth stratum at time τ_{sh} and 0 otherwise. Let Y and U denote the vectors of the $Y_{ijk,h}^{(s)}$ and the random effects U_i and U_{ij}, respectively. Given the random effects $U = u$, Peto's version of the conditional partial likelihood (Cox and Oakes 1984) is

$$\ell_p(\beta; Y \mid u) = \prod_{s=1}^{a}\prod_{h=1}^{q_s} \frac{\Pi_{(i,j,k)\in\Re(\tau_{sh})} u_{ij}^{Y_{ijk,h}^{(s)}} \left\{\exp\left(x_{ijk}^T\beta\right)\right\}^{Y_{ijk,h}^{(s)}} (m_{sh}!)}{\left\{\sum_{(i,j,k)\in\Re(\tau_{sh})} u_{ij}\ \exp\left(x_{ijk}^T\beta\right)\right\}^{m_{sh}}}. \tag{4}$$

We now define an auxiliary random effects Poisson model. Assume that the components of Y are conditionally independent, given random effects $U = u$, with Po (the Poisson likelihood)

$$Y_{ijk,h}^{(s)} \sim Po[u_{ij} \exp(\alpha_{sh} + x^T_{ijk}\beta)]\ (i,j,k) \in \Re(\tau_{sh}). \tag{5}$$

Given the random effects, the conditional likelihood for the random effects Poisson model is

$$\ell(\alpha,\beta; Y \mid u) = \prod_{s=1}^{a}\prod_{h=1}^{q_s} \frac{\Pi_{(i,j,k)\in\Re(\tau_{sh})} u_{ij}^{Y_{ijk,h}^{(s)}} \left\{\exp\left(\alpha_{sh} + x_{ijk}^T\beta\right)\right\}^{Y_{ijk,h}^{(s)}}}{\exp\left\{\sum_{(i,j,k)\in\Re(\tau_{sh})} u_{ij}\ \exp\left(\alpha_{sh} + x_{ijk}^T\beta\right)\right\}}. \tag{6}$$

Since the random effects vector does not depend on the regression parameter vector, as in Ma and colleagues (2003), we can show that

$$\ell\left(\hat\alpha,\hat\beta; Y, U\right) = \prod_{s=1}^{a}\left\{\prod_{h=1}^{q_s} \frac{m_{sh}^{m_{sh}}\ \exp(-m_{sh})}{m_{sh}!}\right\} \ell_p\left(\hat\beta; Y, U\right),$$

regardless of the covariance structures assumed for random effects. The term in braces on the right-hand side does not depend on the parameters of interest. This demonstrates that the maximum joint Poisson likelihood estimators for the regression parameter vector β from equation (6) are the maximum joint partial likelihood estimators for the regression parameter vector β from equation (4). In addition, the nonparametric estimator of the cumulative baseline hazard function remains the same as given in Ma and associates (2003).

Orthodox, Best-Linear, Unbiased Predictor Approach

Prediction of Random Effects As in Ma and colleagues (2003), we can predict the random effects by the following orthodox, best-linear, unbiased predictor of U given Y.

$$\hat U = \mathrm{E}(U) + \mathrm{Cov}(U,Y)\ \mathrm{Cov}^{-1}(Y,Y)\ (Y - \mathrm{E}[Y]), \tag{7}$$

where $\mathrm{Cov}(Y,Y)$ denotes the marginal covariance of Y instead of the conditional covariance of Y given U. This is the linear unbiased predictor of U given Y, which minimizes the mean squared distance between the random effects U and their predictor within the class of linear functions of Y.

Unlike the case of nested random effects in Ma and associates (2003), the explicit expression for the inverse of Var(Y) is no longer available with spatially correlated random effects. We therefore compute the random effects predictor of U given Y shown in equation (7) through numerically inverted Var(Y). However, because the order of covariance matrix Var(Y) includes all ACS data of air pollution and mortality between 1982 and 2000, the size and amount of data in this matrix is exceptionally large (on the order of over 47 million). Since the matrices Cov(Y,Y) and Cov(U,Y) are dense, even the computer memory required to process these matrices may create a serious problem when analyzing the ACS study data.

To facilitate the computation, we have derived the following sparse representations for Cov(U,Y) and Cov(Y,Y) after some algebra:

$$\begin{aligned}\mathrm{Cov}(U,Y) &= \mathrm{Cov}(U,U)B^T \text{ and} \\ \mathrm{Cov}(Y,Y) &= \mathrm{diag}(\mathrm{E}[Y])+B\mathrm{Cov}(U,U)B^T,\end{aligned} \tag{8}$$

where diag(E[Y]) denotes the diagonal matrix with E[Y] on its diagonal. The matrix B is a sparse matrix of the same order as that of Cov(Y,U) = Cov(U,Y)^T in which column i of B corresponds to cluster i. The elements of column i of B are zeros except being $\mu_{ijk,h}^{(s)} = \exp(\alpha_{sh} + \beta^T x_{ijk}^{(s)})$ at the positions corresponding to those of Cov($Y_{ijk,h}^{(s)}, U_i$) in the matrix Cov(Y,U).

These sparse representations not only make the amount of computer memory feasible, but also make inverting Cov(Y,Y) possible as follows. Let matrices diag(E[Y]) and Cov(U,U) be denoted by A and D; we have

$$\begin{aligned}\mathrm{Cov}^{-1}(Y,Y) &= (A + BDB^T)^{-1} \\ &= A^{-1} - A^{-1}B(B^TA^{-1}B + D^{-1})^{-1}B^TA^{-1},\end{aligned}$$

where A^{-1} = diag(E[Y])$^{-1}$ and D = Cov(U,U) is generally small enough to be inverted numerically. In fact, there is a similar sparse representation of Cov(U,U); therefore the inverse of Cov(U,U) can be obtained through inverting numerically the much smaller covariance matrix of cluster-level random effects. (See Appendix B for the algorithm description and Appendix C for the computer program; both are available on the HEI Web site).

The mean squared distances between the random effects U and its predictor can now be evaluated through the following equation:

$$\begin{aligned}&\mathrm{Cov}(\hat{U} - U,\hat{U} - U) = \\ &\mathrm{Cov}(U,U) - \mathrm{Cov}(U,Y)\,\mathrm{Cov}^{-1}(Y)\,\mathrm{Cov}(Y,U).\end{aligned}$$

In addition, we have the following two desirable orthogonality properties concerning the orthodox best linear unbiased predictor:

$$\mathrm{Cov}(\hat{U} - U,\hat{U}) = \mathbf{0} \quad \text{and} \quad \mathrm{Cov}(\hat{U} - U,Y) = \mathbf{0}.$$

Estimation of Regression Parameters Consider the first estimation of the regression parameters in the case of known dispersion parameters.

As in Ma and colleagues (2003), we can estimate the regression parameters through an optimal estimating function. Differentiating the joint log-likelihood of the auxiliary model for the data and random effects yields the joint score function. By replacing the random effects with their predictors, we have an unbiased estimating function for the regression parameters $\gamma = (\alpha^T,\beta^T)^T$:

$$\psi(\gamma) = \sum_{s=1}^{a}\sum_{h=1}^{q_s}\sum_{(i,j,k)\,\in\,\Re(\tau_{sh})}\left\{Y_{ijk,h}^{(s)} - \hat{U}_{ij}(\gamma)\mu_{ijk,h}^{(s)}(\gamma)\right\}. \tag{9}$$

The sensitivity matrix $S(\gamma)$ and the variability matrix $V(\gamma)$ are defined by

$$\begin{aligned}S(\gamma) &= E_\gamma\left\{\frac{\partial\psi(\gamma)}{\partial\gamma^T}\right\}, \\ V(\gamma) &= E_\gamma\left\{\psi(\gamma)\psi^T(\gamma)\right\}.\end{aligned}$$

According to Ma and associates (2003), we have the following global matrix expression for estimating function $\psi(\gamma)$ because their proof holds regardless of the covariance structure assumed for random effects:

$$\psi(\gamma) = X^T\,\mathrm{diag}(\mathrm{E}[Y])\,\mathrm{Cov}^{-1}(Y,Y)\,(Y - \bar{Y}). \tag{10}$$

Similarly, we have

$$\begin{aligned}S(\gamma) &= -V(\gamma) \\ &= 0 - X^T\,\mathrm{diag}(\mathrm{E}[Y])\,\mathrm{Cov}^{-1}(Y,Y)\,\mathrm{diag}(\mathrm{E}[Y])X.\end{aligned} \tag{11}$$

With an appropriate partition of matrix

$$C = X^T\,\mathrm{diag}(\mathrm{E}[Y])\,\mathrm{Cov}^{-1}(Y,Y) = (C_1, \ldots, C_m),$$

it follows from (10) that

$$\psi(\gamma) = \sum_{i=1}^{m} C_i\left(Y_i - \mathrm{E}[Y_i]\right) = \sum_{i=1}^{m}\psi_i(\gamma),$$

where the unbiased estimating function $\psi_i(\gamma) = C_i(Y_i - E[Y_i])$ corresponds to the ith cluster. The estimating function $\sum_{i=1}^{m}\psi_i(\gamma) = 0$ can easily be shown to be optimal in the sense that it attains the minimum asymptotic covariance for the estimator $\hat{\gamma}$ among a certain class of linear functions of Y (Crowder 1986, 1987).

The solutions $\hat{\gamma}$ of the estimating equation $\sum_{i=1}^{m}\psi_i(\gamma) = 0$ provide estimators of the regression parameters; however, the unbiased estimating functions $\psi_i(\gamma)$, ..., $\psi_m(\gamma)$ are no longer independent because of spatial dependence. Under mild regularity conditions, the component-wise asymptotic normality of parameter estimator $\hat{\gamma}$ can be shown (He and Shao 2000; Chen and Shao 2004). Specifically, for any constant vector of appropriate dimension b, $b^T\hat{\gamma}$ is asymptotically normal with asymptotic mean $b^T\gamma$ and asymptotic variance given by $-b^TS^{-1}(\gamma)b$ as $m \to \infty$.

A modification of the Newton scoring algorithm introduced by Jørgensen and colleagues (1996) can be used to solve this estimating equation: $\sum_{i=1}^{m}\psi_i(\gamma) = 0$. In the modified algorithm, the derivative of $\sum_{i=1}^{m}\psi_i(\gamma) = 0$. is replaced by its expectation $S(\gamma)$ and produces the following updated value for γ:

$$\gamma^* = \gamma - S^{-1}(\gamma)\psi(\gamma).$$

The computation of $S(\gamma)$ can be realized through equation (11).

Estimation of Dispersion Parameters When dispersion parameters are unknown, we use moment estimates for the dispersion parameter with bias correction to give an unbiased estimating function for dispersion parameters. (The detailed process of estimating dispersion parameters is given in Appendix B, which is available on the HEI Web site.) Unlike other reported approaches, the asymptotic variance of our regression parameter estimator is not affected by variability in the dispersion parameter estimators because our estimation function is insensitive to dispersion parameters (Jørgensen and Knudsen, 2004).

The computational procedures regarding initial values and iteration steps are exactly as outlined in Ma and associates (2003).

RESULTS

Distributive statistics for the pollutants are given in Table 1. Of special note is the decline in $PM_{2.5}$ concentrations over 20 years. The mean $PM_{2.5}$ measured in 58 MSAs between 1979 and 1983 was 21.2 µg/m^3; when measured in 116 MSAs between 1999 and 2000, it had declined to 14.0 µg/m^3.

Descriptive statistics for the seven ecologic covariates are given in Table 2. Ecologic covariate data were missing for a small percentage (< 5%) of ZCAs due to small population sizes, for which the USCB randomly assigned values.

We initially conducted a screening analysis using the standard Cox model that assumes observations are independent. We then selected only those relationships between a pollutant and a cause of death that were statistically significant ($P < 0.05$; 95% CIs) and conducted further analyses using our random effects Cox model. We chose this two-step approach because the standard Cox model can be performed in a few minutes, whereas our random effects Cox model with two cluster levels requires approximately one day to calculate each pollutant–outcome relationship.

The HRs associated with specific changes in air pollutant concentrations or with the scale (MSA) of the ecologic covariates are presented in Table 3 for all, CPD, IHD, lung cancer, and all other causes of death. The number of subjects and MSAs are included.

Positive and statistically significant associations between both measures of $PM_{2.5}$ mass and both measures of SO_4^{2-} were observed for all, CPD, and IHD causes of death (Table 3). Significant but weaker associations were observed with these same causes of death for the particle mass measurements of larger sizes of particles (PM_{15} and TSP) and for the concentration of SO_2.

Lung cancer deaths were more strongly associated with both measures of $PM_{2.5}$ mass than with other pollutants. All other causes of death tended to be negatively correlated with air pollutants except for both measures of SO_4^{2-} and SO_2, which all displayed a positive association.

Annual average O_3 concentrations were not clearly linked with mortality; but a positive and statistically significant association was observed between O_3 measured in the April-to-September period and both all and CPD causes of death; no association was observed between O_3 and IHD deaths. Neither NO_2 nor CO was strongly associated with any cause-of-death category.

Overall, most ecologic covariates were individually associated with mortality. Increases in the percentage of homes with air conditioning within the ZCA were negatively associated with mortality for all causes of death examined except lung cancer. Unemployment and poverty levels were positively associated with all five causes of death; household income was negatively associated with all five; and income disparity was not associated with any cause.

The correlations between the seven ecologic covariates and air pollutants, except for CO and annual O_3 (which were not related to mortality), are given in Table 4. These correlations were determined at the ZCA and MSA scales. Pollutant levels were determined at the MSA scale and assigned to each participant in the MSA. Ecologic covariate

Table 1. Distribution of Air Pollutants at the Individual Level[a]

Pollutant Monitoring Period[b]	MSAs / Participants (*n*)	Mean	Variance	Percentiles 0	5	10	25	50	75	90	95	100
$PM_{2.5}$ (1979–1983) ($\mu g/m^3$)	58 351,338	21.20	21.40	10.77	13.73	14.91	17.85	21.69	24.12	26.75	27.89	30.01
$PM_{2.5}$ (1999–2000) ($\mu g/m^3$)	116 499,968	14.02	9.12	5.80	8.80	10.20	11.80	14.40	16.00	17.90	20.00	22.20
SO_4^{2-} (1980–1981) ($\mu g/m^3$)	147 572,312	6.54	7.86	1.40	2.69	2.86	4.36	6.45	8.26	10.71	11.03	15.64
SO_4^{2-} (1990) ($\mu g/m^3$)	52 268,336	6.17	3.85	1.96	2.38	2.86	4.87	6.82	7.37	8.39	8.79	10.65
SO_2 (1980) (ppb)	115 513,450	9.71	23.65	0.02	1.62	3.24	6.61	9.60	12.33	15.13	18.78	29.32
PM_{15} (1979–1983) ($\mu g/m^3$)	57 345,824	59.70	110.9	34.23	43.77	46.79	51.56	61.65	66.95	73.38	73.88	100.8
TSP (1980) ($\mu g/m^3$)	152 578,704	68.37	287.0	41.93	49.14	50.66	56.75	64.81	72.39	90.55	106.9	126.5
O_3 (1980) (ppb)	118 531,826	22.91	21.46	10.40	15.06	18.30	20.61	22.46	25.27	27.96	31.24	41.14
O_3 (Summer 1980) (ppb)	118 531,185	30.15	40.91	11.73	17.05	22.75	26.75	30.67	32.71	37.30	40.66	56.36
NO_2 (1980) (ppb)	76 406,917	27.90	85.25	7.75	14.59	15.88	23.12	26.06	33.71	37.14	51.06	51.06
CO (1980) (ppm)	108 508,538	1.68	0.43	0.19	0.75	0.94	1.17	1.72	2.13	2.58	3.05	3.95

[a] The mean MSA concentration of a pollutant was determined by averaging data from all monitors within the MSA. The mean was then assigned as the exposure level to each participant in the MSA. The subject-specific distribution of $PM_{2.5}$ concentrations is shown.

[b] Dates are the monitoring years from which data averages were derived. Both annual and summer data for O_3 are given because O_3 concentrations are higher in warm seasons; people tend to be more exposed because they spend more time outdoors or with windows open. Also, many cities monitor O_3 only in the warm months.

Table 2. Distribution of Ecologic Covariates Based on 1980 U.S. Census Data and Determined at the ZCA Scale

Ecologic Covariate	Participants (*n*)	Mean	Variance	Percentiles 0	5	10	25	50	75	90	95	100
Air conditioning (%)	571,643	61.0	26.8	0	9.8	20.7	42.1	65.8	85.5	90.1	97.5	100
Grade 12 education (%)	571,351	51.9	8.2	0	36.5	40.5	47.2	53.2	57.7	61.4	63.2	100
Not white (%)	571,485	10.7	16.1	0	0.5	0.8	1.8	4.7	11.8	28.0	45.0	100
Unemployment (%)	571,361	11.6	3.1	0	7.1	8.0	9.7	11.4	13.3	15.5	17.0	60.0
Median household income ($000s)	571,206	20.4	6.4	2.5	11.8	13.2	15.9	19.6	23.7	28.5	32.1	75.0
Income disparity (Gini)	571,197	0.4	0.04	0	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.6
Poverty (%)	571,494	11.6	8.1	0	2.2	3.3	5.9	9.6	15.2	22.1	27.3	41.4

Table 3. HRs of Pollutants and Ecologic Risk Factors for Selected Causes of Death from the Standard Cox Model[a]

Covariate	MSA / Participants (*n*)	Incremental Change[b]	All Causes	Cardio-pulmonary	IHD	Lung Cancer	All Other Causes
$PM_{2.5}$ (1979–1983)	58 351,338	10 μg/m^3	**1.03** **(1.01–1.04)**	**1.06** **(1.04–1.08)**	**1.12** **(1.09–1.16)**	**1.08** **(1.03–1.14)**	0.98 (0.96–1.00)
$PM_{2.5}$ (1999–2000)	116 499,968	10 μg/m^3	**1.03** **(1.01–1.05)**	**1.09** **(1.06–1.12)**	**1.15** **(1.11–1.20)**	**1.11** **(1.04–1.18)**	0.97 (0.94–1.00)
SO_4^{2-} (1980)	147 572,312	5 μg/m^3	**1.04** **(1.03–1.05)**	**1.04** **(1.02–1.05)**	**1.06** **(1.04–1.08)**	**1.05** **(1.02–1.09)**	**1.03** **(1.02–1.05)**
SO_4^{2-} (1990)	52 268,336	5 μg/m^3	**1.07** **(1.05–1.09)**	**1.06** **(1.03–1.09)**	**1.14** **(1.10–1.19)**	**1.04** **(0.97–1.11)**	**1.08** **(1.05–1.11)**
SO_2 (1980)	115 513,450	5 ppb	**1.02** **(1.02–1.03)**	**1.02** **(1.01–1.03)**	**1.04** **(1.02–1.05)**	**1.00** **(0.98–1.02)**	**1.02** **(1.02–1.03)**
PM_{15} (1979–1983)	57 345,824	15 μg/m^3	**1.01** **(1.00–1.02)**	**1.03** **(1.02–1.05)**	**1.06** **(1.04–1.08)**	1.00 (0.97–1.04)	0.99 (0.97–1.00)
TSP (1980)	152 578,704	15 μg/m^3	**1.00** **(1.00–1.01)**	**1.01** **(1.01–1.02)**	**1.01** **(1.00–1.01)**	0.98 (0.97–1.00)	0.99 (0.99–1.00)
O_3 (1980)	118 531,826	10 ppb	1.00 (0.99–1.01)	1.01 (1.00–1.03)	1.01 (0.98–1.03)	1.00 (0.96–1.04)	0.99 (0.97–1.00)
O_3 (Summer 1980)	118 531,185	10 ppb	**1.02** **(1.01–1.02)**	**1.03** **(1.02–1.04)**	1.01 (0.99–1.02)	0.99 (0.96–1.02)	1.01 (1.00–1.02)
NO_2 (1980)	76 406,917	10 ppb	0.99 (0.99–1.00)	1.01 (1.00–1.02)	1.02 (1.00–1.03)	0.99 (0.97–1.01)	0.98 (0.97–0.99)
CO (1980)	108 508,538	1 ppm	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.01 (0.99–1.03)	0.99 (0.97–1.03)	0.99 (0.98–1.01)
Air conditioning (%)	133 574,725	40%	0.98 (0.97–0.99)	0.98 (0.96–0.98)	0.97 (0.95–0.98)	1.00 (0.97–1.02)	0.98 (0.97–0.99)
Grade 12 education (%)	130 571,352	10%	1.01 (1.00–1.02)	1.01 (1.01–1.02)	1.02 (1.00–1.03)	1.00 (0.98–1.02)	1.01 (1.00–1.01)
Not white (%)	131 572,745	10%	1.01 (1.01–1.01)	1.01 (1.01–1.02)	1.00 (0.99–1.01)	1.01 (1.00–1.02)	1.01 (1.00–1.01)
Unemployment (%)	130 571,362	5%	1.04 (1.03–1.05)	1.05 (1.04–1.06)	1.05 (1.03–1.06)	1.04 (1.01–1.07)	1.03 (1.02–1.04)
Median household income ($000s)	130 571,217	$10,000	0.95 (0.94–0.96)	0.95 (0.93–0.96)	0.93 (0.91–0.94)	0.94 (0.91–0.97)	0.96 (0.95–0.97)
Income disparity (Gini)	130 571,208	0.05	0.99 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.02)	1.00 (0.98–1.02)	0.99 (0.98–1.00)
Poverty (%)	133 574,664	0.1	1.03 (1.02–1.03)	1.03 (1.02–1.04)	1.03 (1.02–1.05)	1.04 (1.02–1.06)	1.02 (1.01–1.03)

[a] Model adjusted for 44 individual-level covariates. The baseline hazard function was stratified by age (1-year groupings), gender, and race. HRs are followed by 95% confidence intervals. Bolded values refer to text. Some upper confidence limits have been rounded down and no longer appear larger than the HR. HRs are lower than the upper confidence limit.

[b] Incremental change on which the HR is based: pollutant level or covariate level in a ZCA.

values were determined at the ZCA scale and assigned to each participant in the ZCA. Ecologic covariate values for all subjects in ZCAs were averaged to arrive at the MSA value.

The correlations between pollutants and ecologic covariates vary considerably. For example, for grade 12 education, the correlation with both measures of $PM_{2.5}$ mass and with both measures of SO_4^{2-} is negative at both the ZCA and MSA levels, whereas the correlation is positive with PM_{15} and TSP. Although the correlations tended to have the same sign at both the ZCA and MSA scales, the MSA-based correlations tended to be more extreme than the ZCA-based correlations because the same pollutant concentration had been assigned to all ZCAs within an MSA.

Table 4. Pearson Correlations Between Pollutants Determined at the MSA Scale and Ecologic Covariates Enumerated at the ZCA Scale and Averaged for Each MSA[a]

Ecologic Covariate	Geographic Level	$PM_{2.5}$ (1979–1983)	$PM_{2.5}$ (1999–2000)	SO_4^{2-} (1980)	SO_4^{2-} (1990)	SO_2 (1980)	PM_{15} (1979–1983)	TSP (1980)	O_3 (Summer 1980)	NO_2 (1980)
Air conditioning (%)	ZCA	7	13	4	15	−16	6	1	18	−24
	MSA	8	16	6	20	−19	7	2	22	−31
Grade 12 education (%)	ZCA	**−12**	**−18**	**−20**	**−20**	−1	**19**	**21**	−3	3
	MSA	**−22**	**−32**	**−34**	**−42**	−1	**35**	**38**	−6	6
Not white (%)	ZCA	10	15	1	−1	−8	2	2	5	5
	MSA	28	36	2	−2	−19	6	5	13	13
Unemployment (%)	ZCA	−6	−2	−4	−14	−5	12	11	−2	7
	MSA	−17	−4	−11	−33	−12	31	25	−5	17
Median household income ($000s)	ZCA	12	10	6	−1	6	1	0	−6	19
	MSA	25	18	9	−2	10	2	1	−11	35
Income disparity (Gini)	ZCA	−5	0	−8	−10	−15	3	2	−2	−5
	MSA	−13	1	−18	−29	−36	9	6	−4	−12
Poverty (%)	ZCA	−5	−2	−2	−2	−9	2	−1	7	−13
	MSA	−13	−4	−4	−4	−18	7	−3	14	−28

[a] Correlations (× 100) were based on pollutant and ecologic covariate data assigned to each subject. Pollutant concentrations were calculated at the MSA scale and assigned to all participants within the MSA. Ecologic covariate data were determined at the ZCA scale and averaged for the MSA value. Bolded values refer to text.

The correlations between pairs of the seven ecologic covariates are given in Table 5 by ZCA, MSA, and DIFF (the ZCA values after being adjusted for the MSA value). Large differences in correlations between ecologic covariates were observed for the three levels. For example, the correlation between grade 12 education and unemployment is near zero at the ZCA (4%) and DIFF (−4%) levels but clearly positive at the spatially broader MSA level (31%). Air conditioning is negatively correlated with grade 12 education at the MSA level (−30%) but positively correlated at the DIFF level (26%). Unemployment has an unexpected positive correlation (42%) with household income at the ZCA level, but the expected negative correlation was observed after the broader MSA association was removed (a −53% correlation at the DIFF level).

We note that the correlation between an ecologic covariate at the DIFF level and an air pollutant is zero because for analyses at the MSA level, all ZCAs within an MSA were assigned the same pollutant concentration. However, variation in survival between subjects can be explained, in part, by ecologic covariates that vary both between and within MSAs. Thus, incorporating the ecologic covariates at both the MSA and DIFF levels together in a model (noted as "MSA & DIFF") may more fully account for the risks associated with social determinants of health and thus yield less biased risk estimates of exposure to air pollution.

All combinations of a pollutant and a cause of death that were statistically significant at the 5% level based on the results given in Table 3 are presented in Table 6. HRs were calculated in four ways: without adjustment for the ecologic covariates, and with adjustment for all seven covariates simultaneously at the ZCA, the MSA, or the MSA & DIFF levels together. The air pollution risks tended to be equally sensitive to inclusion of the seven ecologic covariates regardless of their level (ZCA, MSA, or MSA & DIFF).

Adjustment for the seven ecologic covariates tended to either inflate the HR for an air pollutant exposure or have little impact, except for six cases in which adjustment reduced the air pollutant HR: PM_{15} and TSP with CPD deaths; SO_4^{2-} (both 1980 and 1990) with other causes of death; and summertime O_3 with all and CPD causes of death.

In Table 7, the HRs for $PM_{2.5}$ (1999–2000) are used to examine in more detail the sensitivity of the association between air pollution and mortality. HRs related to $PM_{2.5}$ exposure are given for all causes of death and for IHD deaths either not adjusted or adjusted for each of the seven

Table 5. Pearson Correlations Between Ecologic Covariates Enumerated at the ZCA, MSA, or DIFF Levels[a]

Ecologic Covariate	Geographic Level[b]	Air Conditioning	Grade 12 Education	Not white	Unemployment	Household Income	Income Disparity	Poverty
Air conditioning (%)	ZCA	1.0	−1	−3	−30	24	−9	−21
	MSA		**−30**	38	−37	2	14	12
	DIFF		**26**	−34	−32	50	−29	−55
Grade 12 education (%)	ZCA		1.0	−33	**4**	12	−49	−4
	MSA			−51	**31**	8	−26	−37
	DIFF			−28	**−4**	14	−57	−48
Not white (%)	ZCA			1.0	36	−33	37	60
	MSA				1	0	35	43
	DIFF				44	−45	38	65
Unemployment (%)	ZCA				1.0	42	18	42
	MSA					11	12	17
	DIFF					−53	20	49
Median household income ($000s)	ZCA					1.0	−56	−75
	MSA						−70	−81
	DIFF						−53	−72
Income disparity (Gini)	ZCA						1.0	64
	MSA							80
	DIFF							60
Poverty (%)	ZCA							1.0
	MSA							
	DIFF							

[a] Correlations (× 100) were based on ecologic covariate data estimated at the ZCA scale and assigned to each subject. Bolded values refer to text.

[b] The MSA value is the average of all ZCA values within the MSA. The DIFF value for a ZCA is the ZCA value minus the MSA value.

44 INDIVIDUAL-LEVEL COVARIATES
From the 1982 ACS Enrollment Questionnaire

The 1982 enrollment questionnaire for the ACS CPS-II study collected data for variables that measure lifestyle, diet, demographic, occupational, and educational factors that may confound the air pollution–mortality association.

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Eight variables represent **active smoking habits** including nonlinear terms for cigarettes per day and number of years smoked, and seven variables characterize **former smoking habits** (percentage who are current or former smokers; cigarettes per day; years of smoking; started smoking at younger or older than 18 yrs; pipe/cigar smoker).

One variable assesses **exposure to passive smoke** (hours/day exposed to smoking).

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Seven variables characterize the subject's main **lifetime occupation** and his or her possible **exposure to PM** in the **workplace.**

One variable represents self-reported **exposure** to **dust and fumes** in the **workplace**.

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Two variables represent **marital status** (separated/divorced/widowed; single versus married).

Two variables characterize **level of education** (high school; more than high school versus less than high school).

****

Two variables represent linear and squared terms for **body mass index.**

Six variables characterize **consumption of** beer, wine, and other **alcohol** (beer, missing beer, wine, missing wine, liquor, missing liquor).

Eight variables represent **diet** (dietary fat and dietary fiber indices).

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Table 6. HRs for Pollutant and Cause-of-Death Relationships With and Without Adjustment for All Seven Ecologic Covariates

Cause of Death	Ecologic Covariate Adjustment[a]			
	None	ZCA	MSA	MSA & DIFF
$PM_{2.5}$ (1979–1983)				
All causes	1.028 (1.013–1.042)	1.043 (1.027–1.058)	1.040 (1.024–1.056)	1.043 (1.027–1.060)
CPD	1.066 (1.044–1.089)	1.085 (1.062–1.109)	1.086 (1.062–1.112)	1.089 (1.064–1.114)
IHD	1.132 (1.099–1.166)	1.168 (1.132–1.204)	1.176 (1.139–1.215)	1.183 (1.145–1.221)
Lung cancer	1.073 (1.019–1.130)	1.090 (1.034–1.150)	1.084 (1.025–1.145)	1.090 (1.031–1.153)
$PM_{2.5}$ (1999–2000)				
All causes	1.034 (1.016–1.053)	1.054 (1.035–1.075)	1.053 (1.031–1.074)	1.056 (1.035–1.078)
CPD	1.094 (1.065–1.124)	1.126 (1.095–1.158)	1.126 (1.093–1.161)	1.129 (1.095–1.164)
IHD	1.153 (1.111–1.197)	1.210 (1.163–1.258)	1.231 (1.181–1.284)	1.240 (1.189–1.293)
Lung cancer	1.108 (1.037–1.183)	1.135 (1.059–1.216)	1.130 (1.050–1.216)	1.137 (1.056–1.225)
All other causes	0.969 (0.944–0.995)	0.978 (0.952–1.006)	0.975 (0.946–1.004)	0.979 (0.950–1.008)
SO_4^{2-} (1980)				
All	1.037 (1.027–1.046)	1.044 (1.034–1.054)	1.043 (1.032–1.054)	1.045 (1.034–1.056)
CPD	1.037 (1.023–1.051)	1.049 (1.034–1.064)	1.052 (1.036–1.069)	1.054 (1.038–1.071)
IHD	1.064 (1.044–1.085)	1.085 (1.063–1.107)	1.100 (1.077–1.124)	1.104 (1.081–1.128)
Lung cancer	1.055 (1.020–1.090)	1.060 (1.024–1.097)	1.074 (1.035–1.115)	1.077 (1.037–1.118)
All other causes	1.034 (10.21–1.048)	1.038 (1.024–1.053)	**1.031 (1.015–1.046)**	**1.032 (1.017–1.048)**
SO_4^{2-} (1990)				
All causes	1.069 (1.049–1.090)	1.089 (1.066–1.112)	1.082 (1.056–1.109)	1.086 (1.060–1.113)
CPD	1.057 (1.027–1.088)	1.095 (1.061–1.130)	1.110 (1.070–1.152)	1.114 (1.074–1.156)
IHD	1.142 (1.097–1.189)	1.196 (1.145–1.248)	1.282 (1.219–1.349)	1.288 (1.225–1.355)
All other causes	1.086 (1.056–1.117)	1.090 (1.057–1.124)	**1.065 (1.027–1.104)**	**1.068 (1.030–1.107)**
SO_2 (1980)				
All causes	1.021 (1.016–1.027)	1.022 (1.016–1.028)	1.019 (1.013–1.025)	1.020 (1.014–1.026)
CPD	1.020 (1.012–1.028)	1.021 (1.012–1.029)	1.021 (1.012–1.031)	1.022 (1.013–1.032)
IHD	1.037 (1.026–1.049)	1.043 (1.031–1.055)	1.057 (1.044–1.071)	1.059 (1.046–1.072)
All other causes	1.025 (1.017–1.033)	1.025 (1.017–1.034)	1.019 (1.009–1.028)	1.019 (1.010–1.029)
PM_{15} (1979–1983)				
CPD	1.034 (1.019–1.048)	1.034 (1.018–1.049)	1.037 (1.019–1.054)	**1.025 (1.013–1.037)**
IHD	1.061 (1.040–1.082)	1.074 (1.052–1.097)	1.095 (1.069–1.122)	1.064 (1.048–1.082)
TSP (1980)				
CPD	1.013 (1.007–1.020)	**1.012 (1.005–1.019)**	**1.010 (1.002–1.018)**	**1.007 (1.002–1.012)**
All other causes	0.992 (0.986–0.999)	0.993 (0.986–1.000)	0.996 (0.988–1.003)	0.998 (0.993–1.003)
O_3 (Summer 1980)				
All causes	1.016 (1.008–1.024)	**1.014 (1.006–1.023)**	**1.006 (0.998–1.015)**	**1.008 (0.999–1.017)**
CPD	1.028 (1.016–1.041)	**1.027 (1.014–1.040)**	**1.015 (1.002–1.028)**	**1.016 (1.002–1.029)**
NO_2 (1980)				
IHD	1.018 (1.004–1.031)	1.030 (1.015–1.045)	1.033 (1.016–1.051)	1.035 (1.017–1.053)
All other causes	0.982 (0.972–0.991)	0.986 (0.976–0.997)	0.990 (0.978–1.002)	0.991 (0.979–1.003)

[a] Determined with the standard Cox model, which included the 44 individual-level covariates. The models with no adjustment for ecologic covariates included only those participants who resided in ZCAs for which ecologic covariate data were available. Ecologic covariate data were derived for each ZCA and averaged for the MSA value. The DIFF value for a ZCA is the ZCA value minus the MSA value. MSA & DIFF indicates both levels of data were included in the model together. HRs are followed by 95% confidence intervals. Bolded values refer to text.

Table 7. HRs for All and IHD Causes of Death Associated with a 10-μg/m^3 Change in $PM_{2.5}$ (1999–2000) from the Standard Cox Model Unadjusted or Adjusted for a Single Ecologic Covariate[a]

Ecologic Covariate Adjustment	All Causes		IHD	
	$PM_{2.5}$ (1999–2000)	Ecologic Covariate[b]	$PM_{2.5}$ (1999–2000)	Ecologic Covariate[b]
No adjustment	**1.034 (1.016–1.053)**	—	**1.153 (1.111–1.197)**	—
Air conditioning (%)	1.040 (1.021–1.059)	0.976 (0.968–0.984)	1.160 (1.118–1.204)	0.972 (0.955–0.989)
Grade 12 education (%)	1.043 (1.025–1.063)	1.016 (1.009–1.023)	1.171 (1.127–1.216)	1.031 (1.016–1.046)
Not white (%)	1.028 (1.010–1.047)	1.009 (1.006–1.013)	1.158 (1.115–1.203)	0.997 (0.989–1.005)
Unemployment (%)	1.036 (1.018–1.055)	1.040 (1.032–1.049)	1.155 (1.113–1.199)	1.046 (1.027–1.064)
Median household income ($000s)	**1.048 (1.030–1.068)**	**0.950 (0.942–0.959)**	**1.177 (1.134–1.222)**	0.924 (0.906–0.942)
Income disparity (Gini)	1.036 (1.017–1.055)	0.993 (0.987–1.000)	1.156 (1.113–1.200)	1.001 (0.988–1.014)
Poverty (%)	1.036 (1.018–1.055)	1.027 (1.020–1.035)	1.156 (1.113–1.199)	1.029 (1.015–1.045)

[a] Model included 44 individual-level covariates and adjusted for a single ecologic covariate at the ZCA scale. The baseline hazard function was stratified by age (1-year groupings), gender, and race. HRs are followed by 95% confidence intervals. Bolded values refer to text.

[b] HRs for the ecologic covariate itself when in the model with $PM_{2.5}$.

ecologic covariates separately. The all-cause mortality HR increased after adjustment for six of the seven covariates; only percentage of population who are not white reduced the risk from 1.034 (95% CI, 1.016–1.053) to 1.028 (95% CI, 1.010–1.047). The IHD risk increased after adjustment for any of the seven ecologic covariates.

The Reanalysis and Updated Analysis (Krewski et al. 2000a,b; Pope et al. 2004) had shown that the subjects' level of education modified the effect of $PM_{2.5}$ exposure on mortality. To explore this further, we stratified educational status based on the individual-level data gathered at ACS enrollment: low education (less than grade 12), medium education (grade 12 completed), and high education (some education beyond grade 12 completed). Models included 42 of the individual-level covariates used in other analyses (two variables that represented education attainment were removed) with and without the seven ecologic covariates. Results are presented in Table 8.

For all-cause and CPD mortality, we observed a slight effect modification by level of education, although in the case of CPD, the effect modification was confounded by including the ecologic covariates.

For lung cancer deaths, the analyses with high education showed the lowest effects of $PM_{2.5}$ exposure on mortality, but there appeared to be little difference between risks in the two lowest strata of education attainment. These findings follow a pattern similar to what was reported in the earlier studies, but the patterns are less clear with the longer follow-up period used here (all P values for effect modification were > 0.10).

For IHD mortality, in contrast to previous findings, level of education produced a positive modification effect; the largest effects were observed in the high education stratum. This pattern was consistent between results from models both with and without controlling all seven ecologic covariates, but was more pronounced when the ecologic covariates were included, which had the effect of increasing the HR in all strata. Yet, the ratio between the high and low educational strata is roughly the same in results from models with and without the ecologic control.

SENSITIVITY OF AIR POLLUTION RISK TO THE ERROR STRUCTURE OF THE RANDOM EFFECTS COX MODEL

We illustrate the sensitivity of the risk estimates and their standard errors to model specification using the ACS data with follow-up from 1982 to 2000. We selected $PM_{2.5}$ (1999–2000) as the pollutant measure and all causes of death and IHD deaths as the outcomes to illustrate the random effects Cox model and the sensitivity of an air pollution–mortality association to the model specification.

The spatial structure of the random effects Cox model was specified by a nearest-neighbor approach at both the MSA and ZCA levels. Here, two ZCAs are assumed to be neighbors if any part of their boundaries are connected. For each ZCA, we constructed a Thiessen polygon, which has the property that any point inside the polygon is closer

Table 8. Modification of HRs by Education at Individual Level for a 10-μg/m^3 Change in $PM_{2.5}$ (1999–2000) from the Standard Cox Model by Cause of Death[a]

Level of Education / Participants (*n*)	Ecologic Covariates in Model	All Causes	CPD	IHD	Lung Cancer	All Other Causes
< Grade 12 education (59,168)	No	1.064 (1.004–1.126)	1.127 (1.044–1.216)	**1.111** (0.979–1.260)	**1.187** (1.020–1.381)	0.955 (0.883–1.034)
	Yes	1.082 (1.024–1.144)	1.157 (1.077–1.245)	**1.173** (1.022–1.347)	**1.217** (1.025–1.446)	0.960 (0.886–1.040)
Grade 12 education (152,024)	No	1.060 (1.013–1.110)	1.086 (1.016–1.160)	**1.195** (1.072–1.333)	**1.192** (1.057–1.344)	0.999 (0.942–1.061)
	Yes	1.072 (1.020–1.127)	1.112 (1.040–1.189)	**1.248** (1.109–1.404)	**1.236** (1.081–1.413)	0.995 (0.931–1.062)
> Grade 12 education (274,941)	No	1.041 (1.001–1.083)	1.083 (1.023–1.146)	**1.225** (1.121–1.339)	**1.024** (0.912–1.150)	1.005 (0.956–1.058)
	Yes	1.055 (1.018–1.094)	1.115 (1.060–1.173)	**1.331** (1.215–1.458)	**1.043** (0.934–1.164)	1.006 (0.956–1.060)

[a] Model included 42 individual-level covariates (the two covariates for education attainment were omitted for this analysis) and with or without adjustment for the seven ecologic covariates at the MSA & DIFF levels together. The baseline hazard function was stratified by age (1-year groupings), gender, and race. HRs are followed by 95% confidence intervals. Bolded values refer to text. All *P* values > 0.10 for effect modification.

to the geographic center (centroid) of the ZCA than to the centroid of any other ZCA. ZCA polygons were joined to create each MSA polygon; following this pattern, the 48 contiguous United States were covered by polygons. The random effects associated with two MSAs (or ZCAs) are assumed to have a common correlation if they are neighbors and to be uncorrelated if they are not neighbors. Two ZCAs in different MSAs are assumed to be uncorrelated.

The HRs for a 10-μg/m^3 change in $PM_{2.5}$ (1999–2000) are given in Table 9 under selected error specifications for the random effects Cox model with: (a) no adjustment for the seven ecologic covariates, (b) adjustment for the ecologic covariates defined at only the ZCA level, and (c) adjustment for the covariates defined at both the MSA & DIFF levels. All and IHD causes of death were examined.

Inclusion of clustering at both the MSA & DIFF levels and at the ZCA level increased the estimate of the $PM_{2.5}$ (1999–2000) HR, with or without adjustment for the ecologic covariates. This is likely due to the manner in which the random effects Cox model weights the importance of the observations. The standard Cox model gives equal weight to all subjects' information whereas the random effects Cox model used here weights the information differently for each cluster. The variation in weight among clusters is positively associated with the cluster variance. Thus the larger MSAs are given less weight in the random effects model than in the standard Cox model in which responses are assumed to be statistically independent. An increase in the HR using the random effects model implies that the larger MSAs did not clearly follow our model specification, particularly the assumptions about there being a log-linear relationship between mortality and the associated exposure to $PM_{2.5}$ (1999–2000). Thus they are given less weight even though their sample size may be larger.

The inclusion of additional variance due to clustering of survival experience at the MSA level also inflates the uncertainty in the $PM_{2.5}$ (1999–2000) HR estimate, as evidenced by wider confidence intervals (CIs) compared with the case in which the MSA and ZCA variances are set to 0 (equivalent to the standard Cox model assumption). There was more unexplained variation in survival between ZCAs than between MSAs for all causes of death, but this pattern is not replicated for IHD deaths.

Inclusion of the seven ecologic covariates defined at the ZCA level reduced both the MSA and ZCA random effects variances. However, a further reduction was observed when these covariates were defined by their MSA & DIFF levels together.

The inclusion of spatial autocorrelation at both the MSA and ZCA levels lowered the $PM_{2.5}$ (1999–2000) HR and widened the CIs, which suggests that there may be some evidence of spatial clustering of residual mortality coinciding with the spatial pattern of $PM_{2.5}$ (1999–2000). However, our estimate of spatial autocorrelation at the MSA level (0.36) was at the boundary of allowable values. This implies that the model is ill-specified, likely due to the very large number of nearest neighbors for each MSA, particularly in the Eastern U.S. Although we need to interpret these results with caution, we can view them as a situation with the maximum spatial autocorrelation permissible, and thus we included them in our sensitivity analysis as an extreme case.

Table 9. Sensitivity Analysis of the Deterministic and Stochastic Parameters of the Random Effects Cox Model for All and IHD Causes of Death[a]

Ecologic Covariate Adjustment	HR for a 10-μg/m^3 Change in $PM_{2.5}$ (1999–2000)	MSA Variance ($\times 10^{-3}$)	MSA Autocorrelation	ZCA Variance ($\times 10^{-3}$)	ZCA Autocorrelation
All Causes					
Standard Cox model					
None	1.034 (1.016–1.053)	0	0	0	0
ZCA	1.054 (1.035–1.075)	0	0	0	0
MSA & DIFF	1.056 (1.035–1.078)	0	0	0	0
No autocorrelation at MSA or ZCA level					
None	1.057 (1.014–1.101)	1.62	0	4.35	0
ZCA	1.080 (1.047–1.114)	1.21	0	3.06	0
MSA & DIFF	1.075 (1.041–1.110)	0.95	0	3.01	0
Autocorrelation at MSA and ZCA levels					
None	1.048 (0.989–1.110)	1.66	0.36	5.65	0.29
ZCA	1.074 (1.036–1.112)	1.25	0.36	3.61	0.23
MSA & DIFF	1.071 (1.032–1.111)	1.06	0.36	3.45	0.22
IHD					
Standard Cox model					
None	1.153 (1.111–1.197)	0	0	0	0
ZCA	1.210 (1.163–1.258)	0	0	0	0
MSA & DIFF	1.240 (1.189–1.293)	0	0	0	0
No autocorrelation at MSA or ZCA level					
None	1.181 (1.092–1.278)	10.51	0	10.36	0
ZCA	1.243 (1.147–1.346)	10.24	0	8.40	0
MSA & DIFF	1.287 (1.179–1.404)	9.47	0	8.05	0
Autocorrelation at MSA and ZCA levels					
None	1.168 (1.065–1.280)	10.49	0.36	15.61	0.30
ZCA	1.229 (1.120–1.347)	10.15	0.36	10.64	0.28
MSA & DIFF	1.276 (1.156–1.409)	9.79	0.36	10.06	0.27

[a] Model included 44 individual-level covariates. The baseline hazard function was stratified by age (1-year groupings), gender, and race. A 0 indicates the parameter was not included in the model. HRs are followed by 95% confidence intervals.

We also considered the sensitivity of our results to the spatial definition of clusters. Here, we used "state" and "MSAs within state" to define the cluster levels. There are far fewer nearest neighbors for the state specification than for the MSA specification. We postulate that state is a natural cluster definition because many health care programs and resources that influence health, and thus longevity, are administered at the state level.

$PM_{2.5}$ data for 1999–2000 were available for 44 states and 116 MSAs. We included the 44 individual-level covariates in random effects Cox models with adjustment for the seven ecologic covariates defined at the MSA & DIFF levels together. Including both state and MSA-within-state clusters increased the $PM_{2.5}$ (1999–2000) HRs compared with results from the standard Cox model (Table 10, top row under each cause of death) and also increased the uncertainty in the estimates, as evidenced by the much wider CIs. Including spatial autocorrelation at both cluster levels reduced the HRs compared with a model that included both state and MSA random effects but no spatial autocorrelation. Similar patterns were observed with and without adjustment for the ecologic covariates and for both all causes of death and IHD deaths (results not shown).

ALTERNATIVE FORMULATION OF THE CONCENTRATION–RESPONSE FUNCTION

We investigated the form of the concentration–response function between $PM_{2.5}$ (1999–2000) and selected causes of death. Our alternative formulation of the function is the natural logarithm of concentration. We selected this for two reasons. First, the logarithm of concentration yields a

flexible mathematical form to relate exposure to survival within the proportional-hazards family of models. Here we have

$$\lambda^e(t) = \lambda_0(t)U^{r(e)}\exp\{\log(PM_{2.5})\gamma + X^e\beta\}$$

$$\lambda^e(t) = \lambda_0(t)U^{r(e)}\exp(X^e\beta) * (PM_{2.5})^{\gamma}$$

where the unknown parameter γ is a scalar. If $\gamma < 1$, the relationship between $PM_{2.5}$ and mortality concaves downward, which yields larger HRs at lower concentrations; and if $\gamma > 1$, the association concaves upward, which yields smaller HRs at lower concentrations. This formulation predicts HRs that are a function of concentration and thus a single risk value will not represent the association between exposure and response throughout the concentration range. The second reason is that the Updated Analysis (Pope et al. 2002) suggested that the logarithm of PM may be a slightly better predictor of risk than the linear form.

The HRs associated with a 10-μg/m^3 change in $PM_{2.5}$ (1999–2000) concentrations based on linear and log-linear functions of PM are given in Table 11 for selected causes of death with and without adjustment for the seven ecologic covariates defined at both the MSA & DIFF levels together. Two separate spans of a 10-μg/m^3 change in $PM_{2.5}$ are examined for the logarithmic formulation: from 5 to 15 μg/m^3 and from 10 to 20 μg/m^3 since the HR based on the logarithmic function varies with concentration. A concentration of 5 μg/m^3 represents the minimum of the distribution of $PM_{2.5}$ (1999–2000) and a concentration of 20 μg/m^3 represents the 95th percentile of the concentration distribution.

Our random effects Cox model was used to estimate the HRs with only one level of clustering at the MSA scale. For $PM_{2.5}$, the logarithmic function was a slightly better predictor of the variation in survival among MSAs than the linear function because the MSA random effect variance is somewhat smaller (than that for the linear function) for each cause-of-death category except all other causes. As

Table 10. Sensitivity Analysis of the Deterministic and Stochastic Parameters of the Random Effects Cox Model Due to Geographic Cluster Definition for All and IHD Causes of Death[a]

Without or With Spatial Autocorrelation	HR for a 10-μg/m^3 Change in $PM_{2.5}$ (1999–2000)	State Variance ($\times 10^{-3}$)	State Autocorrelation	MSA Variance ($\times 10^{-3}$)	MSA Autocorrelation
All Causes					
Standard Cox model	1.056 (1.035–1.078)	0	0	0	0
Clustering by state only					
Without	1.055 (1.019–1.092)	1.61	0	0	0
With	1.045 (1.009–1.083)	1.90	0.23	0	0
Clustering by state and MSA					
Without	1.072 (1.031–1.116)	1.22	0	0.32	0
With	1.066 (1.021–1.112)	1.26	0.20	0.43	0.29
IHD					
Standard Cox model	1.240 (1.189–1.293)	0	0	0	0
Clustering by state only					
Without	1.284 (1.189–1.387)	13.14	0	0	0
With	1.232 (1.141–1.330)	14.04	0.39[b]	0	0
Clustering by state and MSA					
Without	1.320 (1.192–1.460)	9.74	0	3.05	0
With	1.241 (1.112–1.382)	8.83	0.39[b]	4.07	0.15

[a] Analysis based on 44 states and 116 MSAs. The model included 44 individual-level covariates and adjusted for seven ecologic covariates simultaneously. defined at the MSA and DIFF levels. The baseline hazard function was stratified by age (1-year groupings), gender, and race. A 0 indicates the parameter was not included in the model. HRs are followed by 95% confidence intervals.

[b] The estimation algorithm yielded a value of autocorrelation at the boundary of acceptable values, which indicates that the model was not properly specified and the results should be interpreted with caution.

Table 11. Comparison of HRs for Selected Causes of Death Associated with a 10-μg/m^3 Change in $PM_{2.5}$ (1999–2000) Concentrations Based on Inclusion of Linear $PM_{2.5}$ or log($PM_{2.5}$) in the Random Effects Cox Model with Clustering at the MSA Level[a]

	Linear $PM_{2.5}$ (1999–2000)		Log ($PM_{2.5}$ [1999–2000])		
Ecologic Covariate Adjustment	HR for 10-μg/m^3 Change	MSA Variance ($\times 10^{-3}$)	HR for Change from 5 to 15 μg/m^3	HR for Change from 10 to 20 μg/m^3	MSA Variance ($\times 10^{-3}$)
All Causes					
None	1.060 (1.024–1.097)	1.86	1.095 (1.044–1.148)	1.059 (1.028–1.091)	1.81
MSA & DIFF	1.078 (1.043–1.115)	1.07	1.128 (1.077–1.183)	1.079 (1.048–1.112)	1.00
CPD					
None	1.094 (1.040–1.150)	3.96	1.145 (1.068–1.228)	1.089 (1.042–1.138)	3.87
MSA & DIFF	1.128 (1.077–1.182)	1.86	1.208 (1.132–1.290)	1.127 (1.081–1.174)	1.66
IHD					
None	1.196 (1.103–1.298)	12.13	1.315 (1.175–1.470)	1.188 (1.107–1.275)	11.73
MSA & DIFF	1.287 (1.177–1.407)	10.56	1.484 (1.311–1.680)	1.283 (1.186–1.387)	9.80
Lung Cancer					
None	1.122 (1.040–1.210)	2.03	1.193 (1.071–1.330)	1.118 (1.044–1.197)	1.90
MSA & DIFF	**1.142 (1.057–1.234)**	0.56	**1.236 (1.114–1.372)**	1.143 (1.071–1.221)	0.45
All Other Causes					
None	1.008 (0.968–1.051)	1.95	1.023 (0.965–1.083)	1.014 (0.978–1.052)	1.97
MSA & DIFF	1.010 (0.968–1.055)	1.37	1.026 (0.970–1.085)	1.016 (0.981–1.053)	1.39

[a] Model included 44 individual-level covariates with and without adjustment for seven ecologic covariates simultaneously. MSA & DIFF indicates both levels of data were included in the model together. The baseline hazard function was stratified by age (1-year groupings), gender, and race. HRs are followed by 95% confidence intervals. Bolded values refer to text.

expected, the HR based on the logarithm formulation yielded higher values for the difference between 5 and 15 μg/m^3 compared with the linear formulation; and lower values were observed for the difference between 10 and 20 μg/m^3 except for other causes of death in which the logarithmic formulation yielded larger HRs compared with the linear formulation.

The choice of functional relationship between PM exposure and mortality can make a considerable difference in the predicted risk at lower concentrations. For example, the HR for lung cancer adjusted for the ecologic covariates based on the linear formulation is 1.142 (95% CI, 1.057–1.234), whereas the HR based on the logarithmic formulation is 1.236 (95% CI, 1.114–1.372), a 66% increase in risk.

DISCUSSION AND CONCLUSIONS

Our overall objective was to further analyze the association between particulate air pollution and all-cause and cause-specific mortality in large U.S. cities using alternative spatial models and extended follow-up data from the ACS CPS-II cohort. Specifically, we examined whether social, economic, and demographic ecologic covariates confound the relationship between particulate air pollution and mortality, and we explored complex spatial patterns in the CPS-II data with an extended random effects Cox model.

Results of the Reanalysis Project showed that ecologic covariates estimated on the MSA level were unlikely to exert a significant confounding influence on the association between particulate air pollution and mortality (Krewski et al. 2000a,b). Nevertheless, unresolved questions remained about the scale and the construct validity of the variables used. Therefore, in the current study we examined the influence of ecologic covariates at several scales: the ZCA scale (data obtained from the 1980 U.S. Census), the MSA scale (by averaging information on all ZCAs within an MSA), and by the value of the difference obtained between the ZCA-specific value and the MSA value (DIFF).

Results from the CPS-II cohort with an additional eleven years of follow-up in this Extended Analysis revealed positive and significant associations between a 10-μg/m^3 change in $PM_{2.5}$ mass or a 5-μg/m^3 in SO_4^{2-} mass (with the exception of SO_4^{2-} [1990]) and all-cause, CPD, IHD, and lung cancer deaths. Particles of larger size (PM_{15} and TSP) were associated with positive, although smaller, increases in risk of all-cause, IHD, and CPD deaths. Mortality from IHD compared with other causes of death was consistently associated with the largest HR estimates. Indeed, other recent investigations have supported an association between particles and adverse cardiovascular effects (Krewski et al. 2000a,b; Pope et al. 2004; Künzli et al. 2005). Further investigations to examine the cardiovascular health effects of particulate air pollution are critical to understanding the nature of the association.

Fewer significant associations were observed with the gaseous pollutants. SO_2, which is likely to be an indicator of other pollutants related to mortality, was significantly associated with higher mortality from all causes, CPD, and IHD, although the strength of the associations tended to be weaker than the associations observed with particles. Summertime O_3 was related with all-cause and CPD mortality in this study; this relationship was statistically significant in the Reanalysis (relative risk = 1.08, 95% CI, 1.01–1.16; Krewski et al. 2000a,b).

Due to differences in modeling methods and use of multi-level variables, HR estimates presented here are not directly comparable with the Updated Analysis using alternate modeling strategies (Pope et al. 2002) or with the Reanalysis (Krewski et al. 2000a,b), in which different scales or levels of pollutant increases were used to calculate relative risks. This Expanded Analysis evaluated the level of risk associated with a 10-μg/m^3 increase in $PM_{2.5}$ and a 5-μg/m^3 increase in SO_4^{2-}. The Reanalysis evaluated a 24.5-μg/m^3 increase in $PM_{2.5}$ and a 19.9-μg/m^3 increase in SO_4^{2-} (those values were equal to the difference in mean concentrations between the most- and least-polluted cities from the Harvard Six Cities Study [Krewski et al. 2000a]).

We wanted to directly compare the HRs between the three follow-up periods that have been examined: 1982–1989 (the Reanalysis, Krewski et al. 2000a,b); 1982–1998 (the Updated Analysis, Pope et al. 2002); and 1982–2000 (the current Extended Analysis) (see also the section Implications of the Findings / Comparison of Data Sets and Analytic Methods for the Three Follow-Up Time Periods). To do so, we estimated the HR for a 10-μg/m^3 increase in the average $PM_{2.5}$ concentration for 1979–1983 in 58 MSAs, and for 1999–2000 in 116 MSAs, and controlled for the 44 individual-level covariates using the standard Cox model (both with and without control for the ecologic covariates) for mortality from all causes, CPD, IHD, lung cancer, and all other causes. Over the three follow-up time periods, deaths from all causes increased to 90,783 in the 58 MSAs and 128,954 in the 116 MSAs; and deaths from IHD increased to 20,651 in the 58 MSAs and 29,989 in the 116 MSAs (see Table 32). For the $PM_{2.5}$ (1979–1983) sampling period (58 MSAs), we observed a small decrease in the HR estimate for deaths from all causes between the initial follow-up period (1.048, 95% CI, 1.022–1.076) and the later two periods (1.031, 95% CI, 1.015–1.047; and 1.028, 95% CI, 1.014–1.043) (see Table 33). We found no temporal pattern in risk for IHD deaths (1.122, 95% CI, 1.066–1.181; 1.130, 95% CI, 1.094–1.166; and 1.133, 95% CI, 1.100–1.167). Declining risk could be due to exposure misclassification increasing over time. We assigned exposure based on residence location in 1982; and the percentage of cohort members who have moved has to have increased over time. Also, $PM_{2.5}$ concentrations have clearly declined over the follow-up period, so assigning a single exposure measure would not have fully captured this temporal pattern. Finally, as the cohort ages, air pollution effects may decline due to the healthy survivor effect.

The ecologic covariates evaluated were associated with overall and cause-specific mortality and correlated with specific air pollutants, which is consistent with the definition of a possibly confounding variable. Poverty and unemployment were positively associated and household income was negatively associated with all cause-of-death categories. Historically, indicators of community-level socioeconomic status such as these have been associated with overall and cause-specific mortality (Kaplan et al. 1996; Boyd et al. 1999; Winkleby and Cubbin 2003). They likely reflect a complex interaction of environmental, social, and behavioral factors and of available health services that all influence health status and longevity. However, income disparity (a related measure of economic status) was not associated with mortality in the ACS CPS-II cohort. This is surprising; we would have expected income disparity to be positively associated with mortality, as in some previous studies (Cooper et al. 2001; Ram 2005; Singh and Siahpush 2006), although in the Reanalysis (Krewski et al. 2000a,b), income disparity was also not strongly related with mortality. It may be that controlling the 44 individual-level covariates (including such factors as marital status, smoking, and diet) removed any potential effect of income disparity on mortality in that study; or it may be that an inadequate variable was used.

All ecologic covariates were based on data from the 1980 U.S. Census. Spatial patterns of mortality and ecologically defined sociodemographic factors could change

independently of each other over follow-up time and thus lead to misclassification of their values and relationships. Discussion of the impact of population mobility in the ACS cohort is presented elsewhere (Jerrett et al. 2007). Both the positive and negative influences of different ecologic covariates on mortality require careful interpretation as to their potential confounding effects on the air pollution–mortality association.

Spatial patterns of ecologically defined sociodemographic factors and air pollution for the CPS-II cohort are complex. Ecologic covariates were both positively and negatively correlated with concentrations of certain specific air pollutants (see Table 4). Having less than a grade 12 education was most frequently strongly correlated with air pollutant indices — negatively correlated with concentrations of $PM_{2.5}$ and SO_4^{2-}, but positively correlated with particles of larger size. Conversely, percentage of the population that is not white and median household income was positively correlated with $PM_{2.5}$ mass.

Correlations between ecologic covariates varied according to the unit of aggregation (ZCA or MSA), which indicates that spatial patterns in the data differ according to scale. Interestingly, the largest correlations were not necessarily found in the smallest unit of observation (ZCA) as might be expected; this could indicate that complex spatial patterns of sociodemographic factors are also involved. Strong correlations were observed between some of the ecologic covariates; therefore, caution is required in interpreting models that include all of the ecologic covariates simultaneously due to the possible resulting statistical instability.

Since variation in survival between subjects can be explained, in part, by ecologic covariates that vary both between and within MSAs, we conducted analyses that adjusted for the ecologic covariates at both the MSA & DIFF levels together. We hoped to account for sociodemographic risks more completely and thus yield less biased risk estimates of exposure to air pollution. In nearly all models that adjusted for the seven ecologic covariates simultaneously, the HR tended to increase in comparison to models with no adjustment, although many of the differences were small. The largest increases were observed for mortality from IHD associated with $PM_{2.5}$ (1999–2000) and SO_4^{2-} (1990); the magnitude of the inflation of HR was 7.5% and 12.8%, respectively; this model included ecologic covariates at both the MSA & DIFF levels simultaneously.

When we evaluated the independent effect of each ecologic covariate at the ZCA scale on the HR for the association between $PM_{2.5}$ and mortality from all causes and from IHD, we found that each covariate independently increased the strength of the association (except for percentage who are not white with all-cause mortality). We found the largest increases when household income was the only ecologic covariate included — from 1.034 (1.016–1.053) to 1.048 (1.030–1.068) for all causes of death, and from 1.153 (1.111–1.197) to 1.177 (1.134–1.222) for deaths from IHD (Table 7). Household income was positively associated with exposure to $PM_{2.5}$ (1999–2000) and negatively associated with all-cause mortality. (No individual-level information on income was available for CPS-II participants; therefore, we relied on the ecologic-level indicator of income status.)

Percentage of the population with a grade 12 education exerted the next largest influence on HR estimates. The random effects Cox model was adjusted for education attainment at the individual level. This analysis, therefore, suggests that neighborhood education attainment measured at the ZCA level exerts additional influence on the air pollution–mortality association beyond that of individual-level education attainment.

ZCA-level median household income and grade 12 education, therefore, represent the most important sociodemographic ecologic factors that may confound the $PM_{2.5}$–mortality association, although their effects individually are slight.

One of the more remarkable findings in this set of analyses was that when ecologic covariates were included, the HRs increased. This finding likely represents a case of variance suppression (Tabachnick and Fidell 2001), which is documented as one way in which confounding variables may increase the size of their effects on the primary risk variable in the model. Ecologic confounders and the pollutants share some of the model variance, and their common variability also partially overlaps with the variability of the mortality outcome. The part of the variance shared by the ecologic and pollutant variables is the component of variance with mortality that has a relatively less-defined association with pollution. When the ecologic covariates are included in the model, the component of the variance overlap between pollution and mortality is removed, and the remaining relationship becomes more pronounced. These results imply that simultaneous consideration of ecologic covariates and air pollution may be important in models of chronic health effects.

Results from the Reanalysis (Krewski et al. 2000a,b) suggested that SO_2 may exert a more robust effect on mortality than SO_4^{2-}. In the current Extended Analysis, including ecologic covariates at multiple scales exerted little influence on HR estimates for the association between SO_2 and all-cause and cause-specific mortality. An exception was for IHD mortality, in which including ecologic covariates

at the MSA & DIFF levels together increased the HR value slightly (by 2.1%).

The ecologic covariates exerted their greatest effect on mortality from IHD, which was also the outcome most strongly related with $PM_{2.5}$ (1979–1983 and 1999–2000), SO_4^{2-} (1980–1981 and 1990), and SO_2 exposure, and was the only outcome significantly associated with NO_2 exposure. IHD, a significant contributor to mortality in the United States, is associated with a multitude of behavioral risk factors such as smoking, lack of exercise, obesity, and diet, which are likely related to spatial patterns in sociodemographics such as income, education level, and unemployment. Spatial patterns in health services available to diagnose and treat IHD are possibly another important factor not explicitly evaluated here. The HR of IHD mortality associated with air pollution exposure remained elevated even after adjustment for a variety of individual-level and ecologic covariates. The fact that IHD mortality was the outcome most influenced by the ecologic covariates suggests the importance of controlling for these influences in future studies.

Another interesting finding was the fact that, in general, the geographic unit of analysis (ZCA or MSA) of ecologic covariates tended to not make an appreciable difference in their influence on HR estimates. In many cases, though, HR estimates tended to be highest from models with the ecologic covariate considered at the MSA & DIFF levels simultaneously. The sociodemographic ecologic covariates at simply the ZCA or MSA levels, compared with the MSA & DIFF levels, did not substantially alter results of the air pollution–mortality association found in the current study.

The association between air pollution and lung-cancer mortality was found to vary somewhat by level of education attainment recorded at the inception of the cohort. The risk of lung-cancer mortality associated with each 10-$\mu g/m^3$ change in $PM_{2.5}$ (as measured in 1999–2000) was approximately 20% higher for participants who completed only grade 12 education compared with no association observed among those who completed more than high school. Including ecologic covariates increased the point estimates and width of CIs slightly. Similar results were reported in the Reanalysis (Krewski et al. 2000a,b): relative risks of 1.41 (95% CI, 0.87–2.29) and 1.39 (95% CI, 0.90–2.15) were reported for lung-cancer mortality associated with each 24.5-$\mu g/m^3$ change in $PM_{2.5}$ among those who completed less than high school and those who completed high school, respectively, whereas a relative risk of 0.66 (95% CI, 0.46–0.95) was found among those who completed more than high school. Indeed, this finding of increasing mortality from $PM_{2.5}$ exposure associated with declining education attainment represented a key finding of the Reanalysis. In the Updated Analysis, Pope and coworkers (2002) also reported a similar trend. Although the reasons for this finding are unknown, it was suggested that level of education attainment may likely indicate the effects of complex and multifactorial socioeconomic processes on mortality or may reflect disproportionate pollution exposures.

Although the direction of the trend for all-cause and CPD mortality in the current study was similar to that of lung-cancer mortality, a significantly elevated HR was found for these outcomes in each educational stratum and the magnitude of the difference was small. This suggests that education attainment may exert less of a modifying force on these mortality categories. A surprising finding in the current study was increasing IHD mortality associated with $PM_{2.5}$ (1999–2000) and increasing education attainment (Table 8). HR estimates for IHD mortality also increased up to 11% among those with more than high school education with the inclusion of ecologic covariates in the model. Large socioeconomic differences in coronary mortality have been observed in the United States, where individuals of lower socioeconomic status exhibit greater coronary mortality compared with individuals of higher socioeconomic status (Kunst et al. 1999; Mackenbach et al. 2001; Armstrong et al. 2003). The finding of a greater effect of $PM_{2.5}$ exposure on IHD mortality among those with greater education attainment in the current study may suggest that there are a number of individual- or community-level influences on mortality among those with lower education that are more powerful than that of $PM_{2.5}$.

We also explored complex spatial patterns in the CPS-II data. The 2000 Reanalysis, using a random effects Cox model that could handle up to two levels of clustering, showed that spatial risk models attenuate the air pollution effect, both in terms of size and certainty. The presence of spatial autocorrelation has important implications with respect to bias and precision of model-based estimates of risk. In this project we extended the random effects Cox model used in the Reanalysis to be capable of handling more than two levels of clustering in order to evaluate how robust the results from the Reanalysis would be to more sophisticated spatial models.

The spatial random effects Cox model captures additional variation beyond that explained by the standard Cox model. We included random effects at both the MSA and ZCA levels in order to capture variation in survival due to unexplained variation between MSAs and between ZCAs within MSAs. We note that including these random effects tends to increase the estimated HR of death associated with air pollution exposure and to inflate uncertainty in these estimates, as evidenced by wider confidence intervals.

We further note that including the ecologic covariates decreases the variance of the random effects at both the MSA and ZCA level; the largest decrease in residual variation is based on models with the MSA & DIFF specification, which suggests that partitioning the ecologic covariates into between-MSA and within-MSA values more completely captures these sources of variation.

INTRA-URBAN ANALYSIS FOR THE NEW YORK CITY REGION

A LAND-USE REGRESSION MODEL FOR PREDICTING $PM_{2.5}$ CONCENTRATIONS

Background

Exposure to $PM_{2.5}$ has been linked to a wide array of health outcomes such as aggravation of existing heart and lung disease and premature death (Pope et al. 2002). Such health studies, though, often rely on pollutant exposure estimates that are based on a city's central monitors; that same level of exposure is then assigned to the entire population in a metropolitan area and exposure estimates are compared between cities. Recent studies of $PM_{2.5}$ have shown, however, that intra-urban exposure gradients can also be associated with atherosclerosis (Künzli et al. 2005) and with high risk of premature death (Jerrett et al. 2005a). These studies have used geostatistical interpolation models that capture regional patterns of pollution well, but often fail to account for the near-source impact from local traffic and industry. Given the high risks of health effects reported in these studies and others conducted in Europe (Hoek et al. 2002; Nafstad et al. 2003), we need to refine the estimates of pollutant exposures and reduce uncertainties that could be associated with measurement error.

Several recent studies have demonstrated the potential of LUR to supply accurate, small-area estimates of air pollutant concentrations without the financial expense of dispersion or exposure modeling (Brauer et al. 2003; Briggs et al. 2000a). The goal of LUR is to explain, to the extent possible, the variation in existing air quality data for a given pollutant using data on nearby traffic, land use, emissions from local sources, and population variables. In most cases, multiple linear regression is used to develop and validate a model using data from existing monitors and land-use data that can then be applied to unmonitored locations provided the appropriate geographic data are available.

Ross and associates (2006) developed LUR models using traffic data, distance to the coast, and road length measurements to predict NO_2 levels in San Diego, California, that explained nearly 80% of the variation in measured exposure levels. When the predicted levels were compared with measured levels at validation locations — locations that were not included in developing the model — they were accurate to within, on average, 2.1 ppb. LUR models to predict NO_2 levels using traffic and other variables in Montréal and several European cities also produced accurate predictions (Jerrett et al. 2005b).

In contrast to a more localized pollutant such as NO_2, however, PM mass has a significant regional component that includes smaller contributions from local sources (Bari et al. 2003). This complicates estimating intra-urban exposure with LUR. Models of $PM_{2.5}$ in three European cities produced mixed results. One of the only studies to attempt prediction of fine particle concentrations with the LUR methods to date was undertaken in Europe as part of the TRAPCA (Brauer et al. 2003). Researchers measured $PM_{2.5}$ for representative temporal periods over one year in the Netherlands; Munich, Germany; and Stockholm County, Sweden. They found significant differences in the ability of the model to predict monitoring data from region to region: values from LUR models could predict from 73% of the variation of monitored values (the Netherlands) down to 56% and 50% (Munich and Stockholm, respectively). The limited variability of the monitoring sites in Stockholm County was suggested as an explanation for the difference in the Stockholm data (Brauer et al. 2003). When combined with health data, an LUR model was able to predict some childhood respiratory outcomes (Brauer et al. 2002). More recently, in Germany, Hochadel and coworkers (2006) found that LUR predicted $PM_{2.5}$ absorbance (R^2 = 65%–82%), but failed to predict $PM_{2.5}$ mass very well (R^2 = 9%–17%).

North American cities have vastly different transportation and land-use patterns than those in Europe, and the applicability of LUR to predict $PM_{2.5}$ is unknown (Gilbert et al. 2005). To our knowledge this study was the first attempt to apply LUR to analyze $PM_{2.5}$ in North America.

Materials and Methods

LUR uses concentrations of ambient pollutants at monitoring locations as the dependent variable. Surrounding land-use, transportation, emissions from local sources, and population data were obtained using GIS and included in a regression equation as predictor variables. In this study we assembled a database of information on land use and transportation around the $PM_{2.5}$ monitors in the New York City region.

We constructed three models: one covering a 9-county urban area using 3-year averages; another covering all 28 counties using 3-year averages; and a third covering the

28 counties using data for only the winter months of 2000. After describing the data we collected, we present our statistical modeling strategy.

Dependent Variable: Ambient $PM_{2.5}$ Data For the 28-county models, counties were chosen to match those included in the Best Practice Model (BPM; a tool for forecasting regional travel demand) used by the New York Metropolitan Transportation Council (NYMTC), the regional council of governments established to help make transportation-related decisions in the region. Of those, 9 counties were selected to represent the more urbanized area of New York City's five boroughs and adjacent New Jersey and Connecticut counties.

In general, the 28 counties ranged from very urban to relatively rural; 12 counties had fewer than 500,000 people (with a minimum population of 96,000 in Putnam County) and 6 counties had more than 1,000,000 people (maximum population of 2,470,000 in Kings County). Most counties had heavily urban populations (based on population per square mile) — the populations were greater than 90% urban in 22 counties and greater than 99% in 12 of those. The 6 least-urban counties (Hunterdon, Warren, Sussex, Orange, Dutchess, and Putnam), all of which are more than 50 km west or north of downtown Manhattan, range from 40%–76% urban. For comparison, the average county population for the three states is 340,000 and the average urban percentage is 64%.

We calculated 3-year averages (from data in 1999–2001) of $PM_{2.5}$ for monitors in the 28-county region around New York City (Figure 1) using data from the U.S. EPA Air Quality Subsystem (AQS; a repository for ambient air quality data made available for analysis). For each monitor that had at least eight observations in a quarter (i.e., at least half of the scheduled monitoring days), we first computed quarterly means. When we could calculate a complete set of four quarterly means for three years running, we computed 3-year averages from the 12 quarterly means. (We lost only about 5% of the monitors due to incomplete data.)

We were also interested in assessing seasonal variations in exposure, especially for SO_4^{2-}. New York City experiences long-range transport of secondary aerosols with a high proportion of SO_4^{2-} in the warmer months. Because SO_4^{2-} is also formed regionally, the exposure gradient within cities is more spatially homogenous during the warmer months when secondary aerosols are transported. By contrast, in the winter months, SO_4^{2-} concentrations are strongly influenced by local emissions from automobile and truck traffic, shipping, heating, and industry. The exposure gradient within the city is therefore generally steeper during the winter months when the dominant regional exposure is absent. The steeper gradients increase the statistical power of our health effects models to detect associations between air pollution and mortality.

Thus, for winter of 2000 in 28 counties, we computed pollutant averages using data from January, February, and March. We limited the winter-2000 analysis to those sites that could provide both 3-year and winter-2000 averages. Data from 62 monitors in the 28-county region were included in the 3-year analysis of the 28-county area (1999–2001), data from 36 in the 3-year analysis of the 9-county area (1999–2001), and data from 45 for the 28-county area in winter (2000).

At nine monitoring locations, two types of monitors were used concurrently: the Federal Reference Method (FRM) and the tapered-element oscillating microbalance (TEOM) continuous monitoring method. When both TEOM and FRM data were collected at the same site, we used the FRM data.

For most monitors, the AQS included latitudes and longitudes for the monitors, but some were inaccurate. We therefore used locations provided directly by the appropriate state agencies (the Department of Environmental Conservation in New York and the Departments of Environmental Protection in New Jersey and Connecticut). In most instances, the locations were identified by the agencies with either a global positioning system (GPS) or orthophotos in a GIS. For a limited number of older sites, the more accurate methods had not been used by the agencies, so we manually verified their locations in a GIS using a combination of road layers, orthophotos, New York State Department of Transportation Raster Quadrangles, and USGS Digital Raster Graphics.

Independent Variables: Traffic, Land-Use, Population, and Local Emissions Data For each air monitoring location in the AQS for which we had adequate data on $PM_{2.5}$, using our GIS software we generated circular buffers around the monitor location with different radii (50 m, 100 m, 300 m, 500 m, and 1000 m). All of the mapped data in our GIS layers (as described below) were then linked with the circular buffers, and the traffic and land-use data for all buffers around each air monitoring location were calculated. Calculations were performed with a vector data structure using ArcGIS 9.1 (ESRI 2004).

Traffic and Road Data The NYMTC provided traffic estimates for 2002 for New York City and surrounding counties that covered approximately 40,000 road links in 28 counties using the BPM, a tool used for forecasting regional travel demand in the metropolitan area. The BPM makes use of traffic data from more than a dozen

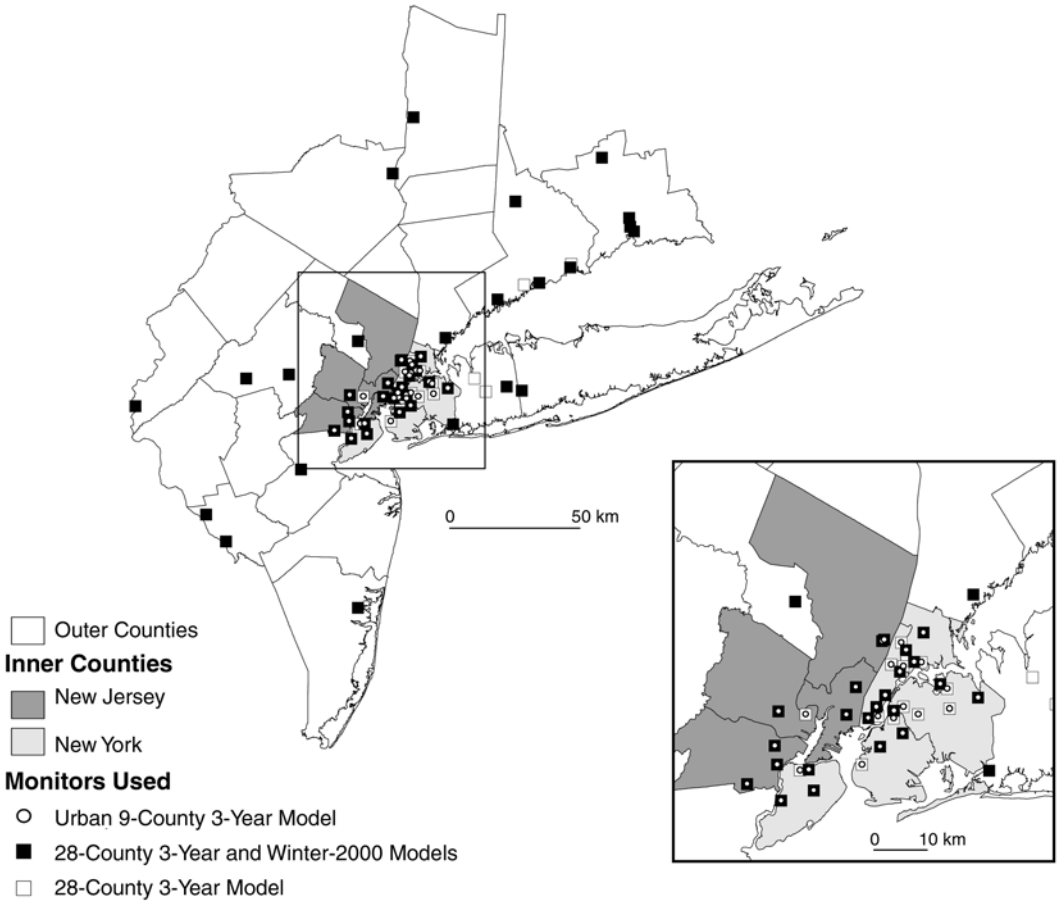


Figure 1. Locations of $PM_{2.5}$ monitors in the New York City region.

municipal and other sources. The road network used in the BPM was developed to include all minor arterial roads or larger from five separate network databases. The five had been conflated to match the LION street centerline file for New York's five boroughs (from the City of New York Department of City Planning 2009) and the USCB Topologically Integrated Geographic Encoding and Referencing Database. A complete description of the BPM model and development of mapped roadways can be found in Parsons Brinckerhoff Quade & Douglas, Inc. (2005). The traffic estimates, divided by vehicle type (heavy- and light-duty trucks, buses, vans, cars), are available for the four time periods of morning, midday, afternoon, and night. We used estimates for afternoon rush-hour traffic flow because a complete set of estimates (for all 40,000 links) for the other time periods was not yet available. We calculated totals for truck traffic and total traffic for each buffer zone around each monitor. Traffic data were scaled to 1000s of vehicle-kilometers per hour. We also used this data source to calculate road density (total length of roadway in kilometers) in each buffer area.

Land-Use Data Layers of land-use data were assembled from several sources: extremely detailed (1 inch = ~250 feet) tax-lot data from the New York City Department of City Planning for all tax lots in the five boroughs (2003); medium-scaled (1 inch = ~40,000 feet) land-use data for New Jersey from the New Jersey Department of Environmental Conservation (1995/1997); and coarse scale (1 inch = ~100,000 feet) land-use data from the USGS National Land Cover Data 1997 (based on Landsat satellite images from 1992 and confirmed using aerial photos). For each land-use layer we calculated the total area of an individual land-use category (e.g., industrial, forest, residence) in each buffer. Although the tax-lot and New Jersey land-use data layers were more detailed, only the data from the USGS covered the entire area of interest.

Similar uses within each land-use layer were grouped to create aggregate variables. The land-use categories within the three layers were not identical but comparable groupings were tabulated. We generated industrial and residential categories from all three land-use layers. In addition, for the New Jersey Department of Environmental Conservation data and the National Land Cover Data, we created water, vegetation, and barren land-use variables.

The "Industrial" category, discussed throughout most of this section, comprises the "Industrial / Commercial / Transportation" category from USGS data and the New Jersey land-use data. We created a comparable grouping using the New York City tax-lot data by combining the categories denoted "Industrial and Manufacturing", "Transportation and Utility" and "Commercial and Office Buildings." The New York City tax-lot data and the New Jersey land-use data were used only for sensitivity analysis because they did not cover the entire region. Land-use areas were converted to acres (1 acre = 4047 m^2).

Population Data Census data for the New York City study area were acquired at the block-group level from the USCB 2000 Summary File 1 (for population and housing data) and Summary File 3 (for income data). All population and housing data are in 1000s or percentages; income data were not scaled (U.S. Census Bureau 2000). These data were used as possible predictor variables in the LUR model.

Local Emissions Data We calculated primary emissions of $PM_{2.5}$ (area, point, off-road mobile, and on-road mobile) for each county and assigned to each monitor the value associated with its county as a possible predictor variable. In addition, for each buffer area, we calculated the number of point sources and the amount of $PM_{2.5}$ emissions using data for 1999 from the U.S. EPA National Emissions Inventory (1999).

Statistical Data Analysis We developed three separate models: two that included data from all 28 counties, one of which used the 3-year-average $PM_{2.5}$ data and one that used the winter-2000 $PM_{2.5}$ data; and a third that used 3-year-average $PM_{2.5}$ but was geographically limited to the nine more urbanized counties.

We started with 62 monitors in the 28 counties. First, based on each monitor's land-use code in the AQS, we divided them into agricultural/forest, commercial, industrial/mobile, and residential categories. Next, to validate our predictions later, we randomly removed 20% of the monitors to use for validating the predictions that would be generated. Samples (monitors) were removed from each of the 28-county and 9-county models separately using the same criteria. The remaining monitors were used to develop the models.

The 28-county 3-year model included 49 monitors for developing the model (plus 13 removed for validation; 62 total), the 28-county winter-2000 model included 36 monitors for modeling (plus 9 removed for validation; 45 total), and the 3-year 9-county model included 29 monitors for modeling (plus 7 removed for validation; 36 total) (Table 12).

We then considered more than 25 separate variables within five different buffer distances around each monitor for possible inclusion in the final three models. These included total traffic, total truck traffic, industrial land use, residential land use, total county-wide emissions, point emissions, total number of point sources of $PM_{2.5}$, total population, number of housing units, median income of population, and the percentage of the population who are not white.

Table 12. Modeling and Validation Monitors by Land-Use Category

	3-Year Models				Winter-2000 Average	
Land-Use Category[a]	28-County Total	28-County Validation	9-County Total	9-County Validation	28-County Total	28-County Validation
Industrial / mobile	8	2	6	1	5	1
Residential	32	6	19	4	24	5
Commercial	18	4	11	2	12	2
Agricultural / forest	4	1	0	0	4	1
Total	62	13	36	7	45	9

[a] Based on codes in the U.S. EPA's AQS.

All of the predictor variables discussed above were included in a combination of forward, stepwise, and all-subsets selection procedures. We included variables in the model based on the explained sums of squares, the Mallows Cp statistic, the variance inflation factor (VIF) method, and other diagnostic tools. In the forward selection process, as the strongest variables are added to the model the remaining variables are reevaluated for inclusion. As such, the same variable at a different buffer distance may be included if it outperformed other related variables. (For example, in a model that included total traffic in the 300-m buffer, total traffic in the 500-m buffer might also be used if it outperformed residential land use.) The sensitivity of model parameters to the sample selection procedure was evaluated with a bootstrap method in which five random samples were excluded, the model was run, the coefficients were recorded, the five samples were returned to the pool, and another random sample of five was removed. This process was repeated 10,000 times.

To evaluate the validity of the assumption that all data points are independent, we tested the spatial autocorrelation in the 3-year-average and winter-2000 $PM_{2.5}$ monitor values themselves and then in the residuals from our final 28-county models using the Moran *I* statistic (Bailey and Gatrell 1995) and two neighborhood constructions — a Queen contiguity matrix based on Thiessen polygons, and a nearest-neighbor approach in which we limited the analysis to the three nearest monitors. Statistical significance was tested using a permutation test with 999 iterations. We also qualitatively assessed the extent of spatial autocorrelation in the $PM_{2.5}$ concentrations using variograms of the residuals from our final models.

For visualization purposes, we created a smooth interpolated surface by predicting $PM_{2.5}$ concentrations at 5600 random point locations (200 per county) with the LUR formula and kriged these predictions. To compare our LUR estimates to the exposure interpolation method that is commonly used in health studies, we also kriged the $PM_{2.5}$ values from the monitors. All the statistical analysis was conducted using R statistical software and the GSTAT library (Pebesma 2004; R Development Core Team 2005).

We evaluated the quality of the predictions at validation locations by calculating the root-mean-squared error (RMSE) at each location. We assessed the quality of the final models (those generated after returning the validation locations to the pool of samples) by calculating the RMSE based on fitted values in a leave-one-out cross validation.

Results

Descriptive Statistics for $PM_{2.5}$ $PM_{2.5}$ 3-year-average values for both the 28- and 9-county regions were approximately normally distributed (Figure 2) with a mean for the 28-county region of 14.3 μg/m^3 (median = 14.3, SD = 1.78) and a mean for the 9-county region of 15.3 μg/m^3 (median = 15.1, SD = 1.42). The highest concentrations were located in 4 counties including Manhattan, New York; Bergen and Hudson, New Jersey; and New Haven, Connecticut. Most of these locations are situated in close proximity to major highways. Locations with higher concentrations tended to be located closer to Manhattan.

Winter-2000 averages were also approximately normally distributed with a mean of 14.0 μg/m^3 (median = 14.3, SD = 2.55); three of the four highest concentrations were

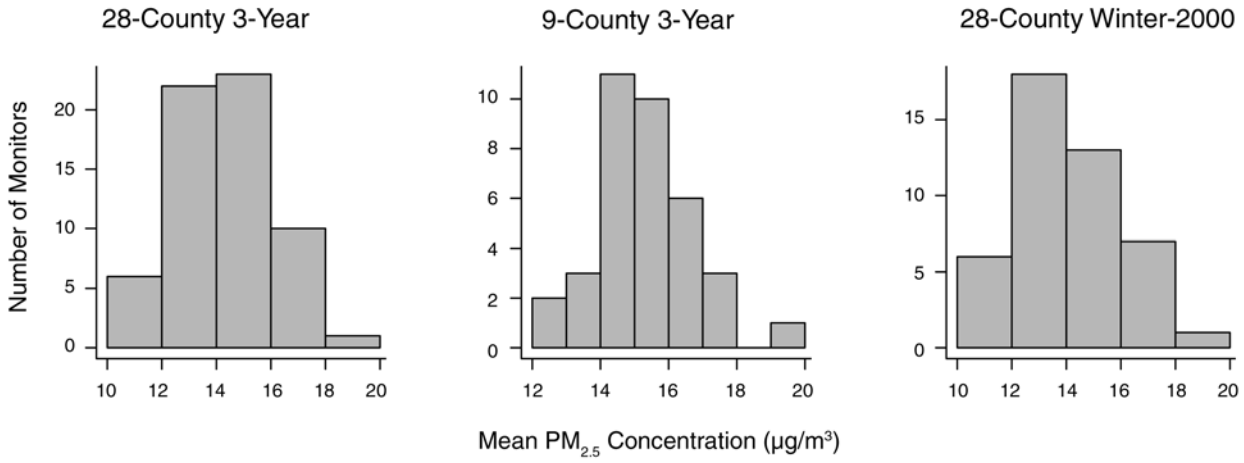


Figure 2. Distributions of mean $PM_{2.5}$ concentrations. Mean for the 28-county 3-year average was 14.3 μg/m^3 (median = 14.3; SD ± 1.78), for the 9-county 3-year average was 15.3 μg/m^3 (median = 15.1; SD ± 1.42), and for the 28-county winter-2000 average was 14.0 μg/m^3 (median = 14.3; SD ± 2.55). Analyses were based on the full set of samples with no validation samples removed.

located in Manhattan and one in New Haven. These statistics are based on the full set of samples with no validation samples removed.

LUR Model Building and Results

28-County and 9-County Models Based on 3-Year-Average Concentrations For both regions, the total traffic variable was the strongest predictor of $PM_{2.5}$ concentrations (see Table 13 for distributional statistics on final predictors). Total traffic in the 500-m buffer and total traffic in the 300-m buffer, in particular, led all other variables in explanatory power. Urbanization-related variables, primarily in the 500- and 1000-m buffers, were also strong predictors of $PM_{2.5}$ concentrations both with and without total traffic in the 500-m buffer included in the model. These included total population in both the 500- and 1000-m buffers and numbers of both households and housing units in the 1000-m buffer.

With total traffic in the 500-m buffer and total population in the 500-m and 1000-m buffers in the model, the next strongest predictor was industrial land use in the 300-m buffer for both the 28-county and 9-county regions.

The final models for both of these regions therefore included total traffic in the 500-meter buffer, total population in the 1000-meter buffer, and industrial land use in the 300-meter buffer (Table 14).

The 28-county 3-year model predicted $PM_{2.5}$ at validation locations to within, on average, 0.93 $\mu g/m^3$ (6.5%) of actual concentrations with a RMSE of 1.10. The 9-county model predicted $PM_{2.5}$ at validation locations to within, on average, 0.77 $\mu g/m^3$ (5.0%) of actual concentrations with a RMSE of 0.87. The predictions for validation sites showed some bias, particularly in the 28-county 3-year model, which was likely to over-predict $PM_{2.5}$ values, though no bias was apparent in the models after including the validation samples (Figure 3).

Within the 28-county 3-year model, the predictions were better for those validation sites located in the more urbanized 9-county area. The nine validation sites located within the 9 counties had a RMSE of 0.90, whereas the four sites located in the other 19 counties had a RMSE of 1.45. This distinction, however, is due primarily to a single large residual in Waterbury, Connecticut, at a site with the second highest industrial land use among all the 62 locations in the 28-county area and relatively high traffic.

When the validation samples were returned to the pool of modeling samples and the models were run again, the regression parameters remained similar; the parameter for the industrial land-use variable changed most between runs. The average absolute value residuals based on the fitted values (for observations included in the modeling rather than the prediction of validation locations) from the full models (no excluded samples) were 0.85 $\mu g/m^3$ or 6.0% of actual concentrations for the 28-county 3-year model (with an RMSE based on a leave-one-out cross validation of 1.15), and 0.69 $\mu g/m^3$ or 4.5% of actual concentrations for the 9-county 3-year model (RMSE of 1.00). The final 28-county 3-year model explained 64% of the variation in the $PM_{2.5}$ measured values from the validation locations, and the 9-county 3-year model explained 62% of the variation. Plots of the fitted and observed values are pictured in Figure 4.

Models included data from a mix of FRM and TEOM monitors: for the 28-county 3-year model, 50 FRM and 12 TEOM; for the winter-2000 model, 42 FRM and 3 TEOM; for the 9-county 3-year model, 25 FRM and 11 TEOM. Although plots of the nine sampling locations with both FRM and TEOM monitors showed little or no bias (four

Table 13. Distribution Statistics for Final Predictor Variables[a]

	28-County 3 Years			9-County 3 Years			28-County Winter-2000		
	Total Traffic (500 m)	Total Population (1000 m)	Industrial Land Use (300 m)	Total Traffic (500 m)	Total Population (1000 m)	Industrial Land Use (300 m)	Total Traffic (300 m)	Total Population (1000 m)	Vegetation Land Use (1000 m)
Minimum	0.00	0.21	0.00	0.00	0.21	0.00	0.00	0.21	4.92
1st quartile	1.46	6.31	1.17	2.41	16.75	3.40	0.33	6.09	31.36
Median	4.55	14.53	9.23	5.38	36.47	7.87	1.07	11.19	96.66
Mean	6.41	27.52	14.26	8.03	42.60	12.85	2.21	22.97	125.90
3rd quartile	9.80	42.28	20.34	13.48	55.01	16.59	3.83	27.22	122.10
Maximum	24.06	119.40	52.70	24.06	119.40	45.77	8.35	119.40	697.10

[a] Traffic units: 1000s of vehicle-km/hour; total population units: 1000s of people; land-use units: acres.

Table 14. Statistics for Final LUR Models

	Parameter Value	SE	*t* Statistic	*P* Value	VIF
28-County 3-Year					
Intercept	12.273	0.261	46.965	0.000	—
Total traffic (500 m)	0.121	0.027	4.530	0.000	1.344
Total population (1000 m)	0.031	0.006	5.704	0.000	1.378
Industrial land use (300 m)	0.028	0.010	2.721	0.009	1.253
Multiple R^2	0.642				
Model *P* value	0.000				
9-County 3-Year					
Intercept	13.171	0.364	36.232	0.000	—
Total traffic (500 m)	0.098	0.025	3.967	0.000	1.196
Total population (1000 m)	0.020	0.006	3.547	0.001	1.359
Industrial land use (300 m)	0.040	0.013	3.005	0.005	1.321
Multiple R^2	0.617				
Model *P* value	0.000				
28-County Winter-2000					
Intercept	12.841	0.509	25.214	0.000	—
Total traffic (300 m)	0.463	0.106	4.370	0.000	1.106
Total population (1000 m)	0.033	0.010	3.355	0.002	1.181
Vegetation land use (1000 m)	−0.005	0.002	−2.453	0.019	1.200
Multiple R^2	0.607				
Model *P* value	0.000				

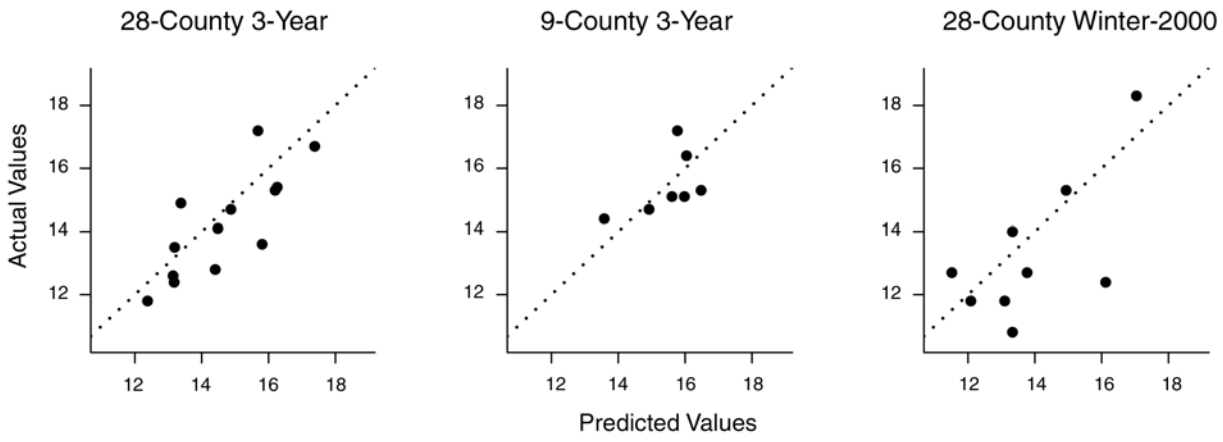


Figure 3. Predicted versus actual values for the validation samples. 13 samples for the 28-county 3-year model; 7 for the 9-county 3-year model; and 9 for the 28-county winter-2000 model.

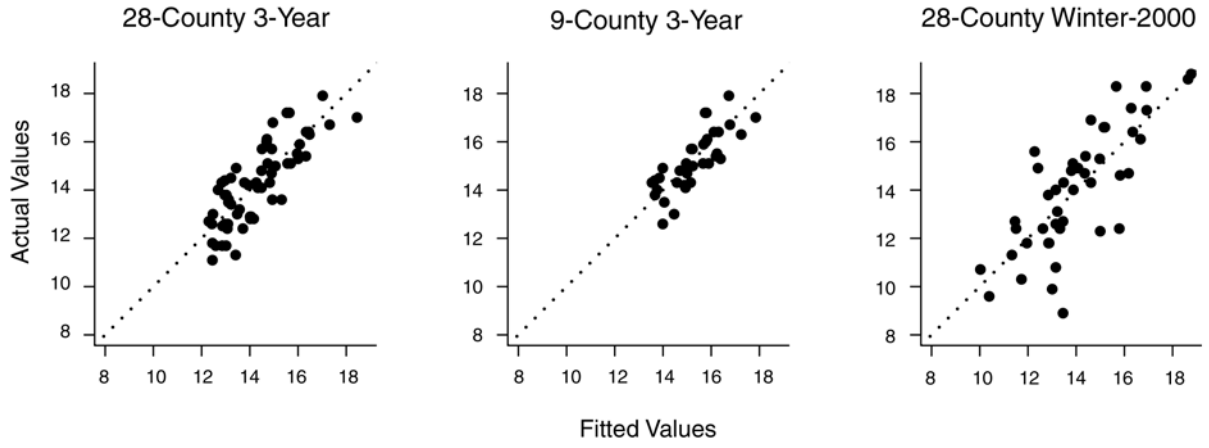


Figure 4. Fitted versus actual values for final models.

locations had higher TEOM values and five had higher FRM values), we tested the inclusion of an indicator variable in the models discussed above to control for a possible effect. This indicator was not significant in any of the models and was excluded.

The 9-county 3-year model was not used for the spatial analysis of mortality and pollution. It was a means of testing whether less detailed land-use data would affect model predictions and whether the same variables would be strong in a more urbanized context (if the more rural counties were eliminated).

28-County Model Based on Winter-2000 Concentrations
Developing the model of winter-2000 concentrations led to a very similar model as those based on 3-year-average $PM_{2.5}$ concentrations. Length of road in the 1000-m buffer, total area of high-density residential land use in the 1000-m buffer, and total traffic within the 1000- and 500-m buffers were, singly, the top predictors of winter $PM_{2.5}$ concentrations after validation samples were removed. Although these variables appeared to individually predict well, their collinearity with other strong candidate predictors and highly influential observations pointed us to more robust variables with slightly less predictive power.

The final 28-county winter-2000 model included total traffic in the 300-m buffer, total population in the 1000-m buffer, and vegetative land use in the 1000-m buffer (Table 14). The inclusion of the vegetative land-use variable was strongly influenced by two rural monitors in New Jersey. Removing these two points reduced the level of statistical significance of the variable to $P < 0.15$. The value of the parameter for vegetative land use remained very similar (-0.00457 vs. -0.00460) with and without these points and we opted to retain the vegetative land use variable because it helped to account for rural–urban differences. The average absolute value residual from the predictions at validation locations was 1.37 $\mu g/m^3$ (within an average of 11% of actual concentrations) with a RMSE of 1.72. These numbers were inflated by one large residual at a Brooklyn location with an unusually high population density. Without this one location, the average absolute value residual is 1.08 $\mu g/m^3$ (9% of actual) with a RMSE of 1.27.

For the 28-county winter-2000 model, the predictions were, on average, better at the five sites outside of the 9 urbanized counties than at the four validation sites inside (RMSE of 1.30 outside vs. 2.14 inside). The distinction between highly urbanized and less urbanized areas, again, is primarily a product of the single large residual at the Brooklyn location. Among the 36 modeling samples used for the winter-2000 model in the 28-county area, 19 were inside the 9 more-urbanized counties and 17 outside.

When the validation samples were returned to the pool of modeling samples and the models were run again, the parameters remained similar in that the greatest change (approximately 15%) occurred in the parameter for vegetative land use. The average absolute value of the residuals based on the fitted data from the full models (no excluded samples) was 1.19 $\mu g/m^3$, which represents an average of 9% of actual concentrations with a RMSE of 1.69 $\mu g/m^3$ based on a leave-one-out cross validation. This final 28-county winter-2000 model explained 61% of the variation in $PM_{2.5}$ concentrations. Interpolated surfaces of LUR predictions are shown in Figure 5.

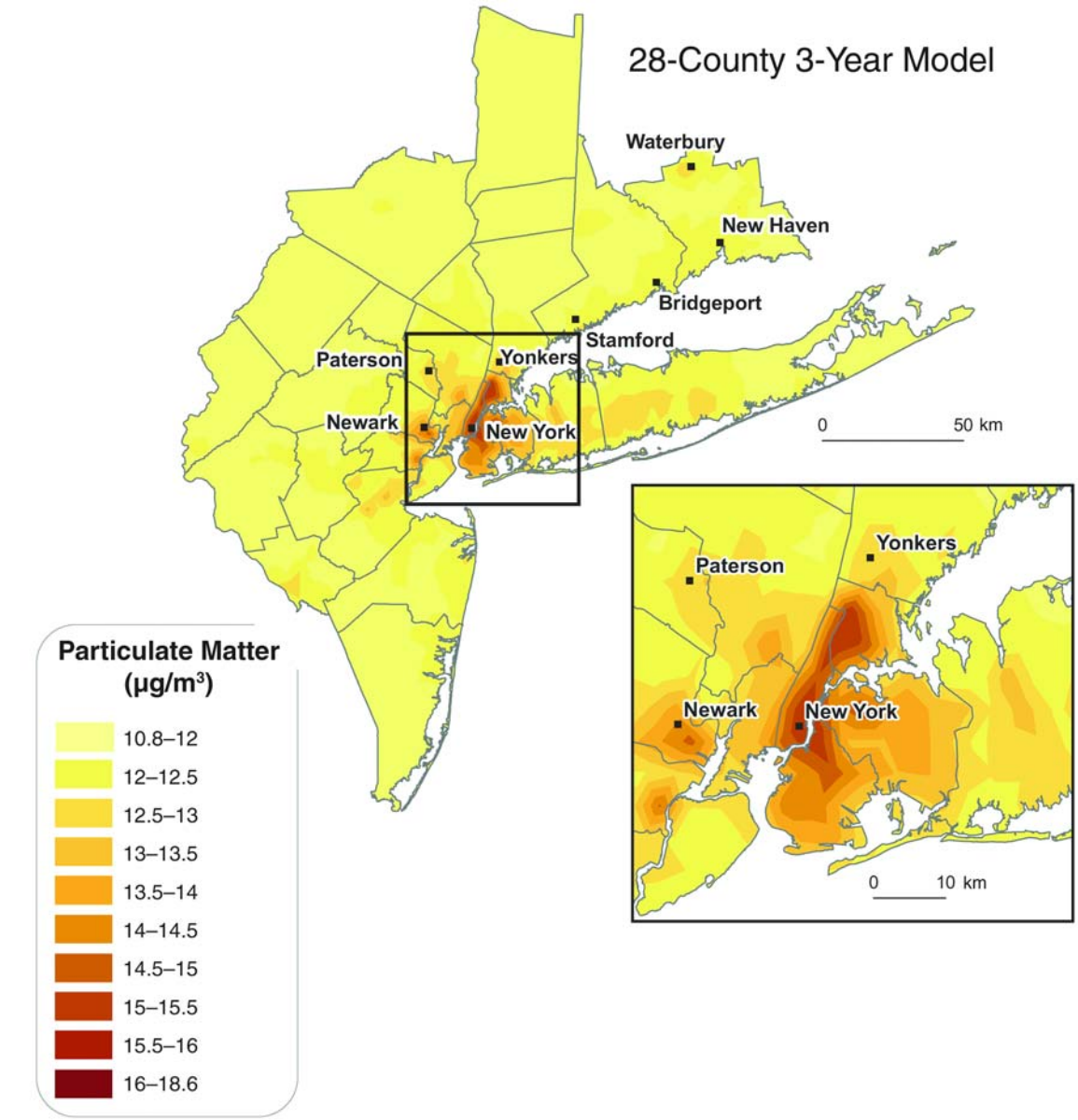


Figure 5. Interpolated LUR predictions for the 28-county and 9-county 3-year models and the 28-county winter-2000 model. (*Figure continues next page.*)

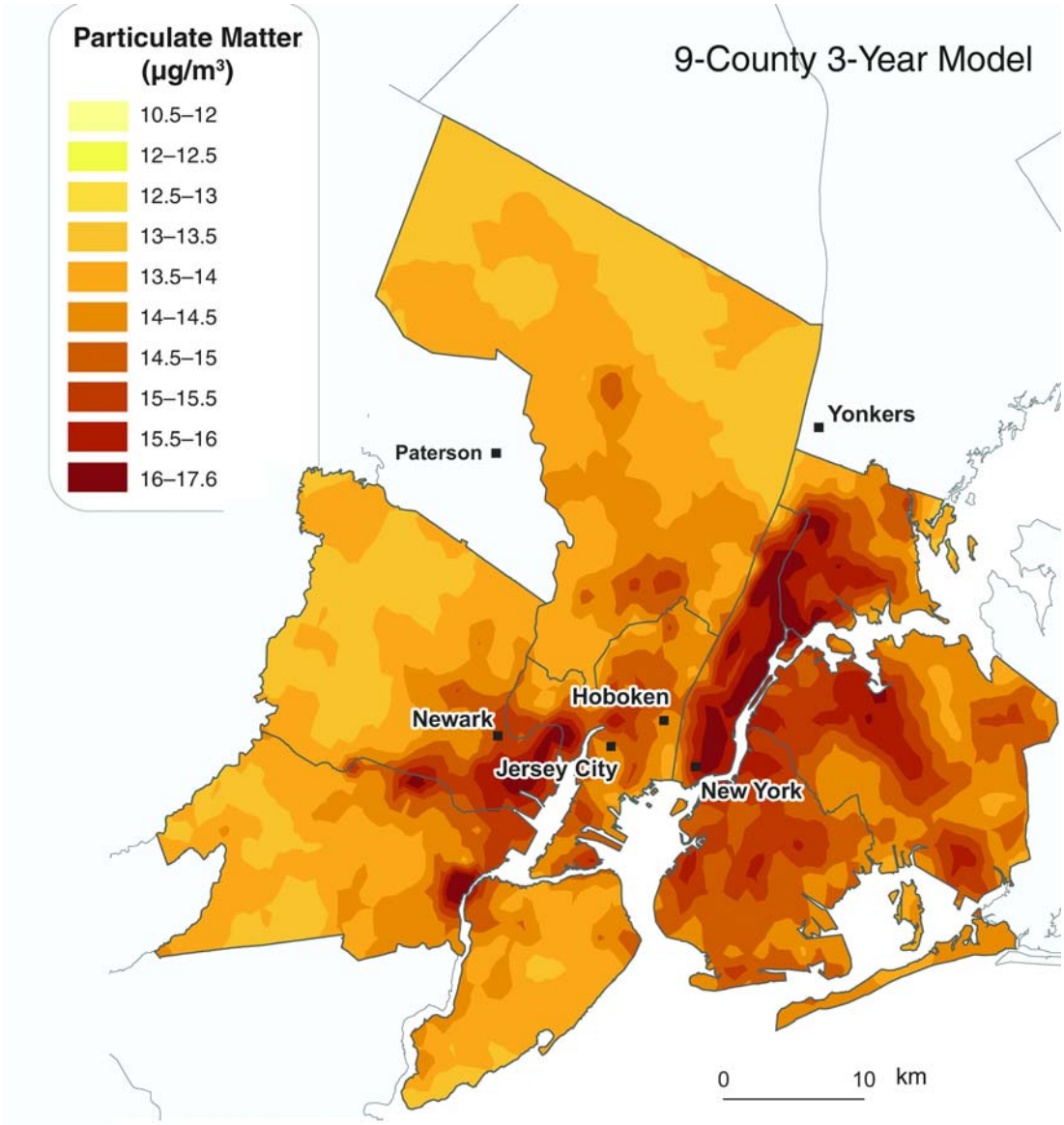


Figure 5 (*Continued*).

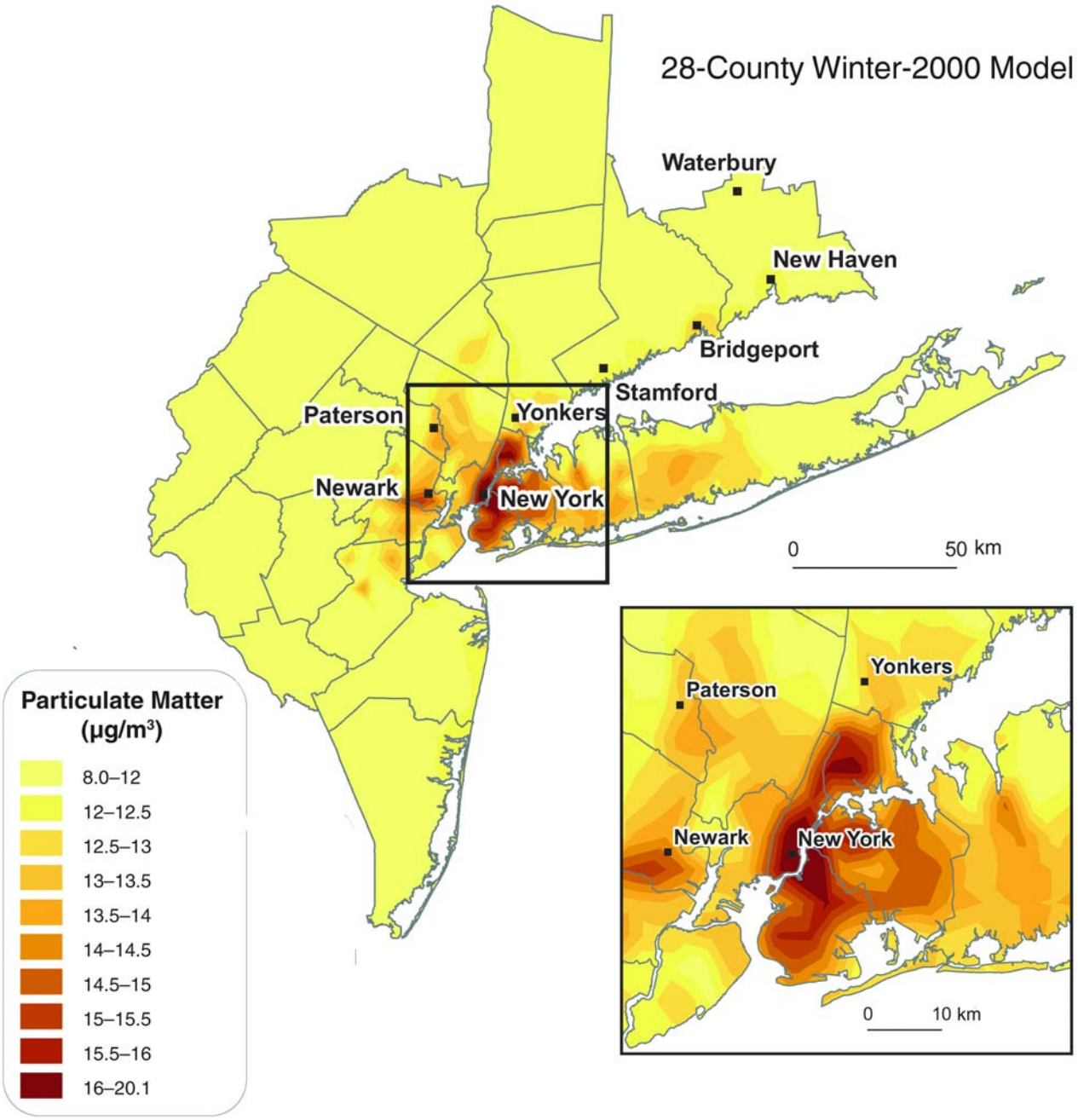


Figure 5 (*Continued*).

Bootstrap Analysis The bootstrap results for all three models showed that they were relatively stable to the choice of samples (Figure 6). We observed a slight bimodal shape in the industrial variable in the 9-county model. In all cases, alterations from normality were caused by a single sample (monitor) (AIRS ID 340030004) located near Fort Lee, New Jersey, just 1.5 miles from Manhattan and extremely close to Interstate 95 and the George Washington Bridge. This one point had the highest $PM_{2.5}$ concentration of all samples. We had no reason to believe that the underlying data for this station were inaccurate and the monitor was not excluded.

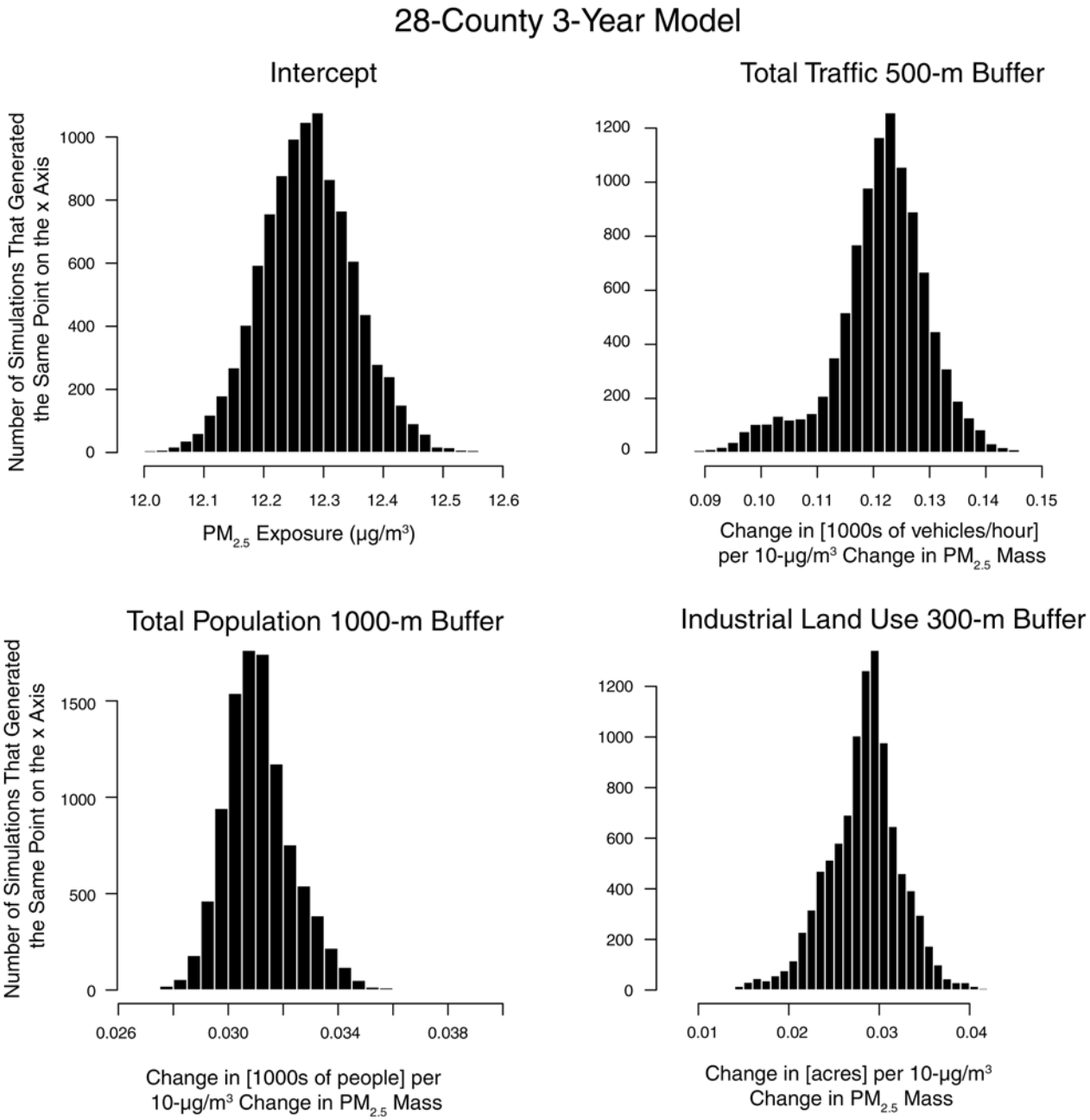
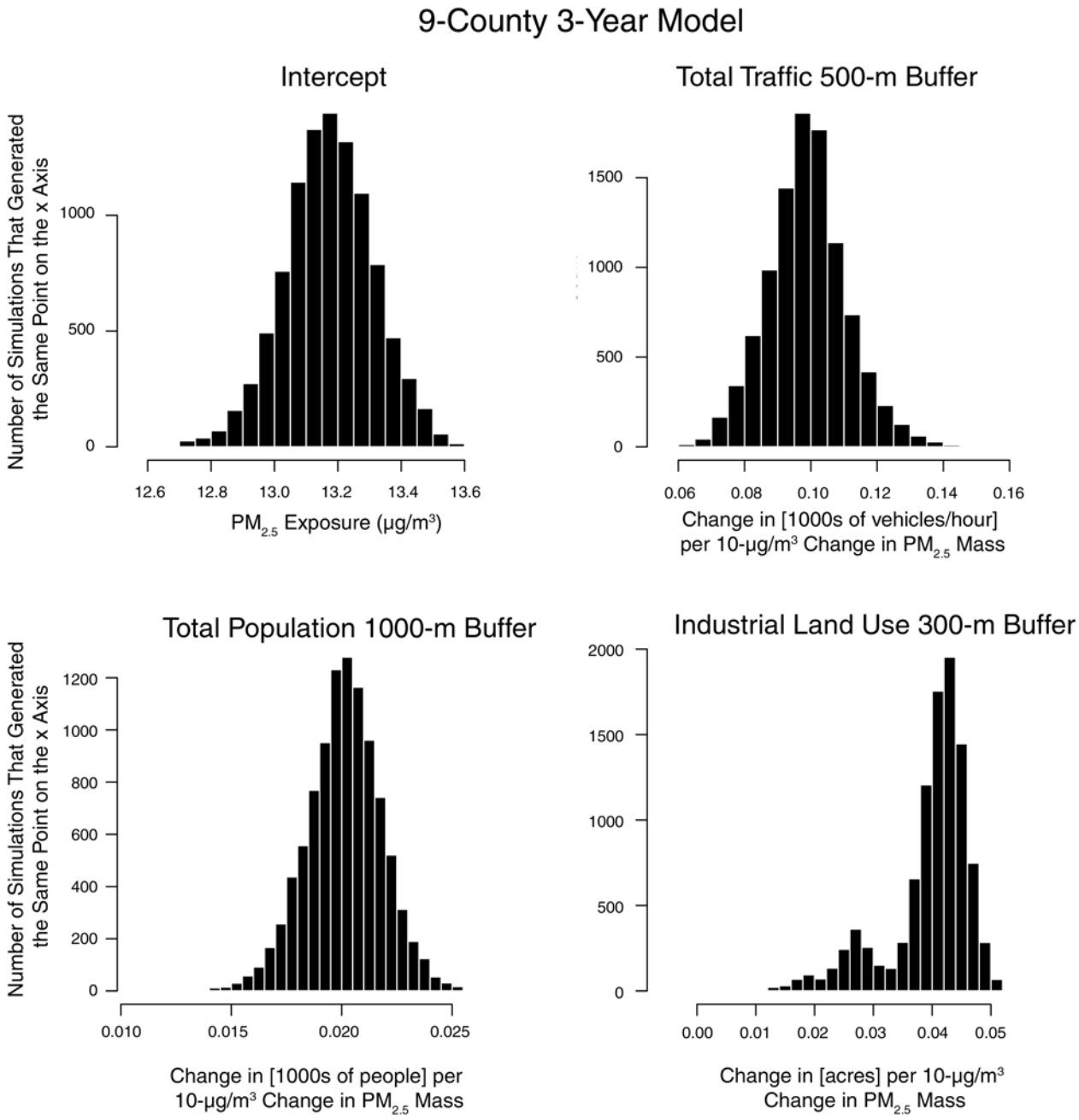


Figure 6. Results of bootstrap analyses for final parameters in the 28-county and 9-county 3-year models and the 28-county winter-2000 model. Example: For total traffic in the 500-m buffer (upper right panel), 0.121 was the parameter from the 28-county 3-year model; the histogram shows how that parameter changed when sites were randomly removed. (*Figure continues next page.*)



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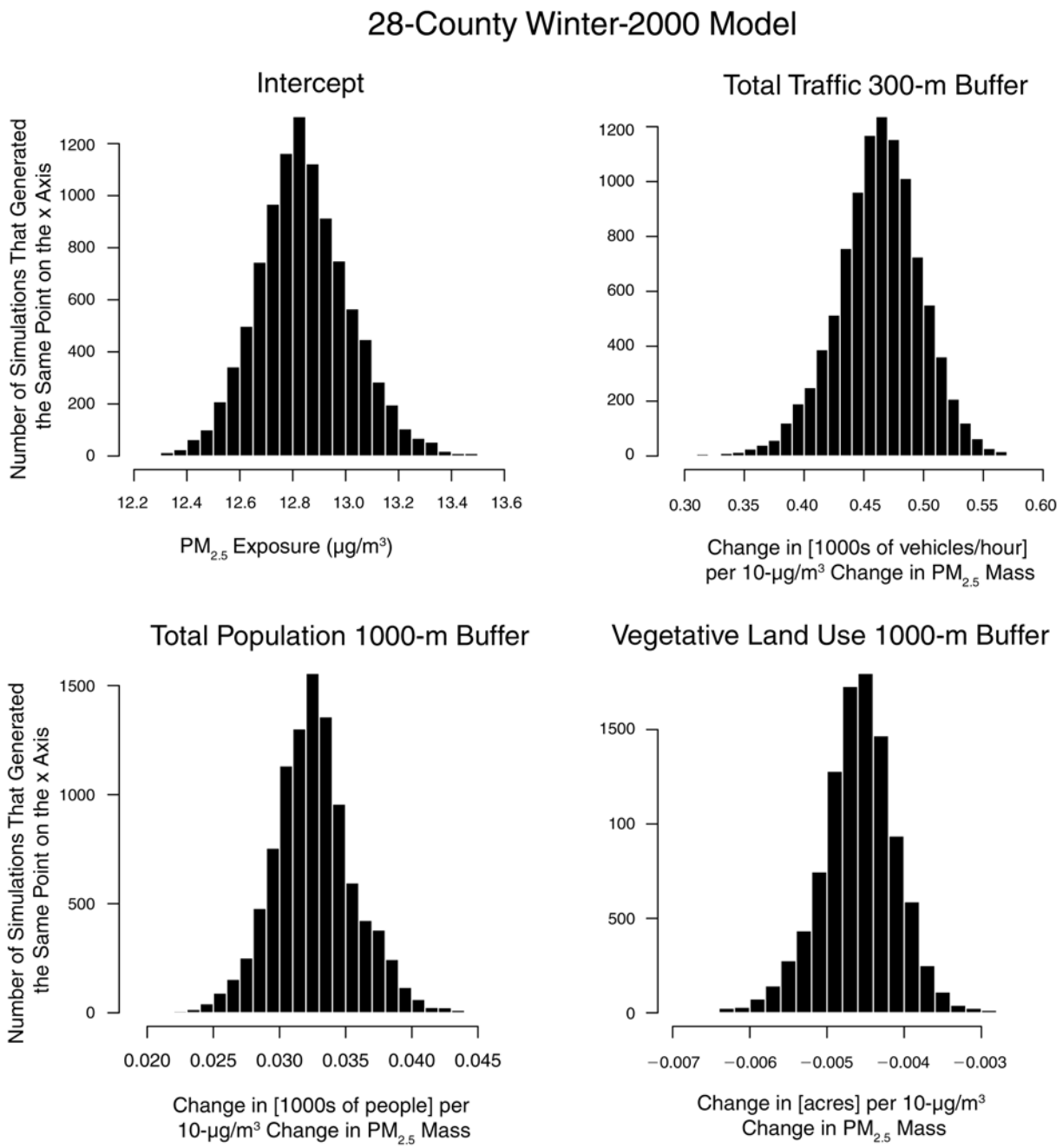

Figure 6 (*Continued*).

Spatial Autocorrelation As expected, we found that the $PM_{2.5}$ values were highly autocorrelated as shown by the Moran *I* values of 0.52 ($P = 0.001$), 0.27 ($P = 0.003$), and 0.43 ($P = 0.001$) for the 28-county 3-year, 9-county 3-year, and 28-county winter-2000 models, respectively, when we used the Queen's contiguity matrix, and 0.49 ($P = 0.001$), 0.38 ($P = 0.002$), and 0.37 ($P = 0.002$) for the same models when we used a three-nearest-neighbor approach. The spatial autocorrelation in our residuals from the full models was considerably diminished and generally nonsignificant, which suggests that the models did not violate the independence assumption and that the included covariates accounted for the autocorrelation. The residuals produced Moran *I* values of 0.21 ($P = 0.003$), 0.09 ($P = 0.108$), and 0.08 ($P = 0.105$) for the 28-county 3-year, 9-county 3-year, and 28-county winter-2000 models, respectively, when we used the Queen's contiguity matrix, and 0.10 ($P = 0.101$), 0.01 ($P = 0.324$), and -0.03 ($P = 0.496$) when we used the three-nearest-neighbor approach. Variograms of the raw $PM_{2.5}$ values showed considerable spatial autocorrelation but the pattern was significantly diminished and barely visible in variograms of the residuals from the full models (variograms not shown).

Kriging $PM_{2.5}$ Values from Monitors Despite the limited number of samples (49, 29, and 36 for the 28-county 3-year, 9-county 3-year, and 28-county winter-2000 models, respectively), kriging based on exponential models performed surprisingly well, and even outperformed LUR at many locations. For the 28-county 3-year model we calculated an average absolute value residual of 0.68 and a RMSE on these predictions of 0.90 (compared with 1.10 for LUR). For the 9-county model, the average absolute value residual was 0.48, with a RMSE of 0.61 (compared with 0.87 for LUR). For the 28-county winter-2000 model, we calculated an average absolute value residual of 1.39 and a RMSE of 1.55 (compared with 1.72 for LUR).

Although kriging performed well when predicting measured $PM_{2.5}$ concentrations at validation locations using only the modeling samples, the LUR model outperformed kriging based on the results of cross validation analyses using the full set of samples. The RMSEs of cross validation predictions, for example, are 1.15, 1.00, and 1.69 for the LUR compared with 1.30, 1.47, and 2.04 for the kriging (28-county 3-year, 9-county 3-year, and 28-county winter-2000 models, respectively).

Discussion

We developed three LUR models for predicting $PM_{2.5}$ concentrations in New York City and surrounding counties using a combination of traffic, land-use, population, and local emissions variables. These models explained more than 60% of the variability in measured $PM_{2.5}$ concentrations and they predicted concentrations at validation locations that were generally within 10% of actual values.

All models included total traffic in the 500-m or 300-m buffer and total population in the 1000-m buffer. The 28-county and 9-county 3-year models also included the industrial land-use in the 300-m buffer variable, whereas the 28-county winter-2000 model included a variable representing vegetative land use in the 1000-m buffer. There was little difference between the 28-county models based on winter-2000 concentrations and on the 3-year averages. The relative strength of a smaller (300-m vs. 500-m) buffer for total traffic in the 28-county winter-2000 model does suggest a stronger local influence; but otherwise, the difference in regional and local contributions did not appear to strongly influence the model.

Given the presumed impact of local traffic, we would have expected variables in smaller buffers to be the strongest predictors of $PM_{2.5}$ concentrations. Although they were indeed good predictors (traffic in the 100-m buffer, for example, explained approximately 25% of variation in the 28-county 3-year concentrations), they did not perform as well as variables in larger buffers. This is attributable to a number of factors. Since $PM_{2.5}$ is a pollutant with both regional and local contributors, it is possible that strong predictor variables are able to explain some variation for both sources. Predictors based on relatively small buffers may also perform better when modeling highly concentrated samples (which was not the case in this analysis). Finally, as demonstrated through European studies (Hochadel et al. 2006), $PM_{2.5}$ varies more gradually over space than elemental carbon and therefore the strength of the larger buffers may reflect this large-area variation in the pollutant.

In general, these variables (total traffic 500 m and 300 m, total population 1000 m, industrial 1000 m, and vegetation 1000 m) were robust regardless of which specific monitoring locations were omitted from the model to use for validation, although we found that the industrial land-use variable was affected by the inclusion or exclusion of a New Jersey site that had the highest $PM_{2.5}$ concentration. Nevertheless, the fact that the variable for industrial land use in the 300-m buffer in the five New York City boroughs was also significant when modeled without the influence of the New Jersey sample lends support to the important role played by industrial land use. Furthermore, we found that an industrial land-use variable derived from New York City's tax-lot data — which are limited to the five boroughs, have a very different resolution, and have slightly different land-use characterizations — was also a statistically

significant predictor of $PM_{2.5}$ levels. This supports the assertion that industrial land use is indeed explaining variation in $PM_{2.5}$ and that the result we found was not due to the idiosyncratic nature of the data we included.

The 28-county 3-year model without validation samples exhibited some bias in that it over-predicted ten values and under-predicted three. The bias was less evident, but still existed, in the full model that included the validation samples (34 were over-predicted and 28 were under-predicted). The under-prediction appears to have occurred in the more urbanized New Jersey counties and over-prediction appears to have occurred in areas distant from New York City and, to a lesser extent, in eastern New York City and Long Island. The bias did not exist in the 9-county model. Although slight bias was present, the models performed well overall on cross-validation.

Although the RMSEs for the 28-county 3-year and winter-2000 models suggest that predictions at validation locations were more precise for the 3-year values than for the winter values, they also disguise differences in variance and spread. The winter-2000 $PM_{2.5}$ values had approximately twice the variance and a 24% greater interquartile range than the 3-year values. The mean absolute percentage error (MAPE) may allow more appropriate comparison; it reveals that the predictions are more similar in percentage terms: The MAPE for the predictions at validation locations was 6.5% for the 28-county 3-year model and 6.2% for the 28-county winter-2000 model (and 5.0% for the 3-year 9-county 3-year model).

We found that when the validation samples (about 20% of the total) were omitted, kriging models more accurately predicted the monitored values at the validation sites than the LUR models; but when the validation samples were returned to the pool of modeling samples, LUR performed better. Since ordinary kriging employs only data on the variable of interest, it is not vulnerable to unusual values in potential predictor variables. The extreme values for traffic in some areas of New York City, for example, could inflate (or deflate) LUR parameters, particularly in models based on a limited number of observations. At the same time, kriging the raw monitoring data limits the potential for kriging to capture small-area variation such as an intersection of major highways. Kriging, as a result, may "over-smooth" and is likely to miss areas with unusually high $PM_{2.5}$ concentrations. It is also possible that kriging in this context violates the fundamental assumption of stationarity — that relationships between exposure levels and pollutant sources are constant over time and space. Points close to high-traffic freeways, for example, may exhibit a different relationship between $PM_{2.5}$ and distance than would points in rural areas far from any major source of $PM_{2.5}$.

$PM_{2.5}$ exhibits strong seasonal and diurnal patterns in New York City; concentrations are higher in the summer months and during the morning (6 AM to 9 AM) and late evening (5 PM to 10 PM) hours (DeGaetano and Doherty 2004). Although this set of analyses makes use of $PM_{2.5}$ concentrations averaged over time, future analyses may wish to consider these patterns and develop, for instance, daily or seasonal maps that could highlight short-term variability (Christakos and Serre 2003).

As mentioned in the Materials and Methods section, incomplete data provided by the NYMTC precluded our use of traffic data for all time periods. For example, it is likely that models based on average daily traffic, rather than average daily afternoon rush-hour traffic, would lead to different parameters. It is also possible that an analysis that relies on rush-hour traffic alone (such as this one) could lead to a wider spread of $PM_{2.5}$ predictions because areas of high traffic in off-peak times may also have a significantly larger increase in traffic during rush hour. Nevertheless, we would expect relative rates of traffic for different areas to remain similar. We found, for example, the Spearman rank correlation coefficient for evening (4 PM to 8 PM) rush-hour traffic compared with night-time (8 PM to 6 AM) traffic for the same road segments is 0.93; this suggests that the results would likely have been similar had we used total average daily traffic.

These models demonstrate that $PM_{2.5}$ can be predicted using LUR in North America. Using a combination of traffic, population, land-use, and local point-source emissions variables we were able to predict $PM_{2.5}$ concentrations well at validation locations and predict more than 60% of the variation in $PM_{2.5}$ measurements over a wide area. Although the three models are not identical in variables or parameters, their similarity reinforces the relationship between $PM_{2.5}$ concentrations and land use near monitors. Given the strong predictive power of both LUR and kriging, we also applied kriging with external drift (a technique that combines aspects of LUR with kriging) to the data. The limited residual autocorrelation from the LUR, however, precluded adequately fitting variograms and predictions were not improved using this technique.

These models, and LUR models in general, hold particular promise in epidemiologic settings in which small-area variations can be associated with significant health effects. Whereas these models seem to predict well, data limitations hampered our ability to investigate all potentially useful predictors. In particular, further research is needed on the possible effects of street canyons and of seasonal variations in $PM_{2.5}$.

SPATIAL ANALYSIS OF AIR POLLUTION AND MORTALITY IN NEW YORK

Materials and Methods

Study Population Mortality data were extracted from the ACS CPS-II database for subjects in 746 ZCAs in the New York City region (28 counties) (Figure 7). In total, 43,930 subjects lived in these ZCAs and 10,525 deaths were recorded during the follow-up from 1982 to 2000.

Assessment of Exposure to $PM_{2.5}$ Regression equations were developed to predict $PM_{2.5}$ concentrations around air monitoring locations in the New York City region using proximate traffic, population, and land-use data (see the section A Land-Use Regression Model for Predicting $PM_{2.5}$ Concentrations for details). The dependent variable in our LUR was $PM_{2.5}$; 3-year averages for 1999 through 2001 were calculated using daily data from the EPA AQS.

In total we assembled complete data for 62 sites in 28 counties. Models were fitted for the 3-year averages and the winter-2000 averages (January through March). The winter average was used to reduce the impact of regional transport of secondary SO_4^{2-} aerosols; this allowed us to assess particles that may be more toxic and are likely to result from local traffic and industry.

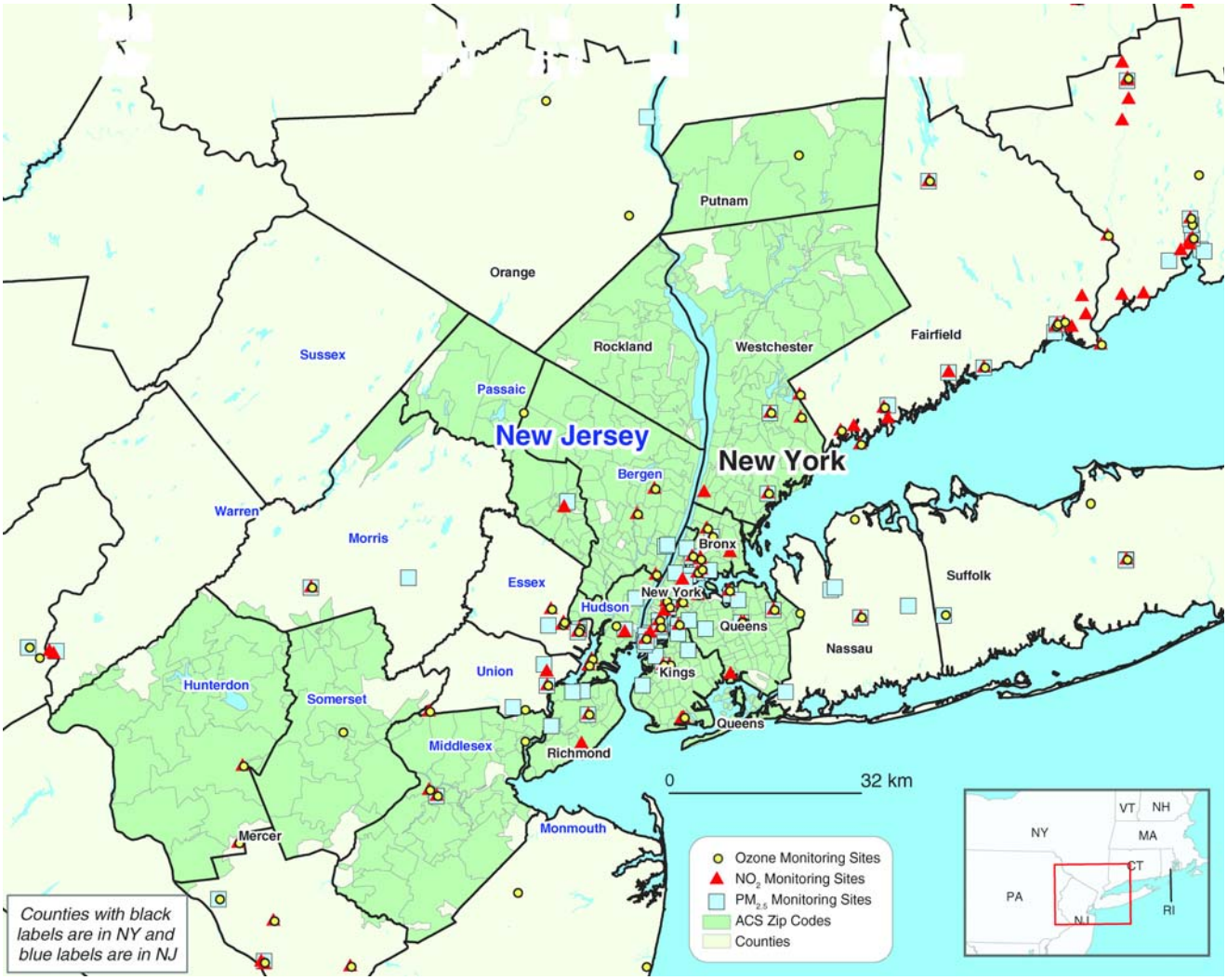

Figure 7. New York City study region.

Land-use data were assembled from several sources at several resolutions. These included detailed (1 inch = ~250 feet) tax-lot data from the New York City Department of City Planning (2003), medium scale (1 inch = ~40,000 feet) land-use data for New Jersey from the New Jersey Department of Environmental Conservation (1995/1997), and coarse scale (1 inch = ~100,000 feet) land-use data (National Land Cover Data) from the USGS (1997, based on Landsat images from 1992 and confirmed using aerial photos). Data on traffic and road conditions were supplied by the NYMTC. (We also conducted sensitivity analyses to compare the results of the LUR models of exposure with results from ordinary kriging models. See details of the model derivation and validation in the section A Land-Use Regression Model for Predicting $PM_{2.5}$ Concentrations; also published in Ross et al. 2007).

Ecologic Covariates Contextual conditions for the ZCAs where subjects lived at enrollment were controlled with the ecologic covariates (from USCB 1980; see sidebar), which included poverty, income disparity, unemployment, median household income, education attainment, and three descriptors of ethnic origin: percentage who are white, Hispanic-American, and African-American (we used only "percentage white" in the statistical models due to its high inverse correlations with the other ethnic categories). Finally, percentage of homes with air conditioning was used to assess possible infiltration of particles; a greater proportion of air conditioning use could lead to lower indoor exposure levels.

Statistical Methods and Data Analysis

Detailed methods are reported in an earlier kriging-based exposure study (Jerrett et al. 2005a) and in the Nationwide Analysis section of this report. Briefly, we used the random effects Cox model with random effects defined at the ZCA scale and assuming positive correlation between random effects in neighboring areas. Sensitivity analyses were also conducted using two levels of clustering (e.g., ZCA and MSA) as well as with controls for the likely correlation of observed values for the cohort (non-independence) in the random effects model, similar to the approach used for the Nationwide Analysis.

Exactly the same 44 individual-level covariates identified in earlier ACS studies of the health effects of air pollution were included. These variables (see sidebar) measure lifestyle, diet, demographics, occupational, and educational factors that may confound the air pollution–mortality association (Pope et al. 2002). There were 12 different smoking variables included in every model. Controls for various ecologic covariates were also included.

Results

LUR Exposure Models The final 28-county 3-year LUR model included the three predictors of total traffic within 500 m, total population within 1000 m, and industrial land use within 300 m of the monitors. This model predicted 66% of the variation in $PM_{2.5}$ and estimated $PM_{2.5}$ concentrations at the 13 validation locations to within 0.93 $\mu g/m^3$ (6.5%) of actual concentrations. Concentrations were generally highest in the central parts of New York City, especially in Manhattan. The 28-county winter-2000 model used similar independent variables, but explained slightly less of the variation, with a correlation coefficient of ~ 0.60.

Mortality Models Table 15 summarizes the health effects estimates for all-cause and cause-specific deaths in the 28-county 3-year model. Only IHD had a significant positive association with $PM_{2.5}$. The IHD results were insensitive to control for the 44 individual-level variables and for most of the ecologic covariates. HR estimates were lower, but positive (with confidence intervals including unity) for models that contained percentage of unemployment, median household income, or all seven ecologic covariates together in the model with the 3-year average $PM_{2.5}$ concentration For the 28-county winter-2000 model, effects were significant and relatively stable for IHD with all variable specifications, including those that controlled for all seven ecologic covariates and for copollutant exposure to O_3 (see Table 16).

We compared the 28-county 3-year average $PM_{2.5}$ concentration at the 90% decile and at the 10% decile in the exposure distribution and found a difference of 1.5 $\mu g/m^3$. For this exposure contrast with the fully adjusted model, the HR for $PM_{2.5}$ and IHD was 1.06 (95% CI, 1.00–1.12). For the 28-county winter-2000 average $PM_{2.5}$ exposure, the difference between the 10% and 90% deciles was 3.9 $\mu g/m^3$ $PM_{2.5}$, and the HR for IHD was 1.21 (95% CI, 1.07–1.34; Table 16). Diabetes and endocrine deaths also had large HR estimates (in the range of 1.2 to 1.4; Table 16), although these were confounded by the ecologic covariates.

Table 15. HRs by Cause of Death Associated with an Interdecile Comparison Value of 1.5 μg/m^3 from the 28-County 3-Year Model[a]

Covariates	All Causes	IHD ICD-9: 410–414	CPD ICD-9: 400–440, 460–519	Lung Cancer ICD-9: 162	Diabetes ICD-9: 250	Endocrine Disorders ICD-9: 240–279
Deaths (*n*)	10,559	2,735	4,625	853	118	206
$PM_{2.5}$ only[b]	1.011 (0.935–1.047)	1.109 (1.039–1.182)[c]	0.977 (0.926–1.031)	1.036 (0.911–1.179)	1.326 (0.999–1.759)	1.249 (1.000–1.561)
+ 44 Individual-level covariates	0.984 (0.948–1.020)	1.072 (1.003–1.147)	0.953 (0.902–1.007)	0.955 (0.836–1.091)	1.329 (0.983–1.797)	1.224 (0.965–1.552)
Ecologic covariates[d]						
Air conditioning (%)	0.987 (0.951–1.024)	1.071 (1.001–1.147)	0.956 (0.904–1.011)	0.962 (0.841–1.102)	1.332 (0.980–1.809)	1.235 (0.973–1.567)
White (%)	0.987 (0.950–1.026)	1.088 (1.013–1.169)	0.950 (0.895–1.008)	1.002 (0.872–1.151)	1.273 (0.920–1.762)	1.206 (0.937–1.554)
Unemployed (%)	0.970 (0.933–1.009)	1.066 (0.992–1.146)	0.927 (0.874–0.984)	0.962 (0.835–1.108)	1.239 (0.891–1.723)	1.172 (0.905–1.518)
Median household income ($000's)	0.968 (0.930–1.007)	1.050 (0.976–1.130)	0.922 (0.868–0.979)	0.950 (0.824–1.095)	1.249 (0.892–1.751)	1.165 (0.895–1.517)
Grade 12 education (%)	1.006 (0.968–1.045)	1.139 (1.059–1.224)	0.983 (0.927–1.042)	0.986 (0.858–1.135)	1.236 (0.892–1.714)	1.191 (0.923–1.537)
Income disparity (Gini)	0.998 (0.959–1.039)	1.102 (1.023–1.188)	0.969 (0.912–1.029)	0.961 (0.832–1.110)	1.293 (0.918–1.823)	1.218 (0.933–1.591)
Poverty (%)	0.979 (0.940–1.021)	1.080 (1.000–1.165)	0.929 (0.873–0.990)	1.004 (0.866–1.163)	1.247 (0.875–1.778)	1.188 (0.902–1.565)
All 7 ecologic covariates	0.977 (0.932–1.025)	1.072 (0.980–1.172)	0.940 (0.875–1.011)	0.985 (0.832–1.166)	1.083 (0.723–1.621)	1.143 (0.835–1.564)
Ozone[e]	0.997 (0.955–1.042)	1.058 (0.975–1.148)	0.963 (0.902–1.029)	0.967 (0.828–1.129)	1.325 (0.918–1.912)	1.319 (0.992–1.754)
Ozone + all 7 ecologic covariates	0.982 (0.934–1.034)	1.054 (0.957–1.161)	0.938 (0.868–1.014)	1.000 (0.836–1.196)	1.099 (0.705–1.711)	1.221 (0.871–1.712)

[a] The $PM_{2.5}$ concentration of 1.5 μg/m^3 for New York City represents the difference between the concentrations at the 90% decile and at the 10% decile in the exposure distribution from the 28-county 3-year model. Analysis was based on 746 ZCAs with ACS CPS-II residents and stratified by age (in 1-year groupings), gender, and race. N = 44,056 CPS-II participants living in the 28 counties. Bolded data refer to text. HRs are followed by 95% confidence intervals.

[b] Predicted using the 28-county 3-year model.

[c] Significant positive association.

[d] Ecologic covariates were included one at a time to a base model with $PM_{2.5}$ + 44 individual-level covariates.

[e] Summer O_3 values for 1999–2001.

Table 16. HRs by Cause of Death Associated with an Interdecile Comparison Value of 3.9 μg/m^3 $PM_{2.5}$ from the 28-County Winter-2000 Model[a]

Covariates	All Causes	IHD ICD-9: 410–414	CPD ICD-9: 400–440, 460–519	Lung Cancer ICD-9: 162	Diabetes ICD-9: 250	Endocrine Disorders ICD-9: 240–279
Deaths (*n*)	10,559	2,735	4,625	853	118	206
$PM_{2.5}$ only[b]	1.036 (0.989–1.085)	1.263 (1.157–1.379)	1.047 (0.978–1.122)	0.984 (0.832–1.164)	1.476 (0.959–2.271)	1.289 (0.927–1.793)
+ 44 Individual-level covariates	1.000 (0.954–1.048)	1.203 (1.099–1.316)	1.013 (0.945–1.087)	0.893 (0.754–1.058)	1.423 (0.907–2.232)	1.214 (0.863–1.708)
Ecologic covariates[c]						
Air conditioning (%)	1.001 (0.953–1.052)	1.194 (1.087–1.312)	1.022 (0.950–1.099)	0.886 (0.739–1.063)	1.404 (0.878–2.247)	1.253 (0.881–1.781)
White (%)	1.002 (0.953–1.053)	1.230 (1.117–1.354)	1.011 (0.938–1.089)	0.941 (0.786–1.126)	1.307 (0.805–2.124)	1.173 (0.815–1.688)
Unemployed (%)	0.981 (0.933–1.032)	1.200 (1.089–1.322)	0.983 (0.912–1.060)	0.894 (0.746–1.072)	1.258 (0.772–2.050)	1.127 (0.781–1.628)
Median household income ($000's)	0.985 (0.938–1.035)	1.180 (1.073–1.297)	0.986 (0.917–1.061)	0.891 (0.747–1.063)	1.290 (0.799–2.082)	1.138 (0.796–1.629)
Grade 12 education (%)	1.015 (0.967–1.066)	1.261 (1.148–1.386)	1.037 (0.964–1.116)	0.917 (0.769–1.092)	1.295 (0.810–2.071)	1.171 (0.822–1.668)
Income disparity (Gini)	1.011 (0.962–1.062)	1.233 (1.120–1.358)	1.029 (0.955–1.109)	0.898 (0.752–1.073)	1.332 (0.822–2.157)	1.182 (0.823–1.697)
Poverty (%)	0.996 (0.946–1.047)	1.216 (1.102–1.341)	0.997 (0.924–1.076)	0.930 (0.775–1.117)	1.270 (0.772–2.091)	1.144 (0.788–1.660)
All 7 ecologic covariates	0.989 (0.929–1.054)	1.220 (1.082–1.375)	1.034 (0.941–1.135)	0.891 (0.710–1.117)	1.026 (0.563–1.870)	1.107 (0.706–1.736)
Ozone[d]	1.024 (0.970–1.082)	1.224 (1.100–1.362)	1.058 (0.974–1.148)	0.892 (0.736–1.082)	1.376 (0.816–2.318)	1.282 (0.863–1.905)
Ozone + all 7 ecologic covariates	0.999 (0.935–1.068)	1.212 (1.066–1.377)	1.047 (0.948–1.157)	0.897 (0.707–1.139)	1.028 (0.539–1.960)	1.182 (0.732–1.909)

[a] The $PM_{2.5}$ concentration of 3.9 μg/m^3 for New York City represents the difference between the concentrations at the 90% decile and at the 10% decile in the exposure distribution from the 28-county winter-2000 model. Analysis was based on 746 ZCAs with ACS CPS-II residents and stratified by age (in 1-year groupings), gender, and race. N = 44,056 CPS-II participants living in the 28 counties. HRs are followed by 95% confidence intervals.

[b] Predicted using the 28-county winter-2000 model.

[c] Ecologic covariates were included one at a time to a base model with $PM_{2.5}$ + 44 individual-level covariates.

[d] Summer O_3 values for 1999–2001.

Results for all models in which the 44 individual-level variables were controlled are shown in Figure 8 for all cause-of-death categories. Figure 9 summarizes the results for causes of death that appeared to be associated with $PM_{2.5}$ exposures. Neither all-cause nor any cause-specific deaths had a positive, significant association with $PM_{2.5}$. All-cause and CPD deaths did have positive HRs, but these were attenuated by some ecologic covariates.

We investigated the sensitivity of the results to alternative model specifications using the random effects models with clustering at the ZCA scale and at the ZCA and MSA scales together, and with the latter model including a spatial autocorrelation parameter based on nearest-neighbor adjacency. These results for IHD are shown in Figure 10. The 3-year average exposure effect was slightly reduced by the clustering on the random effects, but the HRs for IHD were largely unaffected by alternative model specification.

Effect modification by education was investigated based on earlier findings (Krewski et al. 2000a,b) and the results are presented in Tables 17–20. There was a mild suggestion of effect modification; the less-educated group had slightly higher effects, but the differences were not large. The differences between educational groups seemed more pronounced for the 3-year-average $PM_{2.5}$ exposure than for the winter-2000 exposure; the group with grade 12 completed or not (Table 17) had point estimates nearly twice the size of the group with more than a grade 12 education (Table 19). For the winter models effects were similar for both groups.

Discussion

In the New York City region, we did not observe elevated $PM_{2.5}$-associated risk of mortality for all-cause, CPD, or lung cancer deaths, but IHD did show a significant positive association with $PM_{2.5}$ exposure. The large and significant effects for IHD provide additional evidence of a specific association with a cause of death that has high biologic plausibility (Brook et al. 2004). The random effects from the model with one level of clustering (ZCA scale) displayed a spatial pattern of lower residual variance in the central parts of the city and higher residual variance in the suburban and outlying areas. This pattern visually appeared to be the opposite of the pattern for $PM_{2.5}$ concentrations, which had higher levels in the city center and lower levels in the suburbs (see Figure 11).

Despite this visual contrast between residual mortality (mortality that was not explained or predicted by the model) and the pattern of $PM_{2.5}$ concentrations, IHD did have a significant positive association with exposure to $PM_{2.5}$. The IHD results were insensitive to control for the 44 individual-level covariates and control for clustering (nonindependence) in the random effects model (see Figure 11 for a map of the random effects from a model with only individual-level covariates). Effects were mildly reduced when we included unemployment at the ZCA scale (Tables 15–20). There was a suggestion of effect modification that showed larger risks in the lower-education groups in the 28-county 3-year model.

Although the HRs for IHD and $PM_{2.5}$ appeared to be smaller than those reported for Los Angeles, this resulted from the limited range of exposures in New York City. If the coefficient is reported for the same 10-$\mu g/m^3$ exposure contrast used in Los Angeles, the significant HR increases to 1.56 for the 3-year average, which is somewhat higher than the HR of 1.39 for the Los Angeles region. This is a key point about the difference between the two regions: In Los Angeles we found a strong positive association between areas of high pollution and areas of high residual mortality that was not explained by the 44 individual-level covariates. In New York City, the pattern was reversed — pollution appeared worst in areas where people seemed to be healthier and wealthier. Therefore pollution is less likely to have a major effect on health because it must compete with many positive health attributes in the individuals such as good nutrition, clean employment, and access to medical care.

The pattern of high urban and low rural $PM_{2.5}$ exposure and the opposite pattern for mortality that was not accounted for by individual factors complicates the association between air pollution and mortality in New York City. Nevertheless, the association between $PM_{2.5}$ exposure and IHD mortality is biologically plausible and is still evident in this analysis despite these competing gradients of mortality and exposure. Other recent studies have suggested specific links between cardiovascular disease and traffic-related pollution (Hoek et al. 2002) and between $PM_{2.5}$ concentrations and preclinical indicators of atherosclerosis (Künzli et al. 2005), which underlies many of the IHD deaths. Consequently, the results from New York City lend corroborative evidence of an association between $PM_{2.5}$ exposure and mortality for a cause of death likely associated with air pollution exposure.

We also investigated an alternative exposure model in New York City based on spatially kriging the data from the 62 fixed-site air pollution monitors (Ross et al. 2006), as had been done by Jerrett and coworkers (2005a) for Los Angeles. The kriging and LUR models performed similarly in cross-validation studies, although the LUR model was slightly superior for predicting $PM_{2.5}$ concentrations at the validation locations that had not been included in the model formulation. In the health effects assessment, we also tested the kriging exposure model based on the 3-year

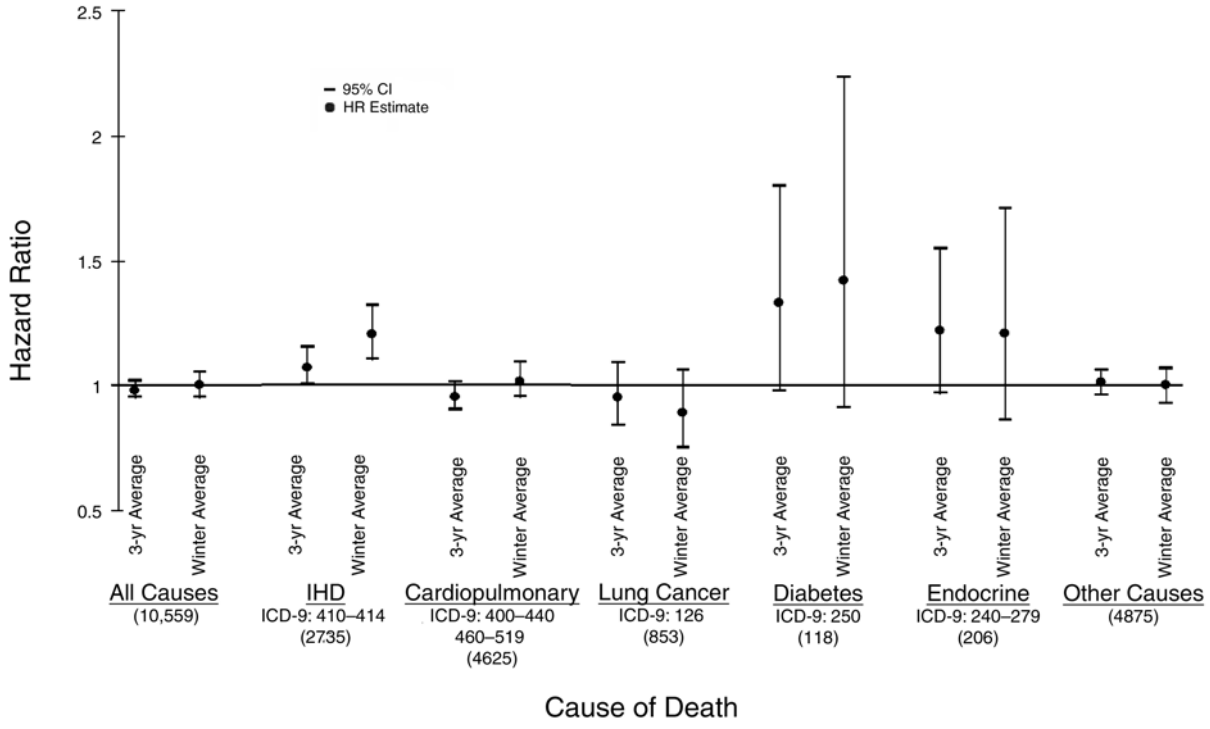

Figure 8. HRs by cause of death associated with an interdecile comparison value of 1.5 μg/m^3 $PM_{2.5}$ from the 28-county 3-year model and 3.9 μg/m^3 $PM_{2.5}$ from the winter-2000 model. Analysis was based on 746 ZCAs with ACS CPS-II residents and stratified by age (in 1-year groupings), gender, and race. N = 44,056 participants living in the 28 counties; number of deaths for each cause is given beneath the ICD-9 codes. (See also Tables 15 and 16.)

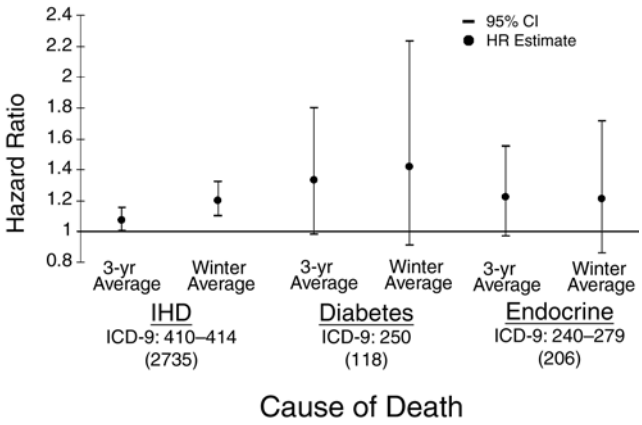

Figure 9. HRs by selected causes of death associated with an interdecile comparison value of 1.5 μg/m^3 $PM_{2.5}$ from the 28-county 3-year model and 3.9 μg/m^3 $PM_{2.5}$ from the winter-2000 model. Analysis was based on 746 ZCAs with ACS CPS-II residents and stratified by age (in 1-year groupings), gender, and race. N = 44,056 participants living in the 28 counties; number of deaths for each cause is given beneath the ICD-9 codes. (See also Tables 15 and 16.)

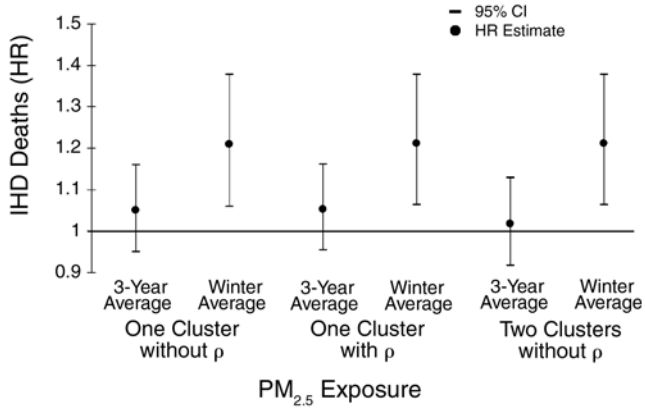

Figure 10. HR results for IHD deaths from analyses with one (ZCA) or two (ZCA and MSA) levels of clustering and with or without ρ (a statistical estimate of the homogeneity of $PM_{2.5}$ exposure within a cluster). Deaths were associated with an interdecile comparison value of 1.5 μg/m^3 $PM_{2.5}$ from the 28-county 3-year model and 3.9 μg/m^3 $PM_{2.5}$ from the winter-2000 model. Analysis was based on 746 ZCAs with ACS CPS-II residents and was stratified by age (in 1-year groupings), gender, and race.

average $PM_{2.5}$ concentrations. Risk estimates were similar to but slightly smaller than those obtained with the LUR model. Because of concerns about attenuation of risk estimates due to exposure measurement error with spatial kriging, we based our risk estimates on LUR. This suggests that differences in results between the New York City and Los Angeles Analyses (see the next section) are likely not due to different methods used to ascertain levels of exposures.

Table 17. HRs by Cause of Death Associated with an Interdecile Comparison Value of 1.5 μg/m^3 $PM_{2.5}$ from the 28-County 3-Year Model as Modified by Grade 12 Education Completed or Not[a]

Covariates	All Causes	IHD ICD-9: 410–414	CPD ICD-9: 400–440, 460–519	Lung Cancer ICD-9: 162	Diabetes ICD-9: 250	Endocrine Disorders ICD-9: 240–279
Deaths (*n*)	5,602	1,537	2,580	469	66	117
$PM_{2.5}$ only[b]	0.993 (0.940–1.049)	1.130 (1.026–1.243)	0.982 (0.907–1.062)	0.892 (0.725–1.097)	1.078 (0.660–1.762)	1.064 (0.734–1.541)
+ 44 Individual-level covariates	0.976 (0.924–1.031)	1.105 (1.003–1.218)	0.968 (0.894–1.048)	0.826 (0.669–1.020)	1.091 (0.663–1.797)	1.051 (0.721–1.533)
Ecologic covariates[c]						
Air conditioning (%)	0.982 (0.929–1.038)	1.104 (1.000–1.220)	0.969 (0.894–1.050)	0.814 (0.654–1.012)	1.116 (0.679–1.837)	1.104 (0.760–1.605)
White (%)	0.987 (0.930–1.047)	1.131 (1.017–1.256)	0.956 (0.877–1.043)	0.864 (0.691–1.080)	1.015 (0.595–1.732)	1.061 (0.711–1.584)
Unemployed (%)	0.972 (0.916–1.030)	1.094 (0.985–1.214)	0.941 (0.864–1.025)	0.851 (0.683–1.062)	0.991 (0.582–1.690)	1.037 (0.695–1.545)
Median household income ($000's)	0.962 (0.906–1.022)	1.104 (0.990–1.230)	0.935 (0.856–1.022)	0.836 (0.665–1.050)	1.028 (0.589–1.795)	1.022 (0.674–1.549)
Grade 12 education (%)	1.003 (0.946–1.063)	1.173 (1.056–1.303)	0.998 (0.917–1.087)	0.880 (0.705–1.100)	1.015 (0.602–1.712)	1.045 (0.706–1.549)
Income disparity (Gini)	1.000 (0.942–1.061)	1.146 (1.029–1.276)	0.987 (0.905–1.077)	0.858 (0.684–1.076)	1.066 (0.619–1.834)	1.053 (0.701–1.580)
Poverty (%)	0.981 (0.921–1.045)	1.136 (1.015–1.272)	0.941 (0.858–1.033)	0.906 (0.716–1.146)	0.942 (0.527–1.683)	1.005 (0.654–1.544)
All 7 ecologic covariates	0.967 (0.900–1.039)	1.096 (0.963–1.247)	0.933 (0.840–1.037)	0.863 (0.657–1.133)	0.804 (0.416–1.554)	0.960 (0.594–1.554)
Ozone[d]	1.000 (0.938–1.066)	1.110 (0.979–1.235)	0.994 (0.905–1.092)	0.831 (0.654–1.056)	1.135 (0.638–2.018)	1.123 (0.725–1.741)
Ozone + all 7 ecologic covariates	0.982 (0.910–1.059)	1.090 (0.950–1.252)	0.948 (0.847–1.060)	0.872 (0.656–1.159)	0.851 (0.420–1.724)	1.026 (0.614–1.716)

[a] The $PM_{2.5}$ concentration of 1.5 μg/m^3 for New York City represents the difference between the concentrations at the 90% decile and at the 10% decile in the exposure distribution from the 28-county 3-year model. Analysis was based on 746 ZCAs with ACS CPS-II residents and stratified by age (in 1-year groupings), gender, and race. N = 18,963 CPS-II with grade 12 education or less. HRs are followed by 95% confidence intervals.

[b] Predicted using the 28-county 3-year model.

[c] Ecologic covariates were included one at a time to a base model with $PM_{2.5}$ + 44 individual-level covariates.

[d] Summer O_3 values for 1999–2001.

Table 18. HRs by Cause of Death Associated with an Interdecile Comparison Value of 3.9 μg/m^3 $PM_{2.5}$ from the 28-County Winter-2000 Model as Modified by Grade 12 Education Completed or Not[a]

Covariates	All Causes	IHD ICD-9: 410–414	CPD ICD-9: 400–440, 460–519	Lung Cancer ICD-9: 162	Diabetes ICD-9: 250	Endocrine Disorders ICD-9: 240–279
Deaths (*n*)	5,602	1,537	2,580	469	66	117
$PM_{2.5}$ only[b]	1.003 (0.938–1.073)	1.248 (1.100–1.416)	1.042 (0.945–1.149)	0.867 (0.683–1.100)	1.435 (0.765–2.692)	1.234 (0.773–1.970)
+ 44 Individual-level covariates	0.984 (0.920–1.053)	1.220 (1.075–1.385)	1.027 (0.931–1.133)	0.803 (0.632–1.020)	1.423 (0.741–2.732)	1.203 (0.746–1.938)
Ecologic covariates[c]						
Air conditioning (%)	0.978 (0.911–1.050)	1.189 (1.041–1.357)	1.021 (0.922–1.132)	0.762 (0.587–0.988)	1.435 (0.730–2.823)	1.302 (0.795–2.131)
White (%)	0.988 (0.919–1.062)	1.241 (1.083–1.422)	1.008 (0.906–1.121)	0.853 (0.662–1.100)	1.287 (0.637–2.603)	1.216 (0.729–2.029)
Unemployed (%)	0.970 (0.902–1.042)	1.194 (1.043–1.368)	0.986 (0.887–1.096)	0.843 (0.654–1.088)	1.249 (0.617–2.529)	1.181 (0.707–1.973)
Median household income ($000's)	0.969 (0.902–1.040)	1.203 (1.051–1.376)	0.993 (0.895–1.102)	0.827 (0.644–1.061)	1.342 (0.667–2.701)	1.189 (0.717–1.971)
Grade 12 education (%)	0.998 (0.930–1.070)	1.258 (1.102–1.436)	1.040 (0.939–1.153)	0.850 (0.663–1.088)	1.320 (0.671–2.599)	1.209 (0.737–1.983)
Income disparity (Gini)	0.996 (0.928–1.069)	1.239 (1.083–1.418)	1.034 (0.932–1.147)	0.840 (0.654–1.078)	1.378 (0.691–2.750)	1.217 (0.737–2.009)
Poverty (%)	0.983 (0.914–1.058)	1.235 (1.075–1.419)	1.001 (0.899–1.115)	0.880 (0.680–1.139)	1.247 (0.608–2.555)	1.173 (0.698–1.970)
All 7 ecologic covariates	0.954 (0.872–1.044)	1.168 (0.988–1.381)	0.993 (0.871–1.132)	0.803 (0.583–1.106)	1.041 (0.433–2.505)	1.194 (0.642–2.221)
Ozone[d]	1.017 (0.941–1.099)	1.240 (1.070–1.437)	1.084 (0.967–1.215)	0.812 (0.621–1.063)	1.584 (0.760–3.301)	1.345 (0.780–2.319)
Ozone + all 7 ecologic covariates	0.971 (0.883–1.067)	1.166 (0.976–1.392)	1.021 (0.889–1.172)	0.810 (0.579–1.132)	1.160 (0.461–2.921)	1.326 (0.689–2.554)

[a] The $PM_{2.5}$ concentration of 3.9 μg/m^3 for New York City represents the difference between the concentrations at the 90% decile and at the 10% decile in the exposure distribution from the 28-county winter-2000 model. Analysis was based on 746 ZCAs with ACS CPS-II residents and stratified by age (in 1-year groupings), gender, and race. N = 18,963 CPS-II participants with grade 12 education or less. HRs are followed by 95% confidence intervals.

[b] Predicted using the 28-county winter-2000 model.

[c] Ecologic covariates were included one at a time to a base model with $PM_{2.5}$ + 44 individual-level covariates.

[d] Summer O_3 values for 1999–2001.

Table 19. HRs by Cause of Death Associated with an Interdecile Comparison Value of 1.5 μg/m^3 $PM_{2.5}$ from the 28-County 3-Year Model as Modified by More Than Grade 12 Education[a]

Covariates	All Causes	IHD ICD-9: 410–414	CPD ICD-9: 400–440, 460–519	Lung Cancer ICD-9: 162	Diabetes ICD-9: 250	Endocrine Disorders ICD-9: 240–279
Deaths (*n*)	4,957	1,198	2,045	384	52	89
$PM_{2.5}$ only[b]	1.022 (0.974–1.072)	1.089 (0.993–1.195)	0.964 (0.892–1.041)	1.121 (0.949–1.324)	1.608 (1.134–2.282)	1.490 (1.121–1.979)
+ 44 Individual-level covariates	0.986 (0.938–1.036)	1.032 (0.937–1.136)	0.924 (0.854–1.000)	1.055 (0.891–1.250)	1.411 (0.959–2.077)	1.393 (1.026–1.893)
Ecologic covariates[c]						
Air conditioning (%)	0.988 (0.940–1.039)	1.038 (0.943–1.144)	0.930 (0.859–1.008)	1.080 (0.910–1.282)	1.326 (0.884–1.989)	1.363 (0.997–1.863)
White (%)	0.985 (0.935–1.038)	1.044 (0.943–1.155)	0.931 (0.857–1.013)	1.095 (0.917–1.306)	1.225 (0.791–1.898)	1.271 (0.905–1.785)
Unemployed (%)	0.964 (0.913–1.017)	1.034 (0.932–1.147)	0.901 (0.827–0.981)	1.037 (0.862–1.247)	1.183 (0.746–1.873)	1.275 (0.898–1.810)
Median household income ($000's)	0.968 (0.919–1.021)	1.004 (0.906–1.112)	0.898 (0.825–0.977)	1.044 (0.871–1.251)	1.227 (0.791–1.904)	1.255 (0.888–1.774)
Grade 12 education (%)	1.000 (0.950–1.054)	1.094 (0.987–1.212)	0.949 (0.873–1.031)	1.054 (0.883–1.259)	1.229 (0.791–1.910)	1.302 (0.929–1.824)
Income disparity (Gini)	0.989 (0.937–1.045)	1.052 (0.945–1.171)	0.935 (0.856–1.020)	1.014 (0.841–1.223)	1.288 (0.803–2.067)	1.307 (0.908–1.882)
Poverty (%)	0.966 (0.913–1.021)	1.013 (0.909–1.128)	0.900 (0.823–0.984)	1.055 (0.873–1.275)	1.200 (0.748–1.927)	1.233 (0.852–1.784)
All 7 ecologic covariates	0.968 (0.907–1.034)	1.036 (0.909–1.181)	0.923 (0.831–1.024)	0.998 (0.799–1.247)	1.040 (0.577–1.875)	1.243 (0.804–1.921)
Ozone[d]	0.982 (0.925–1.043)	1.001 (0.889–1.127)	0.910 (0.827–1.002)	1.060 (0.862–1.304)	1.268 (0.763–2.108)	1.414 (0.958–2.087)
Ozone + all 7 ecologic covariates	0.959 (0.893–1.029)	0.998 (0.866–1.151)	0.895 (0.799–1.003)	1.020 (0.802–1.298)	0.940 (0.484–1.827)	1.257 (0.780–2.024)

[a] The $PM_{2.5}$ concentration of 1.5 μg/m^3 for New York City represents the difference between the concentrations at the 90% decile and at the 10% decile in the exposure distribution from the 28-county 3-year model. Analysis was based on 746 ZCAs with ACS CPS-II residents and stratified by age (in 1-year groupings), gender, and race. N = 25,093 CPS-II participants with more than grade 12 education. HRs are followed by 95% confidence intervals.

[b] Predicted using the 28-county 3-year model.

[c] Ecologic covariates were included one at a time to a base model with $PM_{2.5}$ + 44 individual-level covariates.

[d] Summer O_3 values for 1999–2001.

Table 20. HRs by Cause of Death Associated with an Interdecile Comparison Value of 3.9 μg/m^3 $PM_{2.5}$ from the 28-County Winter-2000 Model as Modified by More Than Grade 12 Education[a]

Covariates	All Causes	IHD ICD-9: 410–414	CPD ICD-9: 400–440, 460–519	Lung Cancer ICD-9: 162	Diabetes ICD-9: 250	Endocrine Disorders ICD-9: 240–279
Deaths (*n*)	4,957	1,198	2,045	384	52	89
$PM_{2.5}$ only[b]	1.053 (0.987–1.124)	1.261 (1.110–1.432)	1.035 (0.937–1.144)	1.056 (0.831–1.340)	1.576 (0.845–2.941)	1.096 (0.655–1.834)
+ 44 Individual-level covariates	1.013 (0.948–1.082)	1.177 (1.033–1.341)	0.987 (0.891–1.092)	0.998 (0.785–1.268)	1.347 (0.721–2.519)	1.047 (0.610–1.800)
Ecologic covariates[c]						
Air conditioning (%)	1.025 (0.957–1.099)	1.206 (1.052–1.381)	1.012 (0.910–1.126)	1.037 (0.802–1.340)	1.218 (0.628–2.360)	0.966 (0.556–1.679)
White (%)	1.015 (0.946–1.089)	1.216 (1.059–1.396)	1.007 (0.904–1.122)	1.032 (0.798–1.333)	1.035 (0.516–2.076)	0.916 (0.462–1.814)
Unemployed (%)	0.990 (0.922–1.063)	1.203 (1.046–1.385)	0.970 (0.869–1.081)	0.954 (0.735–1.238)	0.984 (0.488–1.983)	1.099 (0.611–1.977)
Median household income ($000's)	1.000 (0.934–1.071)	1.162 (1.014–1.330)	0.971 (0.874–1.078)	0.977 (0.761–1.255)	1.068 (0.547–2.085)	0.871 (0.421–1.804)
Grade 12 education (%)	1.028 (0.960–1.101)	1.255 (1.094–1.439)	1.017 (0.915–1.130)	0.989 (0.771–1.268)	1.086 (0.559–2.108)	1.385 (0.849–2.260)
Income disparity (Gini)	1.021 (0.951–1.095)	1.223 (1.062–1.409)	1.012 (0.907–1.128)	0.945 (0.733–1.219)	1.094 (0.544–2.202)	1.233 (0.748–2.034)
Poverty (%)	0.998 (0.929–1.072)	1.181 (1.025–1.361)	0.978 (0.876–1.092)	0.976 (0.752–1.267)	1.003 (0.495–2.034)	1.233 (0.739–2.059)
All 7 ecologic covariates	1.014 (0.927–1.110)	1.274 (1.066–1.524)	1.068 (0.930–1.226)	0.921 (0.663–1.280)	0.746 (0.302–1.842)	1.013 (0.586–1.751)
Ozone[d]	1.022 (0.945–1.104)	1.194 (1.020–1.398)	1.008 (0.893–1.138)	0.972 (0.733–1.288)	1.035 (0.485–2.209)	1.016 (0.590–1.752)
Ozone + all 7 ecologic covariates	1.011 (0.919–1.112)	1.251 (1.034–1.515)	1.057 (0.912–1.224)	0.937 (0.662–1.326)	0.614 (0.229–1.650)	1.029 (0.609–1.738)

[a] The $PM_{2.5}$ concentration of 3.9 μg/m^3 for New York City represents the difference between the concentrations at the 90% decile and at the 10% decile in the exposure distribution from the 28-county winter-2000 model. Analysis was based on 746 ZCAs with ACS CPS-II residents and stratified by age (in 1-year groupings), gender, and race. *N* = 25,093 CPS-II participants with more than grade 12 education. HRs are followed by 95% confidence intervals.

[b] Predicted using the 28-county winter-2000 model.

[c] Ecologic covariates were included one at a time to a base model with $PM_{2.5}$ + 44 individual-level covariates.

[d] Summer O_3 values for 1999–2001.

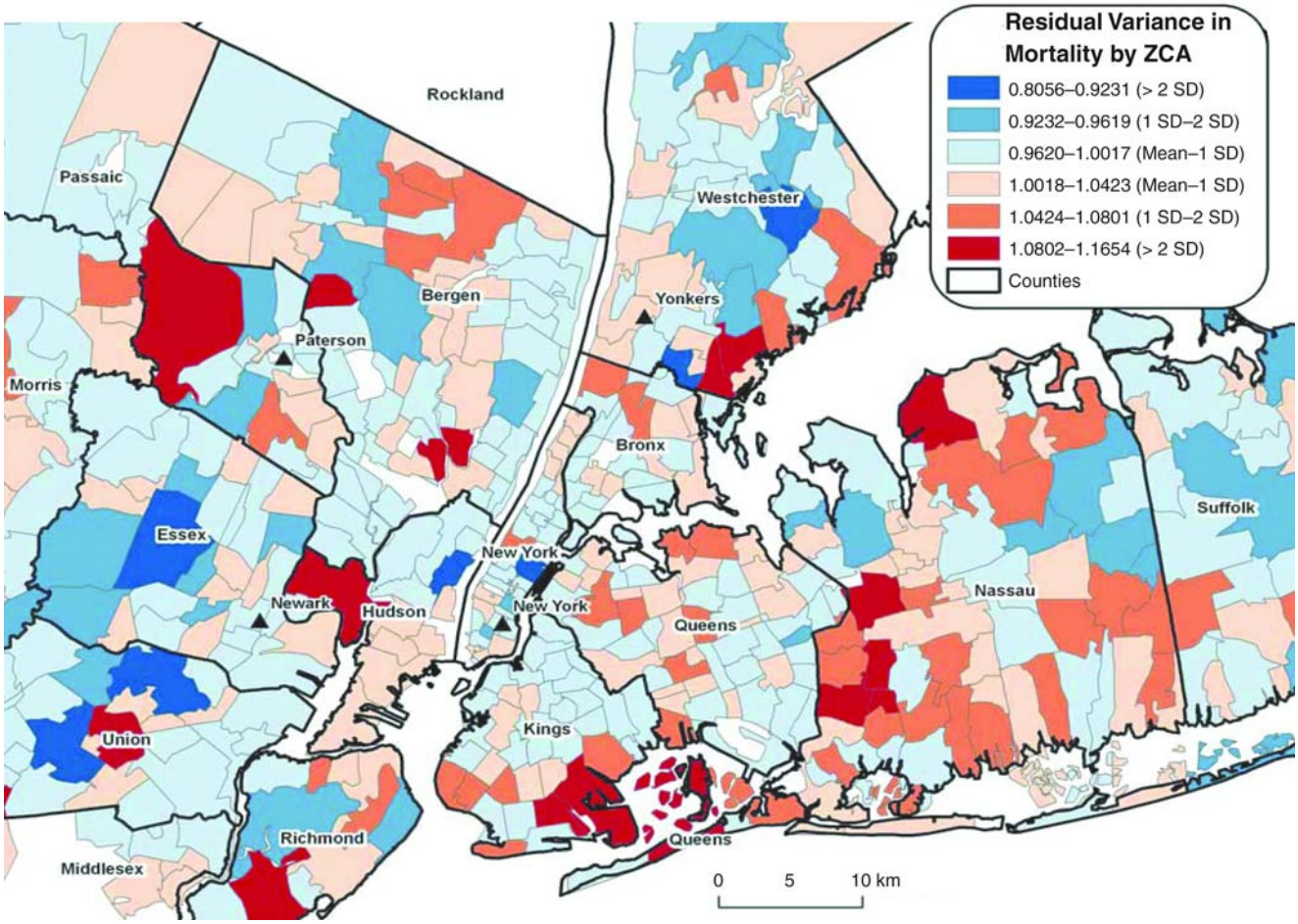

Figure 11. Residual variance in mortality from IHD for 28 counties in the NYC region (shown by ZCA). Mortality levels were predicted by the random effects model with $PM_{2.5}$ exposure and the 44 individual-level covariates. The predicted values are compared with actual measured mortality. Values > 1 indicate higher-than-expected and < 1 indicate lower-than-expected residual mortality.

INTRA-URBAN ANALYSIS FOR THE LOS ANGELES REGION

A LAND-USE REGRESSION MODEL FOR PREDICTING $PM_{2.5}$ CONCENTRATIONS

Background

Developing exposure models that would predict the spatial variation of air pollution within cities has been identified as a research priority (Brunekreef and Holgate 2002). The LUR method is a promising approach that uses monitored pollutant concentrations as the dependent variable and a comprehensive set of land-use, traffic, population, and physical geography variables as predictors of $PM_{2.5}$ concentrations (Briggs et al. 2000a). Most LUR models have been calibrated with NO_2 as a marker for traffic exposure (Briggs et al. 2000a; Gilbert et al. 2005; Sahsuvaroglu et al. 2006). Two European studies that have estimated ambient particles with an LUR model used a reflectance method to measure the presence of ambient particles. This method is more likely to show local variation due to traffic than would $PM_{2.5}$ mass measurements (Brauer et al. 2003; Hochadel et al. 2006). To date, no North American studies have attempted to use the LUR method for deriving $PM_{2.5}$ estimates. In this project, we developed an LUR model for predicting $PM_{2.5}$ mass over the 5-county MSA of Los Angeles (see also Moore et al. 2007).

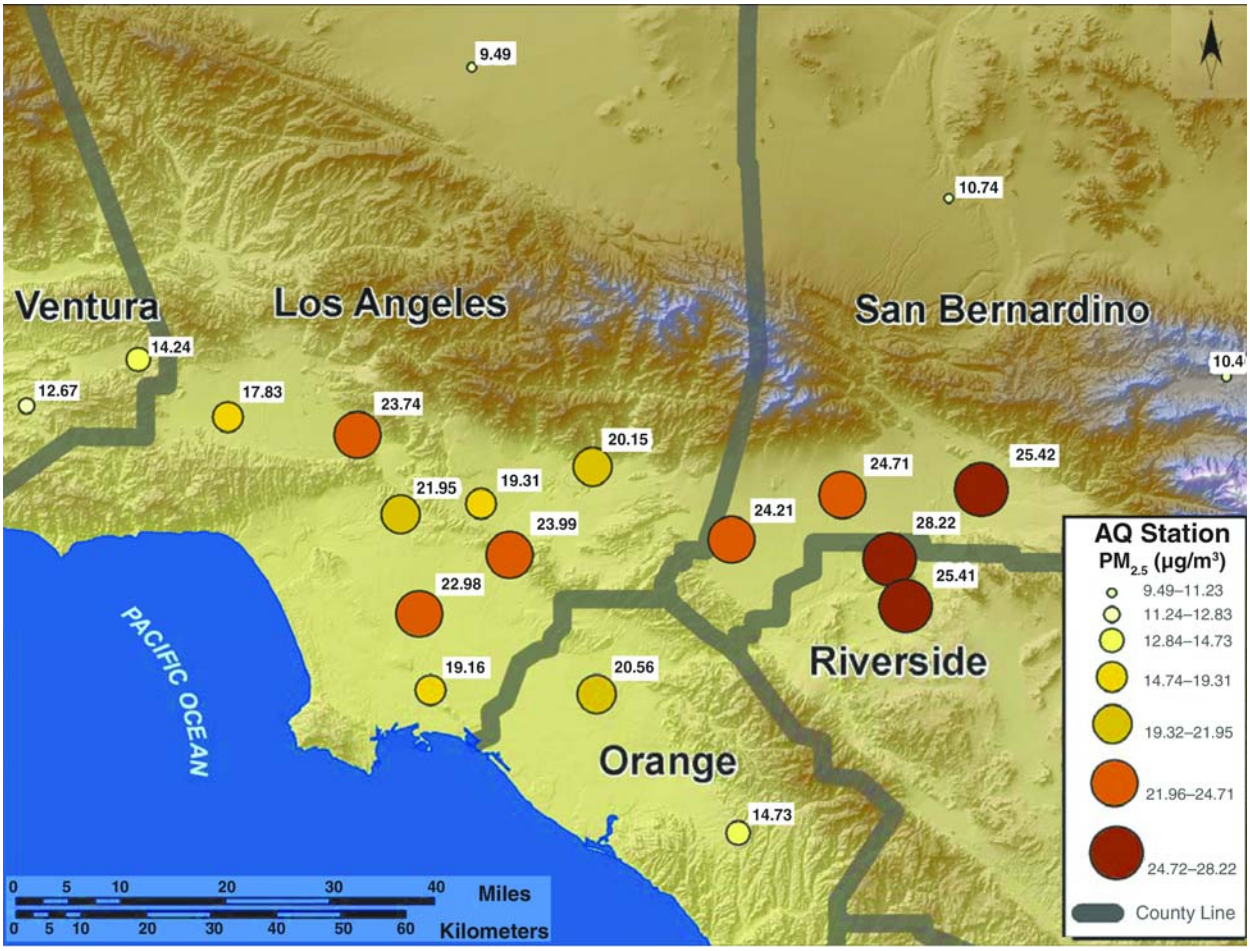

Figure 12. Map including the most densely populated areas in Los Angeles MSA showing $PM_{2.5}$ concentrations at air quality monitoring sites used to support the analysis.

Materials and Methods

Study Area At the 2000 U.S. census, the Los Angeles MSA had a population of about 16.7 million people (Southern California Association of Governments [SCAG] 2004). This MSA encompasses Los Angeles, San Bernardino, Ventura, Riverside, and Orange counties and covers a total area of 98,500 km^2. The Los Angeles MSA is the most congested area in the United States and has some of the highest levels of air pollution (Southern California Compass 2005). As illustrated in Figure 12, the region also has wide variation in $PM_{2.5}$ concentrations, which makes it a suitable site to explore the use of LUR models in North America. Once calibrated, an LUR model can be used to derive a spatially continuous surface map of $PM_{2.5}$ concentrations.

Methods for Handling Spatial Data We used the ArcGIS 9.1 (ESRI 2004) GIS to integrate data about $PM_{2.5}$ concentrations, land use, traffic, population, and physical geography.

Dependent Variable: Ambient $PM_{2.5}$ In 1998, a $PM_{2.5}$ monitoring network was implemented throughout California; we used data from 2000 because it was the first complete year of data collected. The placement of each site was determined by specific criteria: (1) to provide measurements of pollutant concentrations in the air basins to be used for regulatory purposes; (2) to represent populated areas with high pollutant concentrations; and (3) to characterize emission sources in areas of high concentrations. Most (14) of the 23 monitors that we used to estimate

exposure were placed to determine concentrations in populated areas; five were set up close to mountain passes (e.g., Fontana, San Bernardino) to determine the regional transport of pollutants; and four monitors were dedicated to chemical speciation of pollutants (Los Angeles, Fontana, Anaheim, and Rubidoux) (California Environmental Protection Agency and Air Resources Board 2003).

In the Los Angeles MSA, 23 sites measure $PM_{2.5}$ (Figure 12). All of these sites use FRM monitors and collect 24-hour mass data on 1-, 3-, and 6-day cycles. Since the network was established in 1998, annual average $PM_{2.5}$ concentrations have ranged from 9.49 $\mu g/m^3$ in Lancaster (an arid flat agricultural area with generally clear air) to 28.22 $\mu g/m^3$ in Riverside (a large inland city with high pollutant levels). The mean and median for the Los Angeles MSA were 18.42 $\mu g/m^3$ (SD = 6.01) and 19.31 $\mu g/m^3$, respectively. In much of the MSA, $PM_{2.5}$ levels exceed the annual average limits for both federal (15 $\mu g/m^3$) and state (12 $\mu g/m^3$) standards.

Land-Use Data Land use is a significant factor in predicting air pollution levels (Briggs et al. 2000a; Jerrett et al. 2003) because different uses involve certain transportation and other activities and produce different levels of emissions. For example, industrial and heating sources may expel gaseous precursor air pollutants and primary PM, resulting in a relatively high $PM_{2.5}$ concentration surrounding the source; whereas parks and open spaces have fewer sources of pollution and therefore low concentrations of $PM_{2.5}$.

We followed methods from a study completed in Hamilton, Ontario, Canada by Sahsuvaroglu and coworkers (2006) to delineate the land-use categories that would have a reasonable probability of covering an adequate number of pollution monitors: commercial, industrial, residential, agricultural, airports, water, parks, open space, and roads.

We obtained digital land-use data from the SCAG (2004). (These data were first collected in 1993 and were updated in 2000.) We cleaned and aggregated the data into land-use and transportation categories that have been used in other studies and found to be associated with ambient pollutant concentrations (Briggs et al. 2000a; Brunekreef and Holgate 2002; Jerrett et al. 2005b; Ross et al. 2006).

Each of the land-use categories was analyzed as a possible predictor of $PM_{2.5}$ concentrations. We created buffers at 50 to 5000 m in radius around each of the 23 $PM_{2.5}$ monitors. The larger buffer areas were selected based on an analysis of the semivariance of a kriging model, which suggested that monitoring sites within 5 to 10 km would have correlated pollutant levels. In keeping with the focus of deriving local estimates, we used the lower bound of the range (5 km) as the maximum distance to test. The area (in hectares [Ha]; 1 Ha = 2.471 acres or 0.01 km^2) of each separate land-use category was measured within each buffer zone surrounding a monitor.

Traffic Data Personal and commercial vehicles emit primary particulates and precursors such as nitrogen oxides that react with the ambient environment to produce secondary particulate air pollution (Brauer et al. 2003). To improve estimates of traffic-generated particles, we obtained a geographically coded digital road network file from TeleAtlas (Reitscheweg, The Netherlands). This file covered major highways, minor highways, major roads, arterial roads, collector roads, and local roads. We used the same buffering technique used for the land-use data to measure the total length (in kilometers) of specific road types around a given monitor.

Through ESRI, we obtained average annual daily traffic (AADT) counts (of all vehicles) from Business Analyst (ArcView 9.1, ESRI, San Diego, CA 2004) for major traffic corridors in Southern California from 1990 to 2002. The traffic corridors were defined in six categories: (1) major freeways, (2) minor freeways, (3) highways, (4) connector roads, (5) major local roads, and (6) minor local roads. We used a total of 34,310 measurement locations (traffic points) for analyses in the metropolitan area (Los Angeles, Ventura, Orange, San Bernardino, and Riverside). The AADT traffic-point data were spatially assigned to the closest individual road segments in the ESRI Streetmap data set. Each road class included many speed limit categories. The road classes and speed limits were used to calculate an accurate traffic density. We calculated an average traffic count at each road segment for each class of road and speed limit. For those segments that had no traffic count available, we assigned the average traffic count for road segments with the corresponding road class and speed limits. For example, a major road would have a class of 3 and a variation of speed limits; for a class-3 road with a speed limit of 35 mph but no traffic-count data, we assigned the average traffic count of all class-3 roads with a speed limit of 35 mph. The average traffic count for all road segments within each buffer was calculated and assigned to each monitor. Using this method we were able to impute an accurate measurement of AADT throughout the MSA.

Population Data Population density — the number of people, volume of traffic, number of businesses, and area of green space — is an important factor in determining how much and what type of pollution is produced in a given area. Densely populated areas contribute more

traffic-related pollution than sparsely populated areas, and within a city density may also influence the content of emissions (Ross et al. 2006). Higher population density generates more pollution from heating buildings by combustion and from traffic for commuting and traveling to commercial areas.

To determine the population density across the SCAG area (the Los Angeles MSA plus Imperial County), we calculated a kernel estimate by assigning the U.S. Census population data for 2000 for each census tract to the census tract centroid. The radius of the kernel was determined through analyses with a semivariogram. This process revealed that analyzing spatial autocorrelation in the range of 5 to 10 km would be optimal.

Physical Geography Proximity to a large body of water, such as an ocean, reduces the concentrations of pollutants, and the onshore marine breeze helps maintain pollution at lower levels near the coast (Bay Area Air Quality Management District [BAAQMD] 2005). The distance to the Pacific ocean was calculated for each monitor location and was analyzed for its possible relationship to measured pollutant levels in the LUR model. Elevation data were acquired from the USGS at 30-m resolution and each monitoring area was assigned an elevation for analysis in the LUR model.

Modeling Methods Regression and spatial analysis were used to create an interpolated $PM_{2.5}$ pollutant surface. ArcView v3.3, ArcMap v9.0, ArcInfo v9.0 (Redlands, CA), S-PLUS 2000 (Boston, MA) and Stata v8 (College Station, TX) were used for these analyses. We used an inverse distance weighting (IDW) method to create an accurate surface.

Linear regression was conducted using the natural logarithm transformation of the $PM_{2.5}$ measurements. Bivariate linear regressions were first used to determine which variables were most strongly related to $PM_{2.5}$. This first step tested over 140 independent variables because land-use and road variables covered a large number of categories and several sizes of buffers around 23 monitors. A multiple linear regression model was developed using the significant parameters from the bivariate linear regressions with a manual forward selection process based on the highest t test score for each variable. The VIF was then examined to identify variables that were collinear and could be eliminated. Variables with the highest VIF and variables with the lowest t scores were removed until a parsimonious model with the highest R^2 value and acceptable levels of collinearity between included variables was derived.

Using the bootstrap method, we completed a sensitivity analysis to test the stability of the estimates from the multiple regression model (Burrough and McDonnell 1998). From the 23 monitor data points, a random sample of 15 data points was selected with replacement, for 1000 repetitions. This enabled us to determine bias in the estimates and how accurately the model would predict $PM_{2.5}$ concentrations when multiple locations (or monitors) were excluded from the regression analysis. Additional model diagnostics included the Cook-Weisberg test for heteroskedasticity and the degrees of freedom Betas and Cook distance to examine outliers.

Visualizing the Surface Visualization is an important diagnostic tool for assessing the face validity of a predicted LUR model. We used GIS software to identify approximately 18,000 lattice points for the SCAG area with 2.3 km between lattice points. We created lattice points that were relatively close together in distance to more finely estimate the $PM_{2.5}$ surface, but we were partly constrained by computational capacity. Buffers for the land-use variables in the final LUR model were created around each lattice point, where the areas of each variable were once again calculated in hectares. Using the fitted regression equation, we calculated a predicted $PM_{2.5}$ value for each of the 18,000 lattice points. This method allowed us to visualize the PM surface; for subsequent health analysis, geographic points corresponding to study subjects could serve as the lattice assignment points to minimize exposure assignment error.

We then used the IDW method to interpolate the pollutant surface. The IDW interpolator assumes that at each $PM_{2.5}$ sample point the local influence lessens with distance (ESRI 2004). A specified number of predicted $PM_{2.5}$ points, or all points within a specified radius, can be used to determine the output value for each location, creating a surface. The power in the IDW interpolation determines how influential surrounding points are to the point being interpolated (Burrough and McDonnell 1998). A higher power results in less influence from distant points (Burrough and McDonnell 1998). For this analysis we used the default power of 2, which is a common power used in inverse distance squared weighting.

Results

The land-use variables most correlated with $PM_{2.5}$ concentrations from monitors were used to develop the multivariate model; correlation coefficients are shown in Table 21. The final LUR model included three independent variables (Table 22): (1) traffic count within 300 m (as a direct proxy for particulate emissions and gaseous

Table 21. Land Use Variables with $R \geq 0.4$ That Were Significantly Associated with $PM_{2.5}$ Concentrations[a]

Description	Buffer Size (m)	*R* Value
Commercial areas	5000	0.67
Industrial areas*	5000	0.58
Parks and recreation	5000	0.55
Population density	20 km	0.54
Collector roads	5000	0.53
Arterial roads	3000	0.52
Government areas*	5000	0.51
Population density	10 km	0.48
Arterial roads	2000	0.48
Traffic*	300	0.48
Arterial roads	5000	0.47
Collector roads	2000	0.46
Arterial roads	1000	0.45
Collector roads	3000	0.45
Industrial areas	3000	0.42
Arterial roads	750	0.4
Minor roads	750	0.39
Commercial areas	750	0.35
Industrial areas	50	0.32
Open areas	2000	−0.43
Open areas	3000	−0.48
Secondary roads	2000	−0.51
Secondary roads	1000	−0.54
Open areas	5000	−0.55

[a] Arranged from highest to lowest correlation. An * indicates the three variables used in the final model.

precursors), (2) industrial areas within 5000 m (to represent primary and precursor emissions), and (3) government areas within 5000 m (as a proxy for traffic intensity around major destinations such as schools, government service offices, and hospitals). The R^2 value for the LUR was 0.69 (F = 14.07, $P < 0.00001$), with a few geographic areas near the intersections of freeways displaying over-prediction (see Figure 13).

Regression diagnostics were used to assess the validity of the LUR model. Table 22 shows little collinearity among the independent variables; the average VIF was 1.06. The visualization surface in Figure 14 shows a 63% R^2 between the measured and predicted values of $PM_{2.5}$ from the LUR model. Although the residuals showed a slightly greater variance with higher $PM_{2.5}$ concentrations (Figure 15), the Cook-Weisberg test for heteroskedasticity indicated a nonsignificant difference in the variance around the residuals (P = 0.81), and the degrees-of-freedom Betas-and-Cook distance indicated few outliers in the data. An additional sensitivity analysis used the bootstrap method, in which we resampled 15 locations with 1000 repetitions and jackknife residual statistics. For the bootstrap, the bias values and standard errors were extremely close to 0, and the statistics for the jackknife residuals were less than 0.01, indicating that no single $PM_{2.5}$ monitor's data drove the values predicted.

Discussion

Accuracy of Predictions Using the LUR Model We derived a multiple linear regression model that explained 69% of the variance in $PM_{2.5}$ concentrations, with the main predictors being traffic count within 300 m, industrial areas within 5000 m, and government areas within 5000 m (Table 22). In some areas, the LUR predicted $PM_{2.5}$ concentrations slightly higher than those measured — within the Los Angeles Basin near the intersection of high-traffic freeways (605 and 210, 110 and 405, and 405 and 55) and in Long Beach near the two ports (Los Angeles and Long Beach) and the 710 freeway (Figures 13 and 14).

All of the observed over-predictions were located near intersections of major freeways (Figure 13) and some were upward of 126 μg/m^3. Due to unregulated fuel combustion, ships are one of the leading sources of particulate air pollution in the Los Angeles Basin (Hricko 2004). Surrounding the ports is a network of freeways and railroad

Table 22. Land-Use Regression Model Statistics Along with Collinearity Diagnostics

Variables	Buffer (m)	β	*t* Value	SE	*P* Value	VIF
Constant		2.28621	22.81	0.1002109	0.000	
Traffic	300	0.00001	2.99	0.0000034	0.007	1.09
Industrial area	5000	0.00032	3.33	0.0000958	0.004	1.05
Government area	5000	0.00072	3.35	0.0002139	0.003	1.04

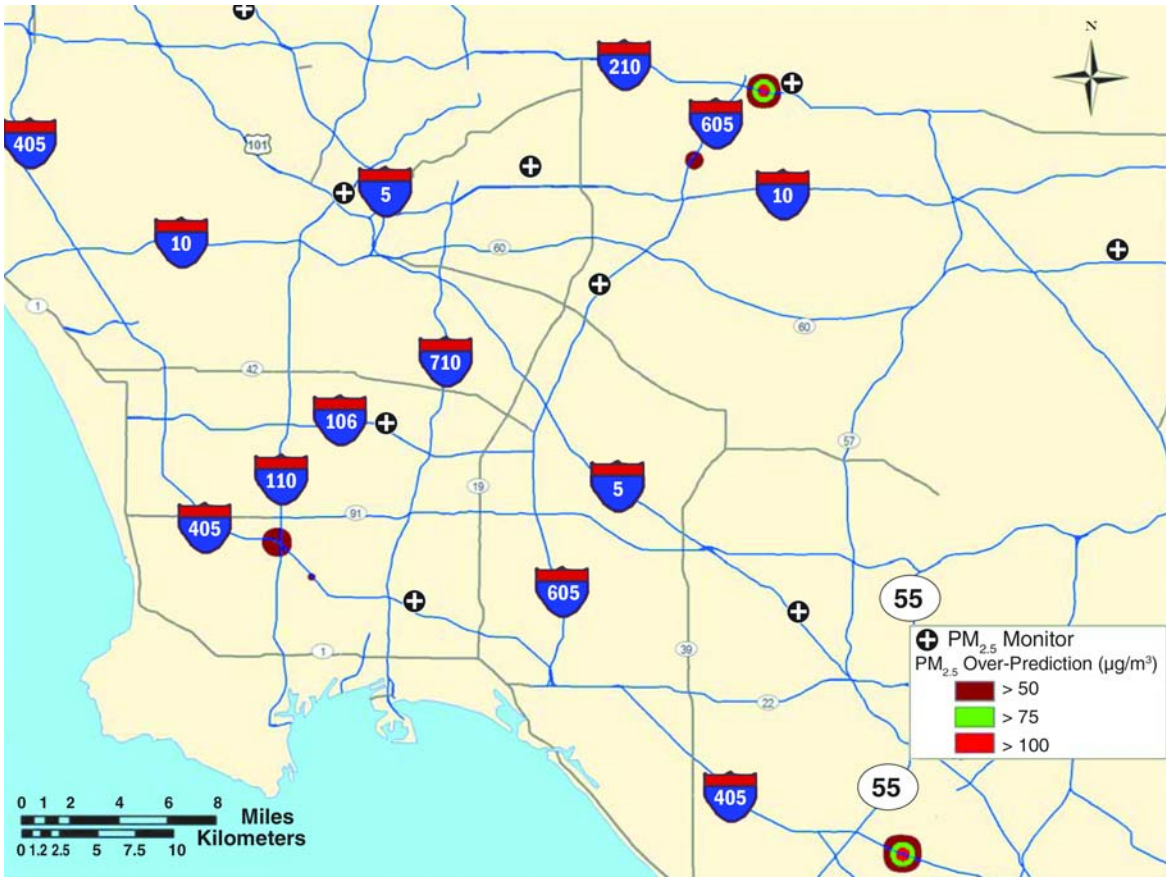

Figure 13. Map of over-predicted values from the LUR model, shown as > 50, 75, or 100 µg/m^3 higher than the measured value. Most over-predictions occurred at freeway intersections. $PM_{2.5}$ monitor positions are marked with a +.

tracks used to disperse cargo to distribution and storage centers in inland areas. More transport trucks, which combust diesel fuel, travel the 710 freeway than any other freeway in Los Angeles (Meyer 2003). Westerdahl and colleagues (2005) found that measured freeway concentrations of $PM_{2.5}$ had a range of 60 to 820 µg/m^3 on the 10 East freeway and that concentrations along major roadways with high-traffic density were up to 20 times higher than residential concentrations. Those measurements were taken over a 5-day period in April of 2003, whereas our LUR model estimates were based on data from 2000. Moreover, in the Westerdahl study, increased concentrations of $PM_{2.5}$ were associated with high diesel traffic along freeways. Thus, the over-predicted values in our analysis are at plausible levels, although further field validation work is needed to assess whether annual average levels on or near freeway intersections are indeed this high.

Brauer and associates (2003) and Hochadel and colleagues (2006) have also used LUR to predict $PM_{2.5}$ concentrations in Europe. Brauer's team modeled air pollution in communities throughout the Netherlands, in Munich, Germany, and in Stockholm, Sweden. Although they used only traffic indicators and did not use land-use classifications in their multivariate regression model, they were able to derive significant prediction models for each of the three locations, for both $PM_{2.5}$ mass and $PM_{2.5}$ filter absorbance, which is used as a marker for diesel exhaust (Brauer et al. 2003). For the Netherlands, Munich, and Stockholm, the R^2 values for the $PM_{2.5}$ mass prediction model were 0.78, 0.76, and 0.63, respectively; and 0.9, 0.83, and 0.76, respectively, for the $PM_{2.5}$ absorbance prediction model. Since absorbance models are typically used to assess traffic-related pollutants, the absorbance model results are a better predictor of measured $PM_{2.5}$ than the $PM_{2.5}$ mass model because the variables used in the absorbance model were chosen specifically to measure traffic. Hochadel and coworkers (2006) conducted a study in Wesel, Germany, using primarily traffic-based indicators as the geographic factors. The regression models predicted strongly for $PM_{2.5}$ absorbance (R^2 = 0.65), but not for $PM_{2.5}$ mass (R^2 = 0.094).

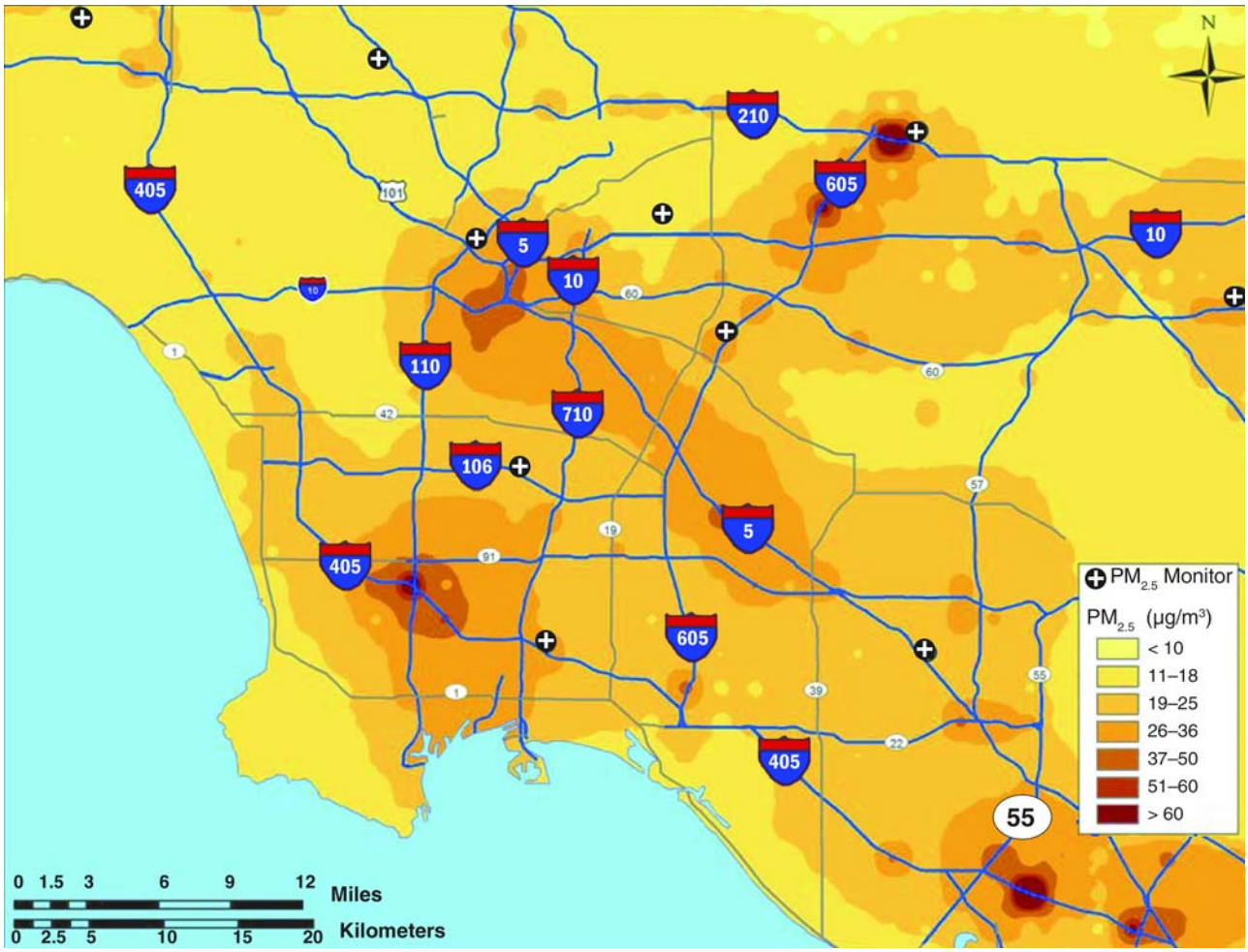

Figure 14. $PM_{2.5}$ surface created by IDW using predicted $PM_{2.5}$ concentrations from an LUR model with the variables of traffic within a 300-m radius, industrial areas within a 5000-m radius, and government areas within a 5000-m radius. $PM_{2.5}$ monitor positions are marked with a +. Notice the high $PM_{2.5}$ concentrations near intersections of major highways.

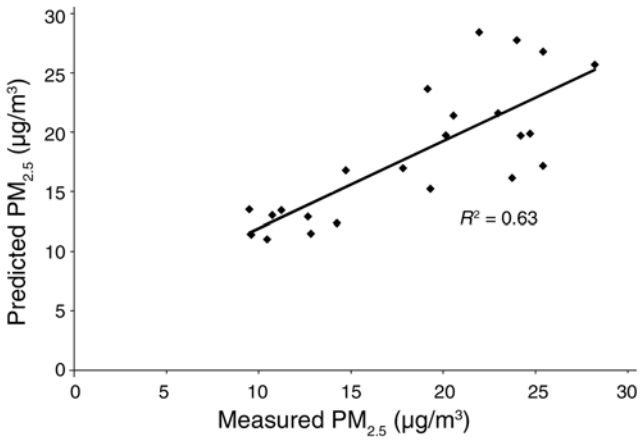

Figure 15. Graph showing predicted $PM_{2.5}$ versus measured $PM_{2.5}$ concentrations from the LUR model. The measured and predicted values for each monitor are plotted on the *x* and *y* axes.

Effects of Buffer Size Selection The buffers we used to measure areas of land-use categories were quite large compared with other studies (generally 100 to 300 meters; Brauer et al. 2003; Hochadel et al. 2006; Ross et al. 2006; Sahsuvaroglu et al. 2006). The Los Angeles MSA is a massive and sprawling urban area and has one of the highest levels of employment and population dispersion in the United States (Gordon and Richardson 1996). This dispersed urban structure, transected by major highways and commercial areas, leads to a broader regional scale of influence for processes that generate PM pollution, and the 2000- to 5000-m buffers surrounding the $PM_{2.5}$ monitors probably reflect this dispersed form of urban development.

The study that is most closely related geographically to this Los Angeles Analysis was done by Ross and associates (2006) in San Diego County, California, in which they predicted ambient NO_2 concentrations. The study area in San

Diego County was much smaller than the Los Angeles MSA — 11,721 km^2 versus 98,500 km^2 for the SCAG region. The traffic-count variable and the industrial land-use variable were common to both models, but the Ross study found that smaller-radius buffers were more effective predictors than those we used in Los Angeles. This makes sense because NO_2 arises from local sources and is known to vary over smaller areas in proximity to traffic (Gilliland et al. 2005), whereas $PM_{2.5}$ is a mixture generated by primary and secondary sources that we would expect to be more regionally dispersed. Data from the larger buffer sizes in this study may reflect either an inherent spatial scale of variation in the pollutants or the more dispersed urban structure of Los Angeles.

Modeling Spatial Variability in Exposure A kriging model was previously developed for the Los Angeles Basin based on $PM_{2.5}$ values from the same 23 monitors (Jerrett et al. 2005). That model did not show as much of the local-area variations in exposure as did the LUR model developed for this study (see Figures 14 and 16). The success of this LUR model demonstrates that traffic and land uses are strong predictors of $PM_{2.5}$ concentrations. Although the scale of variation of $PM_{2.5}$ values around an emissions source appears to be larger than what we might expect from purely local processes, the covariance of $PM_{2.5}$ concentrations with land-use predictors suggests that local land uses and traffic have a significant role in distributions of $PM_{2.5}$ across this large urban area. The kriging model may not be generalizable, because the monitors were established by government agencies in certain locations for the purpose of regulatory compliance and therefore may not reflect the true variability in $PM_{2.5}$ levels represented by the mixture of land uses in the LUR model.

If the monitoring network is not representative of the spatial variability in actual pollutant exposures, we would expect to see bias in the pollutant levels predicted from models based on those monitoring locations. Our use of the bootstrap method demonstrated that it is unlikely that single influential points drove the results of the LUR model. For example, none of the monitors were specifically located to measure traffic impact, and the closest proxy we have is monitors located in densely populated urban areas. Although there is some overlap between dense population and areas of heavy traffic, we would be able to create kriging models to reflect greater local variation if we could include data from monitors located near heavy-traffic sites.

Although the spatially modeled exposures depend intrinsically on land use and local emissions sources such as traffic, the fact that some covariates are related to factors

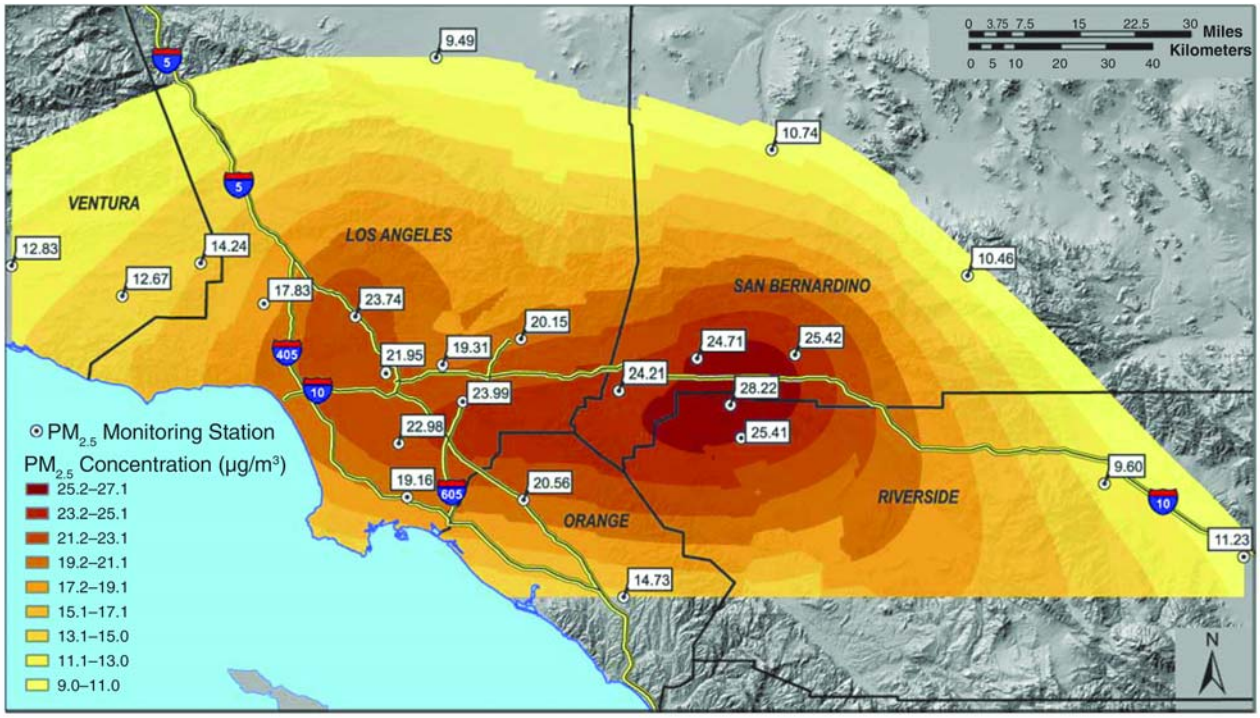

Figure 16. Universal kriging map of $PM_{2.5}$ in the Los Angeles area. $PM_{2.5}$ monitor positions are marked with a circled dot (⊙). (Adapted from Kuenzli et al. [2005].)

that affect health and mortality (such as socio-economic position) means that the LUR model may include some hidden confounders. Consequently, to use LUR for pollution and health analyses, researchers must adjust for other contextual confounders that may be related to the land-use and traffic input to ensure unbiased estimates of the health effects of air pollution.

We found that LUR predicted 69% of the variance in $PM_{2.5}$ mass in the Los Angeles MSA. With sensitivity analysis, we observed that few monitors influenced the results. Traffic, industrial, and government areas were of most significance because of their associated particulate emissions from increased traffic and industrial point sources. Further investigation is needed into the extraordinarily high levels of $PM_{2.5}$ predicted around the intersections of freeways; these levels may constitute a significant threat to public health if they are validated by monitoring.

SPATIAL ANALYSIS OF AIR POLLUTION AND MORTALITY IN LOS ANGELES

Materials and Methods

Study Population Mortality data were extracted from the ACS CPS-II cohort database for metropolitan Los Angeles at the ZCA scale (average population per ZCA in Los Angeles is approximately 35,000; average area is approximately 22.5 km^2). ZCA centroids were weighted by population distribution using spatial boundary files based on 1980 and 1990 USBC data. The centroids were used to assign $PM_{2.5}$ and O_3 exposure levels to the 22,905 ACS subjects living in the 267 ZCAs (this cohort included 5,856 deaths based on follow-up from 1982 through 2000). Some subjects reported only PO Box addresses and were therefore excluded. As in earlier ACS analyses (Pope et al. 2000; Jerrett et al. 2005), availability of air pollution data and other relevant information (e.g., ZCA-level data about ecologic covariates) led to the subset of study subjects to be used in the health effects assessment. Although the ACS cohort is not representative of the general population, the cohort allows for internally valid comparisons within large samples of the American population.

Assessment of $PM_{2.5}$ Exposure An LUR prediction model was developed to predict $PM_{2.5}$ from 23 monitoring locations in the Los Angeles MSA using GIS to integrate data from land use, transportation, and physical geography (see A Land-Use Regression Model for Predicting $PM_{2.5}$ in the Los Angeles Region). The LUR method explained 69% of the variance in $PM_{2.5}$ with three predictors around each monitoring site: (1) traffic count within 300 m, (2) industrial land area within 5000 m, and (3) government land area within 5000 m. Model validation suggested that only a few areas were over-predicted in the downtown section and near freeway interchanges. (See above for details of the LUR model's derivation and validation [also described in Moore et al. 2007]).

Assessment of O_3 Exposure In earlier ACS studies that used between-city comparisons, few associations have been found between O_3 exposure and mortality (Pope et al. 1995, 2002; Krewski et al. 2000a,b). Nevertheless, exposure to this pollutant is considered a health threat in the Los Angeles region, which has some of the highest levels in the United States (Künzli et al. 2003). For O_3, we obtained data at 42 sites in and around the Los Angeles Basin from the California Air Resources Board (ARB) database. We interpolated two surfaces using a universal kriging algorithm: one surface based on the average of the four highest 8-hour concentrations during 2000 at each monitoring site, and another based on the expected peak daily concentrations (EPDC). Expected daily peaks have been used as a statistical measure to assess the likelihood of exceeding the 8-hour average California standard at each site; expected peaks are based on data recorded at each site on a specific date in the previous 3 years (1999–2001). Both 8-hour concentrations and daily peaks are used for federal and state designations of nonattainment areas. They both capture extreme events, but the expected daily peak concentration provides more stability for estimating spatial patterns than the one-year measures based on the four highest days. Few studies of long-term health effects have found significant association with O_3 exposure, although acute effects of a small magnitude have been observed (Bell et al. 2004). Thus, it seems plausible that an O_3 effect would be manifest in those areas most likely to experience exceedances.

Traffic Data To assess the impact of traffic, we defined buffers at both 500 and 1000 meters of a freeway. Each ZCA centroid within those buffers was assigned a value of 1 and others were assigned 0. The resulting variables were used as indictors of proximity to freeways in the health effects models. For each ZCA centroid within those buffers we collected land-use and $PM_{2.5}$ data from monitors. The U.S. Census Feature Class Codes define freeways as having limited access, a numbered assignment (e.g., a major state or U.S. route), and a speed limit higher than 50 miles per hour (USCB 2004). The distance from the ZCA centroid to the freeway was used as a proxy for exposure to traffic-related pollution, which may exert effects independent of and in addition to specific pollutants such as $PM_{2.5}$ and O_3 that vary over larger areas (Hoek et al. 2002).

Ecologic Covariates We assembled data from the 1980 USCB for seven ecologic covariates for the ZCAs to control for contextual neighborhood covariates (see sidebar). Contextual effects occur when individual differences in a health outcome are associated with the group of variables that represent the social, economic, and environmental settings where the individuals live, work, or spend time (e.g., poverty or unemployment in a neighborhood) (Curtis and Taket 1996; Macintyre and Ellaway 2000; Pickett and Pearl 2001; Diez Roux 2002). These contextual effects often operate independently from (or interactively with) the individual-level covariates, such as smoking and diet, from the ACS enrollment questionnaire. We used the ecologic covariates that have been identified as important in the population health literature and have been previously tested as potential confounders with the ACS dataset at the metropolitan scale (Evans and Kantrowitz 2002; Willis et al. 2003). These included income, income disparity, grade 12 education, total population, racial composition (black, white, Hispanic in percentages), and unemployment (Jerrett et al. 2003).

We used the proportion of homes that have air conditioning to measure possible exposure misclassification on the premise that air-conditioned houses are more tightly sealed and have lower penetration of particles from outdoors. Similar housing variables have been used in a meta-analysis of acute effects (Levy et al. 2000); and a recent study of personal exposures in Los Angeles reported that particle penetration is largely reduced in air-conditioned homes (Meng et al. 2005). This variable added partial control for the impact of air conditioning, which may relate both to health outcomes (through prevention of heat stress) and to air pollutant concentrations (because high concentrations and low proportions of air conditioning are related in our study area). We thus expected the proportion of air conditioning in the ZCA to correlate with lower PM exposures and effects.

We also computed principal components from the seven ecologic covariates (excluding AC) to provide maximal control for confounding while avoiding multicollinearity among the ecologic covariates (Luginaah et al. 2001; Krieger et al. 2002).

Statistical Methods and Data Analysis

The statistical methods are similar to those employed by Jerrett and colleagues (2005a) in a previous intra-urban analysis of data from Los Angeles using spatial kriging to estimate air pollutant concentrations at the ZCA scale. (The underlying statistical model is the random effects Cox model described in the section Nationwide Analysis / Statistical Methods and Data Analysis / The Random Effects Cox Model.)

In brief, we used the 44 individual-level covariates (see sidebar) identified as possible confounders of the air pollution–mortality association in the Updated Analysis (Pope et al. 2002). These variables included lifestyle, diet, demographics, occupational, and educational factors along with 12 variables that measure aspects of smoking. Sensitivity analyses revealed that removing individual variables had little influence on the estimated risk of pollution exposure; therefore, to promote comparability with results from earlier studies, we report the results for our analyses that included this standard set of 44 individual-level variables. Eight ecologic covariates (discussed above) were also included.

We used the standard Cox model for our main analyses of association between air pollution and mortality (Hosmer and Lemeshow 1999). Because the units of analyses were small ZCAs and previous analyses had indicated spatial autocorrelation in the residual variation of some health effects analyses, we also used the spatial random effects Cox model as a cross-validation of the standard Cox model. We have previously shown that survival experience is clustered by community and the clusters are spatially autocorrelated between communities (Krewski et al. 2000a,b; Jerrett et al. 2003). Lack of statistical control for these factors can bias the estimates of the effects of air pollution and underestimate associated standard errors (Jerrett et al. 2003; Ma et al. 2003). We specified a model in which the random effects were assumed to be positively correlated for neighboring ZCAs. Thiessen polygons, which ensure that all points within the polygon are closer to the centroid of that polygon than to any other centroid, were used to assign first-order nearest-neighbor contiguity between the ZCAs. The polygons were derived using ArcView 3.2 (ESRI Corp., Redlands, CA).

Results

Using the new LUR model documented in the last section, we assigned exposure concentrations based on the traffic, government, and industrial land use for the 267 ZCAs (see also Jerrett et al. 2005a). These exposure assignments were then compared with the earlier analysis, with exactly the same causes of death, individual and ecologic covariates, and copollutants. The results are shown in Table 23 (six causes of death are shown in each section of the table).

The results show the effects of LUR-predicted $PM_{2.5}$ exposure with different levels of control for confounding variables. HRs are expressed for a 10-μg/m^3 change in

Table 23. HRs by Cause of Death Associated with Each 10-μg/m^3 Change in $PM_{2.5}$ 2000 Concentrations (from LUR Model) Based on 267 Los Angeles ZCAs[a]

Covariates	All Causes (n = 5856)	IHD ICD-9: 410–414 (n = 1462)	CPD ICD-9: 400–440, 460–519 (n = 3136)	Lung Cancer ICD-9: 162 (n = 434)	Digestive Cancer (n = 429)	Other Cancers (n = 992)
$PM_{2.5}$ only	**1.197 (1.082–1.325)**	1.415 (1.154–1.735)	1.179 (1.025–1.356)	1.460 (1.013–2.105)	1.277 (0.880–1.854)	1.036 (0.814–1.319)
+ 44 Individual-level covariates	**1.143 (1.033–1.266)**	1.331 (1.084–1.634)	1.114 (0.968–1.282)	1.392 (0.964–2.010)	1.191 (0.816–1.738)	1.010 (0.791–1.289)
Ecologic covariates[b]						
Air conditioning (%)	1.142 (1.031–1.265)	1.333 (1.085–1.638)	1.121 (0.974–1.290)	1.376 (0.952–1.989)	1.165 (0.797–1.702)	1.002 (0.784–1.281)
Black (%)	1.145 (1.033–1.269)	1.347 (1.096–1.656)	1.120 (0.972–1.289)	1.411 (0.976–2.041)	1.188 (0.812–1.738)	1.009 (0.789–1.290)
White (%)	1.151 (1.036–1.278)	1.362 (1.103–1.682)	1.127 (0.976–1.302)	1.471 (1.008–2.147)	1.162 (0.787–1.717)	1.027 (0.798–1.321)
Hispanic (%)	1.132 (1.016–1.261)	1.322 (1.065–1.641)	1.113 (0.960–1.290)	1.415 (0.956–2.096)	1.117 (0.749–1.667)	1.021 (0.788–1.323)
Unemployment (%)	**1.127 (1.015–1.252)**	1.328 (1.075–1.641)	1.129 (0.977–1.305)	1.279 (0.879–1.862)	1.187 (0.803–1.755)	0.966 (0.751–1.243)
Median household income ($000s)	1.146 (1.035–1.268)	1.332 (1.086–1.635)	1.115 (0.970–1.283)	1.388 (0.963–2.001)	1.195 (0.823–1.735)	1.014 (0.796–1.293)
Total population	1.141 (1.030–1.264)	1.322 (1.076–1.624)	1.108 (0.963–1.275)	1.396 (0.967–2.016)	1.202 (0.823–1.755)	1.012 (0.792–1.292)
Income disparity (Gini)	1.110 (0.999–1.234)	1.254 (1.014–1.552)	1.056 (0.913–1.222)	1.306 (0.893–1.910)	1.213 (0.823–1.786)	1.015 (0.790–1.304)
Grade 12 education (%)	1.144 (1.033–1.266)	1.334 (1.087–1.637)	1.118 (0.972–1.286)	1.386 (0.961–2.000)	1.183 (0.811–1.725)	1.006 (0.788–1.284)
Covariate groupings						
All social factors	**1.142 (1.026–1.272)**	1.322 (1.064–1.642)	1.107 (0.954–1.285)	1.399 (0.949–2.061)	1.185 (0.800–1.755)	1.037 (0.803–1.340)
Air conditioning, median household income, > grade 12 education, social factor	**1.115 (1.003–1.239)**	1.263 (1.020–1.563)	1.072 (0.926–1.241)	1.290 (0.881–1.890)	1.189 (0.809–1.748)	1.011 (0.786–1.299)
Parsimonious ecologic covariates[c]	**1.126 (1.014–1.251)**	1.264 (1.022–1.563)	1.086 (0.939–1.256)	1.311 (0.897–1.915)	1.199 (0.817–1.758)	1.012 (0.788–1.299)
Copollutant control[d]						
44 Individual-level covariates + ozone (EPDC[e])	**1.191 (1.069–1.327)**	1.455 (1.171–1.810)	1.187 (1.023–1.378)	1.446 (0.982–2.128)	1.163 (0.777–1.742)	1.059 (0.818–1.371)
44 Individual-level covariates + ozone (average[f])	1.176 (1.057–1.307)	1.431 (1.155–1.772)	1.152 (0.996–1.334)	1.489 (1.018–2.178)	1.166 (0.784–1.734)	1.053 (0.816–1.358)
44 Individual-level covariates + freeways within 500 m[g]	1.170 (1.054–1.299)	1.393 (1.127–1.721)	1.134 (0.982–1.310)	1.439 (0.989–2.095)	1.208 (0.819–1.783)	1.057 (0.824–1.356)
Copollutant risk estimates						
Ozone (EPDC[e])	0.985 (0.964–1.006)	0.973 (0.932–1.015)	0.966 (0.938–0.994)	0.989 (0.917–1.068)	1.008 (0.933–1.089)	0.989 (0.941–1.040)
Ozone (average[f])	0.993 (0.977–1.010)	0.984 (0.952–1.017)	0.985 (0.963–1.008)	0.970 (0.912–1.032)	1.007 (0.947–1.070)	0.993 (0.954–1.033)
Freeway within 500 m[g]	0.987 (0.875–1.113)	0.898 (0.706–1.143)	0.915 (0.775–1.081)	1.440 (0.939–2.208)	0.841 (0.526–1.346)	1.184 (0.883–1.588)
Freeway within 1000 m[g]	0.974 (0.894–1.062)	1.048 (0.885–1.241)	0.982 (0.874–1.104)	0.942 (0.685–1.295)	0.879 (0.634–1.220)	0.897 (0.721–1.117)

Table continues next page

[a] Baseline HRs were stratified by age (in 1-year groupings), gender, and race. Total number of participants was 22,905. HRs are followed by 95% confidence intervals. Bolded data refer to text.

[b] Ecologic covariates were included one at a time in the model with $PM_{2.5}$ and the 44 individual-level covariates.

[c] Parsimonious individual-level (23) and ecologic (4) covariates were considered. The ecologic covariates were air conditioning, household income, grade 12 education, and the predicted values of the third principal component analysis based on all social variables (except air conditioning).

[d] All models included $PM_{2.5}$.

[e] Based on expected peak daily concentrations.

[f] Average of four highest 8-hour maximum readings.

[g] Intersection with a freeway within 500 or 1000 m of a ZCA centroid.

Table 23 (*Continued*). HRs by Cause of Death Associated with Each 10-μg/m^3 Change in $PM_{2.5}$ 2000 Concentrations (from LUR Model) Based on 267 Los Angeles ZCAs[a]

Covariates	Endocrine Disorders ICD-9: 240–279 (n = 95)	Diabetes ICD-9: 250 (n = 57)	Digestive Disorders (n = 151)	Male Accidents (n = 75)	Female Accidents (n = 47)	All Other Causes (n = 497)
$PM_{2.5}$ only	3.344 (1.565–7.148)	2.313 (0.803–6.660)	1.868 (0.993–3.514)	1.226 (0.512–2.938)	1.126 (0.367–3.456)	0.978 (0.692–1.381)
+ 44 Individual-level covariates	3.037 (1.384–6.664)	2.022 (0.687–5.948)	1.709 (0.902–3.238)	1.078 (0.443–2.627)	0.928 (0.284–3.035)	1.006 (0.709–1.427)
Ecologic covariates[b]						
Air conditioning (%)	3.025 (1.374–6.660)	2.021 (0.685–5.969)	1.683 (0.885–3.199)	1.156 (0.470–2.847)	1.070 (0.322–3.563)	0.977 (0.688–1.387)
Black (%)	2.919 (1.328–6.419)	1.991 (0.680–5.830)	1.734 (0.918–3.277)	1.029 (0.417–2.535)	0.987 (0.302–3.222)	0.981 (0.689–1.396)
White (%)	2.815 (1.256–6.306)	1.971 (0.657–5.915)	1.682 (0.875–3.236)	0.973 (0.387–2.447)	0.943 (0.279–3.192)	0.979 (0.682–1.405)
Hispanic (%)	2.949 (1.283–6.780)	2.006 (0.640–6.286)	1.456 (0.744–2.853)	1.088 (0.424–2.793)	0.693 (0.198–2.425)	1.033 (0.713–1.496)
Unemployment (%)	2.359 (1.065–5.225)	1.664 (0.568–4.877)	1.572 (0.818–3.022)	1.190 (0.474–2.987)	0.944 (0.279–3.193)	0.975 (0.679–1.399)
Median household income ($000s)	2.907 (1.329–6.357)	1.992 (0.681–5.829)	1.709 (0.897–3.256)	1.075 (0.439–2.734)	0.885 (0.261–2.999)	1.021 (0.723–1.441)
Total population	3.090 (1.401–6.816)	2.017 (0.686–5.924)	1.735 (0.916–3.286)	1.083 (0.445–2.638)	0.835 (0.249–2.797)	1.000 (0.704–1.421)
Income disparity (Gini)	3.121 (1.423–6.844)	2.048 (0.692–6.059)	1.691 (0.875–3.271)	1.027 (0.411–2.563)	0.920 (0.267–3.178)	1.013 (0.705–1.453)
Grade 12 education (%)	3.058 (1.384–6.759)	2.038 (0.682–6.089)	1.705 (0.901–3.228)	1.096 (0.449–2.680)	0.923 (0.279–3.059)	1.002 (0.708–1.417)
Covariate groupings						
All social factors	2.676 (1.213–5.904)	1.985 (0.669–5.895)	1.571 (0.804–3.071)	0.927 (0.355–2.420)	0.650 (0.175–2.414)	1.057 (0.733–1.525)
Air conditioning, median household income, > grade 12 education, social factor	2.796 (1.203–6.496)	1.885 (0.584–6.080)	1.311 (0.649–2.649)	1.088 (0.432–2.745)	0.910 (0.256–3.230)	1.006 (0.702–1.441)
Parsimonious ecologic covariates[c]	2.559 (1.131–5.791)	1.735 (0.569–5.290)	1.330 (0.660–2.679)	1.210 (0.488–3.002)	1.096 (0.320–3.746)	0.988 (0.690–1.413)
Copollutant control[d]						
44 Individual-level covariates + ozone (EPDC[e])	2.926 (1.305–6.557)	2.063 (0.686–6.200)	1.630 (0.839–3.167)	1.097 (0.424–2.841)	1.157 (0.319–4.195)	0.939 (0.645–1.368)
44 Individual-level covariates + ozone (average[f])	3.040 (1.376–6.715)	2.154 (0.735–6.311)	1.575 (0.814–3.049)	1.060 (0.414–2.712)	1.014 (0.292–3.525)	0.967 (0.667–1.401)
44 Individual-level covariates + freeways within 500 m[g]	2.813 (1.252–6.321)	1.820 (0.595–5.574)	1.869 (0.981–3.560)	1.114 (0.448–2.769)	0.761 (0.221–2.618)	1.010 (0.704–1.450)
Copollutant risk estimates						
Ozone (EPDC[e])	1.044 (0.884–1.232)	0.982 (0.791–1.220)	1.036 (0.910–1.179)	1.015 (0.843–1.224)	0.872 (0.682–1.114)	1.063 (0.988–1.144)
Ozone (average[f])	0.999 (0.877–1.137)	0.944 (0.795–1.121)	1.063 (0.959–1.178)	1.037 (0.892–1.206)	0.931 (0.766–1.132)	1.043 (0.986–1.104)
Freeway within 500 m[g]	0.660 (0.264–1.651)	0.439 (0.116–1.665)	2.490 (1.082–5.730)	0.559 (0.167–1.874)	0.868 (0.279–2.704)	0.868 (0.584–1.290)
Freeway within 1000 m[g]	1.515 (0.855–2.687)	1.774 (0.835–3.766)	0.495 (0.246–0.995)	1.077 (0.527–2.202)	2.011 (0.883–4.579)	1.152 (0.868,1.529)

[a] Baseline HRs were stratified by age (in 1-year groupings), gender, and race. Total number of participants was 22,905. HRs are followed by 95% confidence intervals. Bolded data refer to text.

[b] Ecologic covariates were included one at a time in the model with $PM_{2.5}$ and the 44 individual-level covariates.

[c] Parsimonious individual-level (23) and ecologic (4) covariates were considered. The ecologic covariates were air conditioning, household income, grade 12 education, and the predicted values of the third principal component analysis based on all social variables (except air conditioning).

[d] All models included $PM_{2.5}$.

[e] Based on expected peak daily concentrations.

[f] Average of four highest 8-hour maximum readings.

[g] Intersection with a freeway within 500 or 1000 m of a ZCA centroid.

$PM_{2.5}$ exposure (followed by the 95% CI). For example, we follow the successive analyses for all-cause mortality:

- with $PM_{2.5}$ alone (stratified for age, sex, and race), the HR was 1.197 (95% CI, 1.082–1.325);
- whereas with the 44 individual-level covariates the HR was 1.143 (95% CI, 1.033–1.266).
- All subsequent results include the 44 individual-level covariates and one or more ecologic covariates.
- With the 44 individual-level covariates and the ecologic covariate of unemployment, the HR of $PM_{2.5}$ was 1.127 (95% CI, 1.015–1.252).
- When we added four social factors extracted from the principal component analysis (which account for 81% of the total variance in the social variables), the HR was 1.142 (95% CI, 1.026–1.272).
- Including all ecologic covariates that were individually associated with mortality in bivariate models with $PM_{2.5}$ exposure (air conditioning, median income, and education attainment) reduced the HR to 1.115 (95% CI, 1.003–1.239).
- For the parsimonious model that included ecologic confounder variables that both reduced the pollution coefficient and had associations with mortality, the HR was 1.126 (95% CI, 1.014–1.251).
- When controlled for the expected peak daily O_3 levels the HR was 1.191 (95% CI, 1.069–1.327). (Thus, similar to earlier results [Jerrett et al. 2005], O_3 had no primary effect in these models for all-cause mortality.)

Discussion and Conclusions

In general, the associations for $PM_{2.5}$ and mortality in this set of analyses are similar in magnitude with those reported earlier from geostatistical kriging estimates (Jerrett et al. 2005a) with three minor differences. First, the HR for $PM_{2.5}$ alone is somewhat smaller than the risks from the kriging model. Second, although the risk estimates were smaller in this study, the CIs were tighter. Third, the results from this study appear to be less sensitive to ecologic confounding. For example, in the earlier study, the parsimonious model for all-cause mortality that included all the individual-level variables and the significant ecologic confounders resulted in the lower confidence bound below 1. In this analysis, the same model had a lower confidence bound higher than 1 (1.126, 95% CI, 1.014–1.251; only the income disparity variable confounded the estimate to below 1, but that estimate was still extremely close to 1; see Table 23). We consider the model containing the social factors from the principal components analysis to be the most reasonable on the grounds that it maximally controls for confounding without inducing as much collinearity. The estimates from the model that contains only the 44 individual-level covariates (1.143, 95% CI, 1.033–1.266) and the model with all social factors (1.142, 95% CI, 1.026–1.272) produce nearly identical point estimates. The CIs are only slightly wider for the model with social factors from the principal component analysis incorporated in the model in the same manner as the ecologic factors. Thus, results from this LUR exposure model appear to be more robust to adjustment for confounders than the earlier results using the kriging surface.

The Los Angeles Analysis was extended using the random effects Cox model with and without allowance for spatial autocorrelation. The earlier study (Jerrett et al. 2005a) using the kriging estimates demonstrated significant autocorrelation in the risks, which was diminished to acceptable levels when the ecologic covariates were included in the model. That analysis did not explicitly incorporate a spatial autocorrelation parameter in the model, but in the current analysis we used the full random effects formulation.

Table 24 displays results from the random effects models, organized to compare results between models with and without allowance for spatial autocorrelation. It also compares models with various levels of control for confounding, beginning with a model that contains only the 44 individual-level covariates and no pollutant variable (all models were stratified for age, sex, and race). The initial model (with only the 44 individual-level covariates) thus demonstrates the residual random effects variance attributable to variability in mortality patterns between ZCAs. For all-cause mortality, when $PM_{2.5}$ was included in the model, random effects variance declined about 37% for the model with no autocorrelation (7.008 vs. 4.386) and about 24% for the model including autocorrelation (10.02 vs. 7.591). This large decline suggests that approximately one-third to one-quarter of the residual variation is accounted for by the $PM_{2.5}$ variable. The drop in the random effects variance for models including ecologic covariates was much larger, which indicates that these variables account for much of the residual variation in mortality across Los Angeles. Including the freeway intersection variable (distance from a ZCA centroid to a freeway) yielded only a minimal change in the random effects variance. Substantial autocorrelation was still found in the data after inclusion of all the variables, as evidenced by the fact that our estimate of ZCA autocorrelation reached the maximum value allowable in the model formulation.

This high level of residual autocorrelation, even with a very small random effects variance, may have resulted from a number of phenomena. First, the nearest-neighbor

Table 24. Sensitivity Analysis Using the Random Effects Cox Model for a 10-μg/m^3 Change in $PM_{2.5}$ Exposure with Allowance for Spatial Autocorrelation[a]

	No Spatial Autocorrelation		Spatial Autocorrelation		
Covariates[b]	HR	ZCA Variance ($\times 10^{-3}$)	HR	ZCA Variance ($\times 10^{-3}$)	ZCA Auto-correlation
All Causes					
44 Individual-level covariates	—	**7.008**	—	**10.02**	0.3307[c]
+ $PM_{2.5}$	1.158 (1.035–1.295)	**4.386**	1.160 (1.021–1.317)	**7.591**	0.3307[c]
+ Parsimonious ecologic covariates[d]	1.152 (1.034–1.283)	**0.229**	1.152 (1.032–1.286)	**0.623**	0.3307[c]
+ Freeway intersection[e]	1.156 (1.036–1.289)	0.233	1.156 (1.034–1.293)	0.847	0.3307[c]
IHD					
44 Individual-level covariates	—	**4.357**	—	4.357	0.000[f]
+ $PM_{2.5}$	**1.402** (1.137–1.728)	**0.582**	1.402 (1.137–1.728)	0.582	0.000[f]
+ Parsimonious ecologic covariates[d]	**1.347** (1.083–1.675)	**0.189**	1.347 (1.083–1.675)	0.189	0.000[f]
+ Freeway intersection[e]	**1.339** (1.074–1.669)	0.189	1.339 (1.074–1.669)	0.189	0.000[f]

[a] Bolded data refer to text.

[b] Covariates accumulate in the model with each addition.

[c] Estimate of ZCA autocorrelation reached its maximum value.

[d] Parsimonious individual-level (23) and ecologic (4) covariates were considered. The ecologic covariates were air conditioning, household income, grade 12 education, and the predicted values of the third principal component analysis based on all social variables (except air conditioning).

[e] Intersection with a freeway within 500 or 1000 m of a ZCA centroid.

[f] Estimate of ZCA autocorrelation was < 0.

formulation of the random effects Cox model may not capture what is likely to be a more complex residual spatial structure. Second, the autocorrelation may not be stationary over the entire study area, and more flexible models based on spatial moving averages may be needed to capture this nonstationarity. Third, the presence of spatial autocorrelation may also suggest that one or more important covariates have been excluded from the model. We have visually examined the residuals, and there seems to be a clustering of autocorrelation in residual mortality on the downwind side of roadways with high volumes of truck traffic. The assignment of residence locations to the ZCA centroid prevented us from precisely assigning exposures, but this autocorrelation suggests that possible effects from truck traffic merit attention in future studies. Although these theoretical possibilities are present, the point estimates and CIs are insensitive to model specification.

In analyses of IHD mortality, including $PM_{2.5}$ had a marked effect on the residual random effects variance, with a drop of more than 86% (4.357 vs. 0.582). The subsequent decline in the random effects variance due to inclusion of the ecologic covariates was also large, but much less pronounced than with all-cause mortality. For IHD, the residual autocorrelation was negligible. We expected this in a model in which the individual, ecologic, and air pollution variables predicted the mortality data more completely than they did for the analysis of all-cause mortality. With IHD we did observe some confounding effect of the point estimates when we included the ecologic and freeway variables. Models with and without the autocorrelation parameter produced nearly identical results, as would be expected with such a small amount of residual autocorrelation.

Results from the more refined exposure surface from the LUR model largely confirm the earlier findings from the kriging models. This is somewhat surprising given the different visual appearance of each surface, with the LUR detecting smaller variations in areas around highways and industry. The effect sizes were slightly diminished compared with the earlier study, but the effects shown in this study tended to be less sensitive to control for confounding and to alternative model specification. The larger decline in the random effects variance for IHD mortality supports a growing body of research on the mechanisms of systemic pulmonary inflammation and atherogenesis (Brook et al. 2004; Künzli et al. 2005).

CRITICAL EXPOSURE TIME WINDOWS

We constructed individual time-dependent exposure profiles for particulate and gaseous air pollution for a subcohort of the ACS CPS-II in order to examine if there is a critical exposure time window that is primarily responsible for the increased mortality associated with ambient air pollution. We examined air pollution exposures in three separate time windows: 1 to 5, 6 to 10, and 11 to 15 years in the past.

MATERIALS AND METHODS

Study Population

The ACS CPS-II cohort consists of nearly 1.2 million Americans enrolled in 1982. In 1992 and 1993, the Nutrition Cohort was established within the larger ACS CPS-II cohort (Calle et al. 2002). The purposes of selecting the Nutrition Cohort were to update a variety of behavioral, medical, and demographic information that had first been collected in 1982, and to collect more detailed data regarding diet, physical activity, and other lifestyle factors that had not been obtained at the time of enrollment. The ACS cohorts and survey questionnaires are detailed elsewhere (Pope et al. 1995; Calle et al. 2002). Briefly, CPS-II participants who were alive and between the ages of 50 and 74 years and who resided in one of the following 21 states that have population-based cancer registries were included in the Nutrition Cohort: California, Connecticut, Florida, Georgia, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Missouri, New Jersey, New Mexico, New York, North Carolina, Pennsylvania, Utah, Virginia, Washington, and Wisconsin. A total of 184,194 participants from the CPS-II cohort who lived in these states completed the self-administered questionnaire mailed in 1992–1993, and were contacted again in 1997–1998, 1999–2000, and every 2 years thereafter for follow-up information. Mortality of the study participants was ascertained by volunteers in 1984, 1986, and 1988, and subsequently by ACS staff using the National Death Index (Calle and Terrell 1993). The Emory University School of Medicine Human Investigations Committee approved all aspects of the CPS II study.

Individual Exposure Profiles

Previous analyses of the ACS cohort have assumed that each individual's exposure was determined by the average level of ambient air pollution in that person's city of residence at one point in time, either the beginning or the end of the study (Pope et al. 1995, 2002; Jerrett et al. 2005a; Krewski et al. 2000a,b). In this project, we sought to establish time-dependent exposure profiles for each individual in the study and to investigate the association between mortality and ambient air pollutant concentrations in specific time windows that could reflect past exposures. We hypothesized that a critical exposure time window may be primarily responsible for the increased mortality associated with ambient air pollution.

Individual time-dependent exposure profiles for $PM_{2.5}$ and SO_2 were constructed for each participant by matching the reported addresses at different times with the air pollutant exposure for the MSA where they lived. Individual exposures were determined using mean annual $PM_{2.5}$ and SO_2 levels that may have been experienced by the individual during specific time windows. For example, to test the possibility that current excess mortality is primarily due to pollution exposure 5 to 10 years ago, a person's exposure would be modeled as the average of his or her annual exposures during the interval extending from 5 to 10 years before the current time.

Residential Histories Residential histories for the Nutrition Cohort participants were constructed based on the place of residence when enrolled in the CPS-II study (1982), again when enrolled in the Nutrition Cohort (1992–1993), and at subsequent follow-up times in 1997–1998 and 1999–2000. Zip Code information was used to assign participants to an MSA. Since no information was collected on the number of moves between follow-up stages, we assumed that if a new Zip Code was reported at the time of follow-up, the participant had moved only once directly from the previous Zip Code to the new one (Hansen 1998). Since no information on the time of a move was collected between questionnaires, we randomly assigned a year of move to each participant (Schachter 2000) and assumed they had moved mid-calendar year (Hansen 1998). We constructed residential histories before enrollment in 1982 under the assumption that participants had lived in the same residence they reported in 1982.

$PM_{2.5}$ A total of 60,941 Nutrition Cohort participants resided in one of 83 MSAs for which average annual $PM_{2.5}$ exposure data had been estimated based on measured values of TSP and PM_{10} for the period of 1972–2000 (calculated by Lall and colleagues [2004]). For each MSA, either annual TSP or PM_{10} data were used in addition to the specific $PM_{2.5}$/TSP or $PM_{2.5}/PM_{10}$ ratio. This subcohort was designated as the $PM_{2.5}$-A group and $PM_{2.5}$ exposure levels were assigned to each participant (Figure 17). A total of 8181 (13.4%) participants in the $PM_{2.5}$-A group moved at least once during the study period. A small proportion of these participants (8.1%) did not reside in one of the 83 MSAs for some portion of the follow-up period.

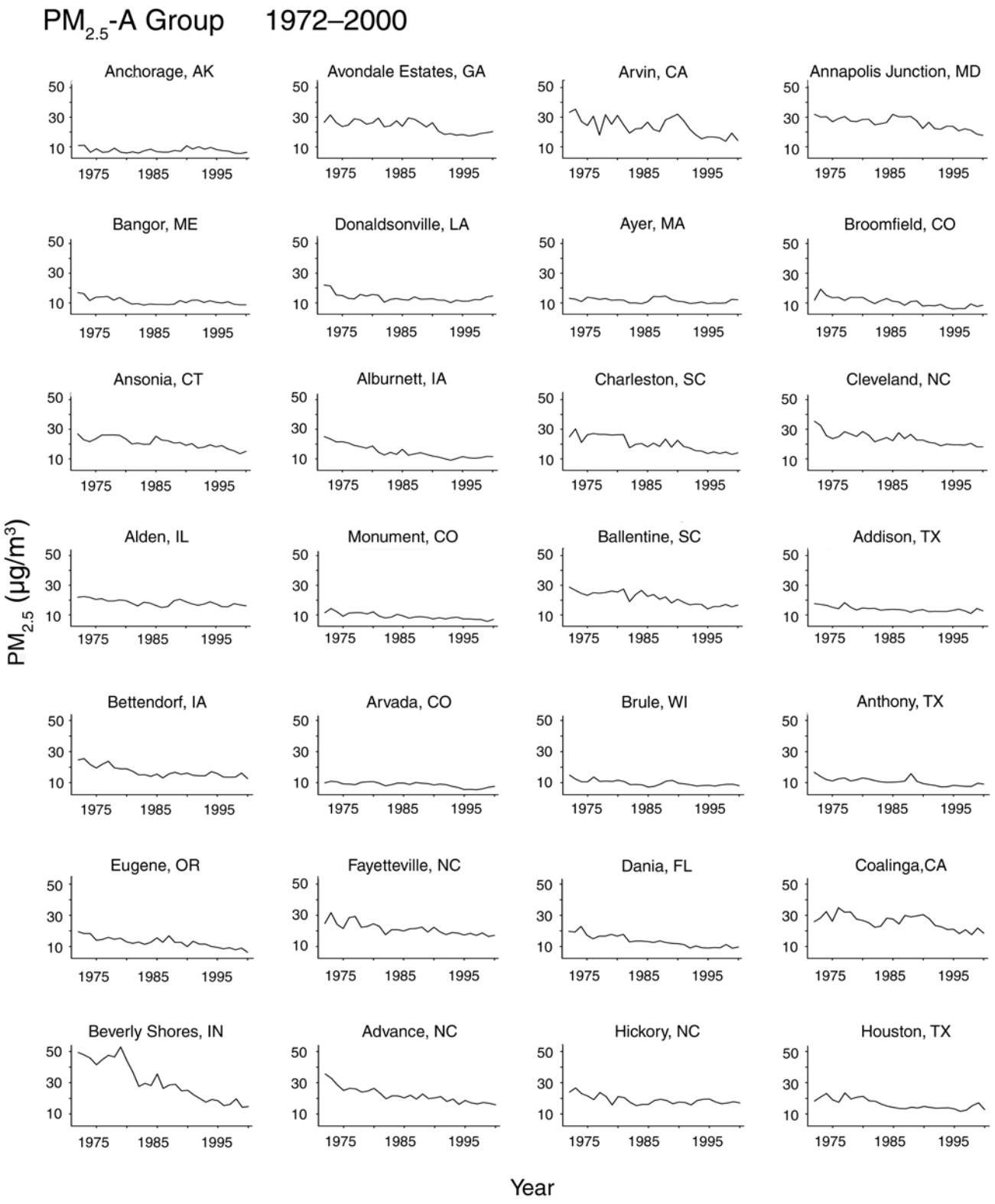

Figure 17. Profile of time trends (1972–2000) in average annual $PM_{2.5}$ concentrations based on measured values of TSP and PM_{10} in 83 MSAs and on linear interpolation of measured $PM_{2.5}$ data for the years 1979–1983 and 1999–2000 for an additional 23 MSAs. (*Figure continues next page.*)

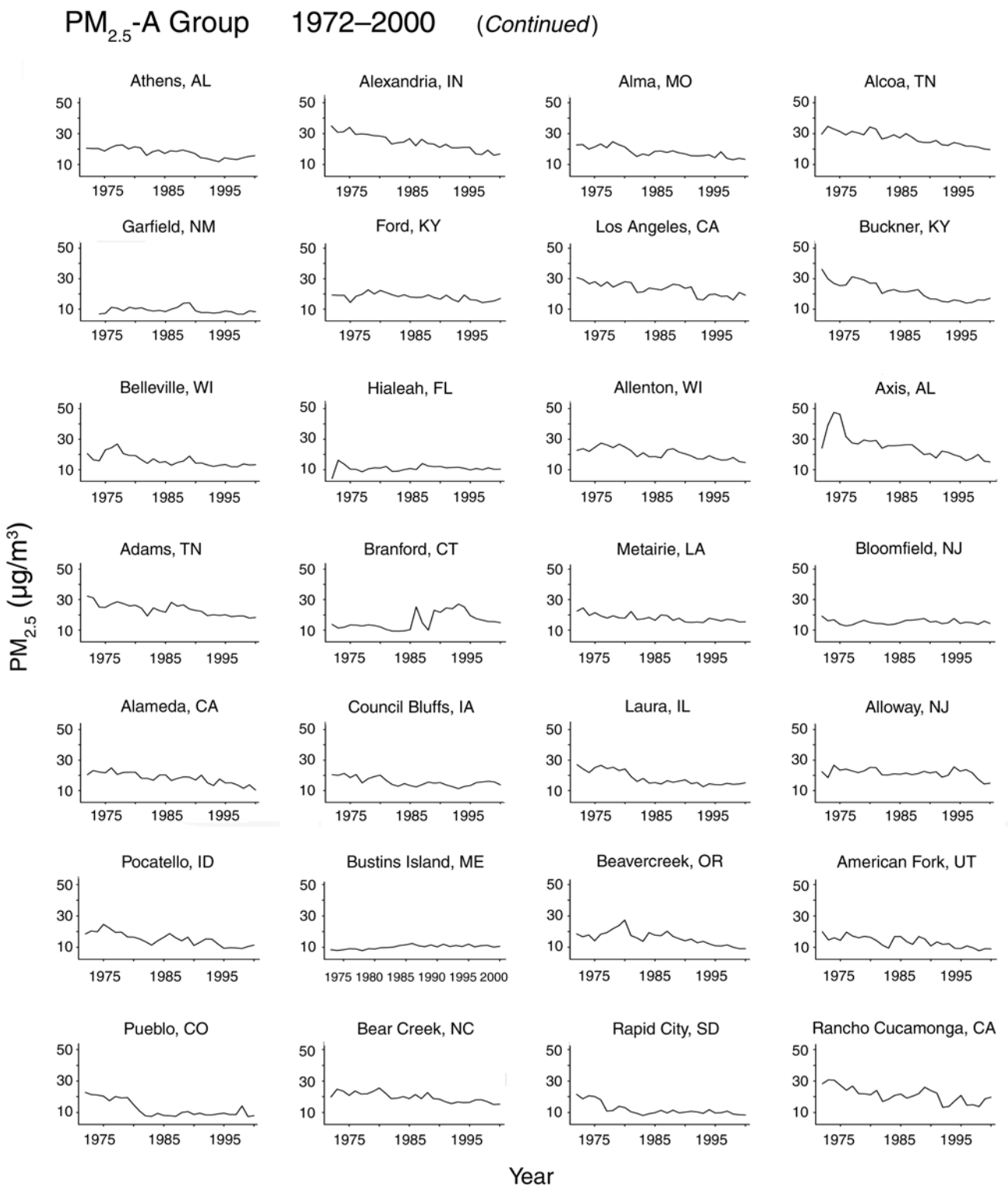

Figure 17 (*Continued*).

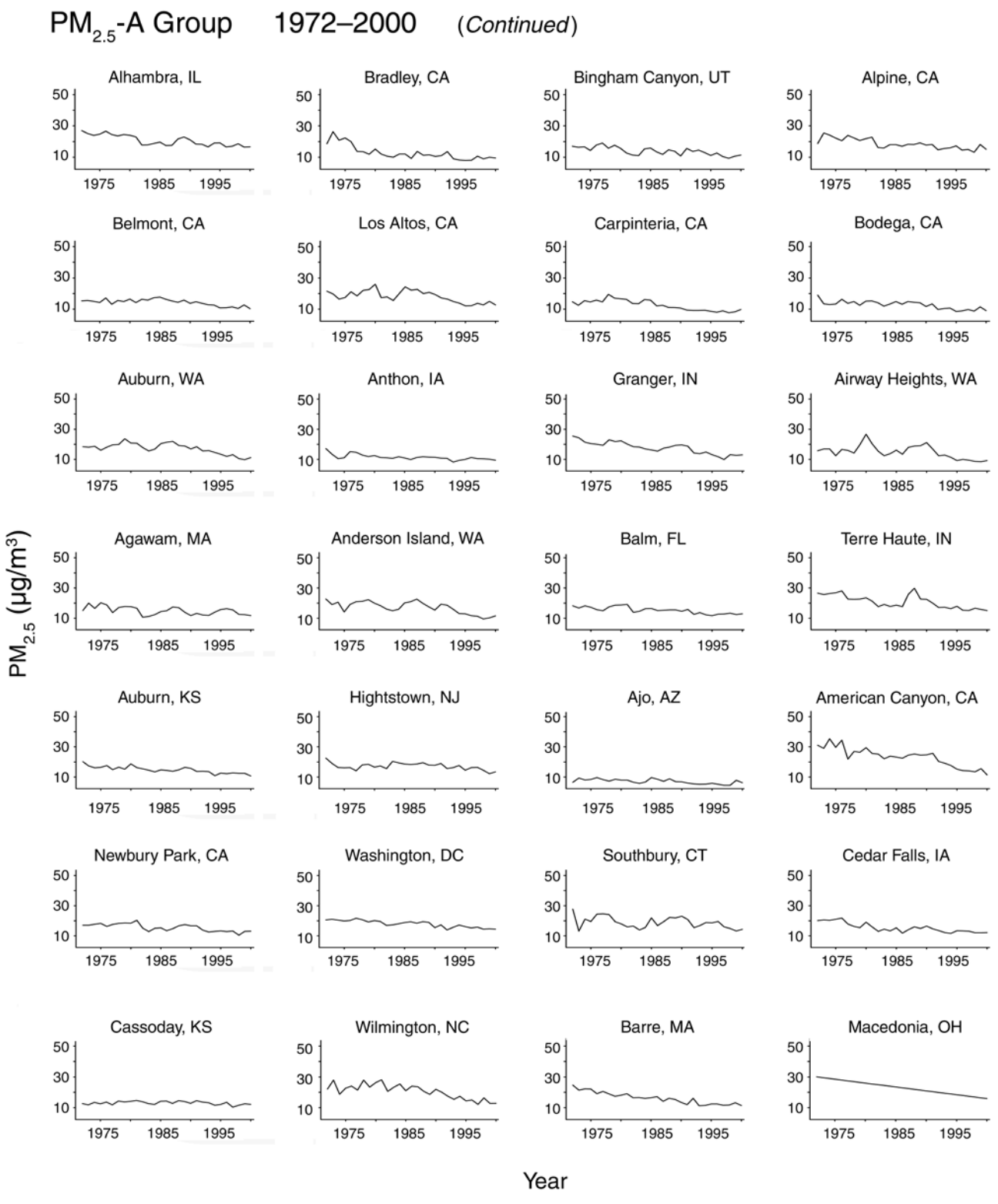

Figure 17 (*Continued*).

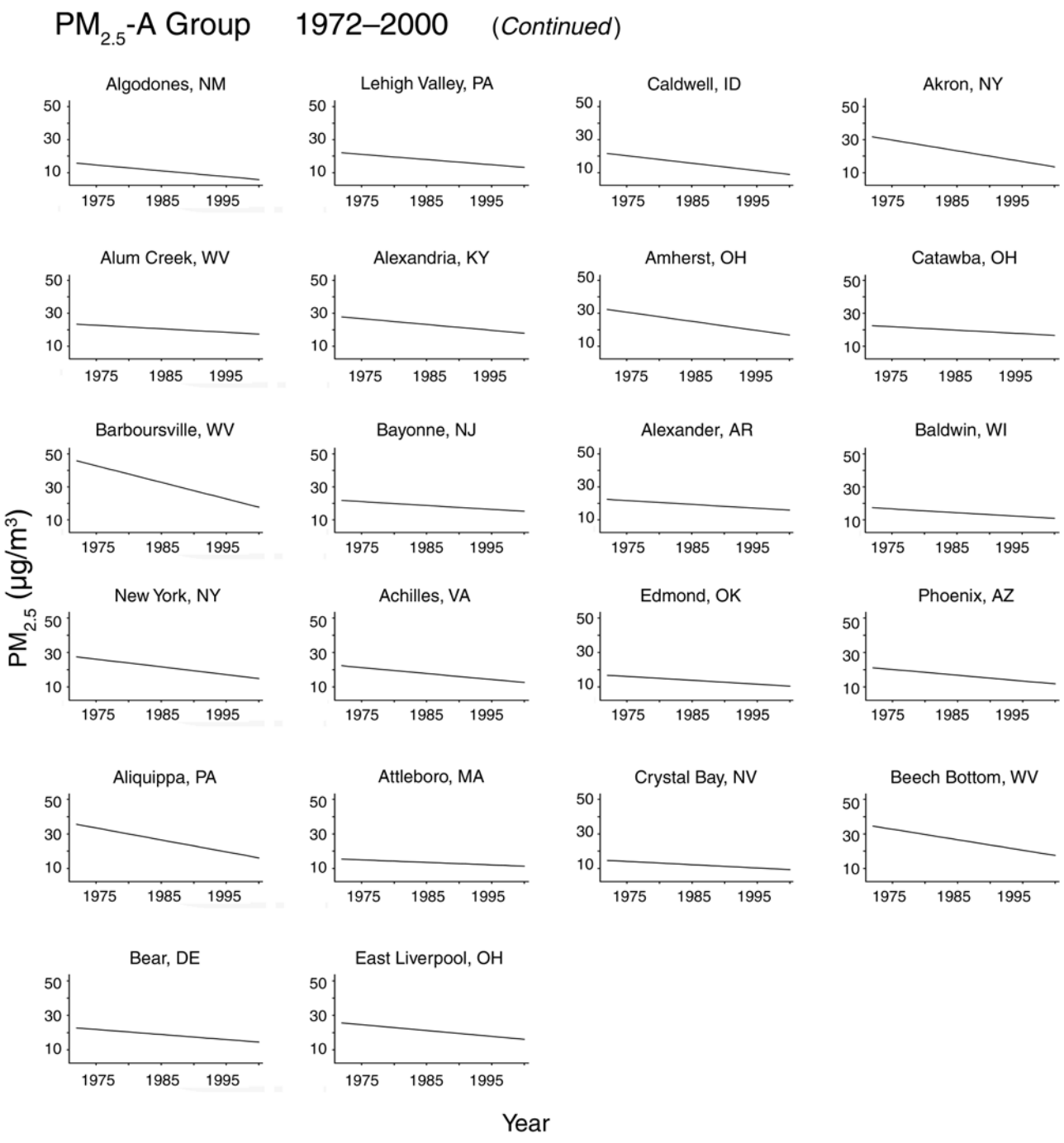

Figure 17 (*Continued*).

For those individuals, average annual $PM_{2.5}$ concentrations were estimated using linear interpolation of data from an additional 23 MSAs for which measured $PM_{2.5}$ data were available for the periods 1979–1983 and 1999–2000 (Pope et al. 2002). The first participant in this group died in 1992; therefore, the entire exposure period we examined for this group started in 1977 (15 years before the first death) and ended in 2000 (the end of follow-up).

A second analytic cohort was formed to include 81,466 deceased participants from the full CPS-II cohort who (1) were not in the $PM_{2.5}$-A group, and (2) died in the same MSA where they had resided at enrollment in 1982. They were designated as the $PM_{2.5}$-B group. We assumed that these participants had not moved between enrollment and death. $PM_{2.5}$ values were assigned using average annual data from Lall and colleagues (2004) for 50,915 participants in 30 MSAs, and by linear interpolation of data for 23 MSAs from Pope and colleagues (2002) for the remaining 30,551 participants (Figure 18). The first participant in this group died in 1982; therefore the exposure period ranged from 1967 (15 years before the first death) to 2000 (end of follow-up). The 1972 $PM_{2.5}$ concentrations were used to represent exposures before 1972. Participants in the $PM_{2.5}$-A and $PM_{2.5}$-B groups were mutually exclusive.

SO_2 A third analytic group was formed with 80,711 Nutrition Cohort participants who resided in one of 120 MSAs for which at least 20 years of annual average SO_2 measurements were available. For most of the period from 1972 to 2000, measured average annual SO_2 data were available from the EPA AIRS (Pope et al. 2002). Linear interpolation between adjacent time points was used for years in which average annual measurements were missing (Figures 19 and 20). As with the $PM_{2.5}$-A group, the entire exposure period examined was 1977 to 2000. A total of 5762 (7.1%) participants moved at least once during the exposure period.

STATISTICAL METHODS AND DATA ANALYSIS

Standard Cox models with time-dependent $PM_{2.5}$ and SO_2 exposure data were used to obtain adjusted HRs and 95% CIs (SAS version 9.1; SAS Institute, Cary, NC) for all-cause, lung-cancer (ICD9: 162), and CPD (ICD9: 400–440, 460–519) mortality. For the $PM_{2.5}$-A group and the SO_2 group, HRs were calculated from enrollment in the Nutrition Cohort in 1992–1993 through 2000. For the $PM_{2.5}$-B group, the HRs covered the period from enrollment in the CPS-II full cohort in 1982 through end of follow-up in 2000.

The baseline hazard function was stratified by age (in 1-year groupings), sex, and race (white/other; from CPS-II enrollment questionnaire). Models were adjusted for the standard suite of 44 lifestyle and demographic variables collected at enrollment in 1982 (see sidebar) including: smoking, education, marital status, body mass index, alcohol consumption, occupational exposure, and diet (Jerrett et al. 2005a; Pope et al. 2002).

When fitting the standard Cox model, the partial likelihood is updated each time a death occurred in a group. For each of the three groups ($PM_{2.5}$-A, $PM_{2.5}$-B, and SO_2), the risk set for the partial likelihood consisted of all subjects in the group who were alive at the time a member died. The exposure for each subject in the risk set was based on their time-dependent exposure profile up to the death of a cohort member and was updated at each subsequent death time. Estimates of the parameters of the standard Cox model with time-dependent covariates were then obtained by maximizing the product of the partial likelihoods that corresponded to each death time.

Differences in HRs and AIC values between separate 5-year time-window models allowed us to investigate which time window would be most relevant to the association between air pollution and mortality. AIC values provide a measure of goodness of fit, or show how well the model that relates exposure to outcome fits the available data, taking into account the complexity of the model. Models with lower AIC values imply that the model has a better fit (Burnham and Anderson 2002). In this investigation, the number of parameters did not change between the separate time-window models. Models were fitted for an overall 15-year time window, and separately for 1- to 5-year, 6- to 10-year, and 11- to 15-year time windows. Since education attainment had been found to be a powerful modifier of the air pollution–mortality association in the Reanalysis (Krewski et al. 2000a,b), results were also examined by level of education recorded at enrollment in 1982 (less than high school compared with high school or more).

A multiple exposure-time-window model was also tested as a type of weighted model to consider the three 5-year time windows simultaneously. In this model, the log-HR was modeled as a linear combination of average annual exposures that had occurred during each of the three time windows. If each of the three fitted effects (the three 5-year periods) were positive, we could interpret them as a single overall pollutant effect calculated as a weighted average of the exposures in the three time windows. The weights, represented by the coefficients in the linear combination, would represent the "relative effectiveness" of exposure during that time window (Goddard et al. 1995). To be interpretable, this model would require the additional constraint that all of the weights be nonnegative, or, equivalently, that

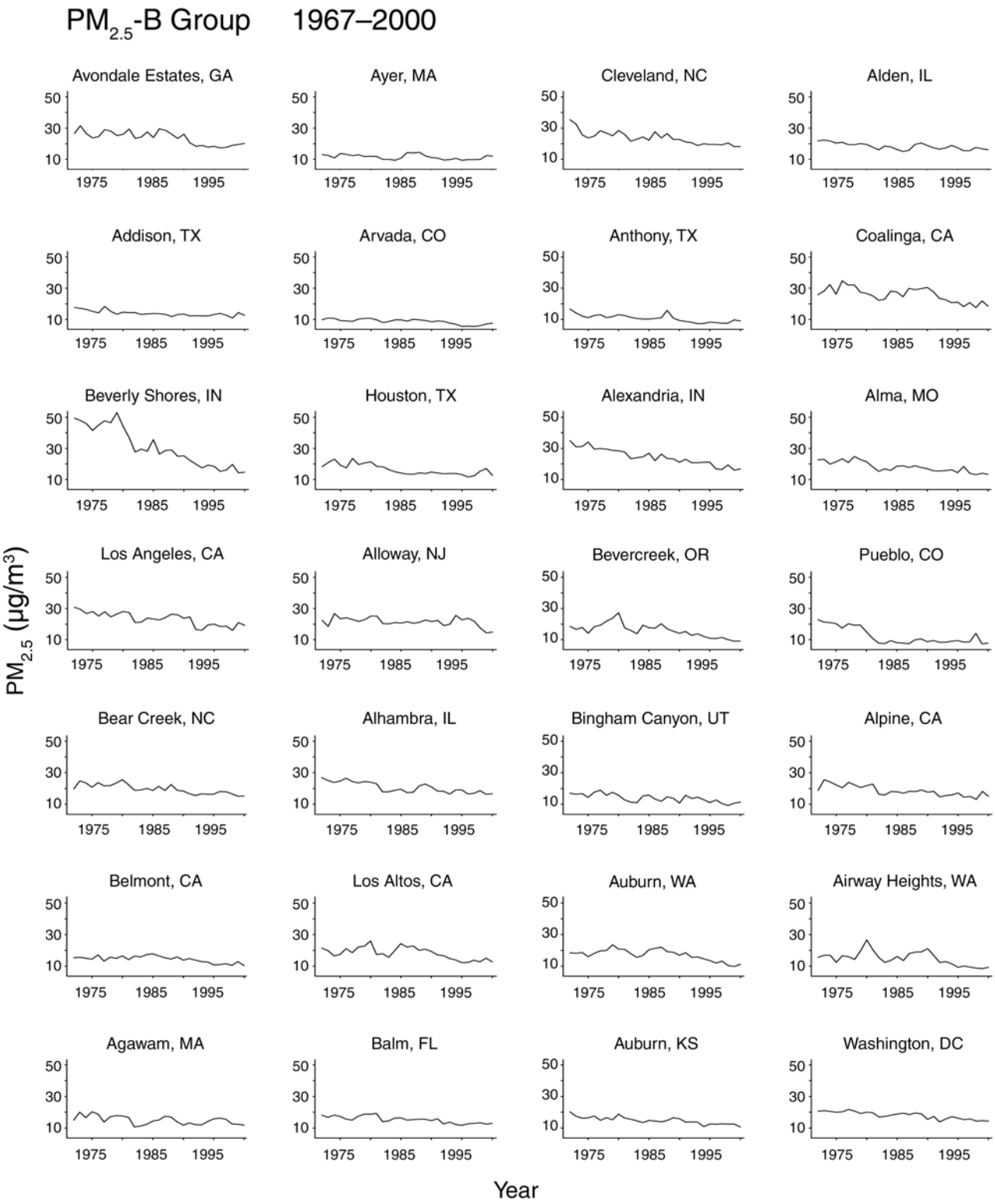

Figure 18. Profile of time trends (1972–2000) in average annual $PM_{2.5}$ concentrations for 53 MSAs in which $PM_{2.5}$-B participants (from the full CPS-II cohort) lived. $PM_{2.5}$ exposure concentrations assigned to the participants were based on (1) average annual data for 50,915 participants in 30 MSAs and (2) linear interpolation of data for the remaining 30,551 participants in 23 MSAs. The 1972 $PM_{2.5}$ concentrations were used to represent exposures before 1972. (*Figure continues next page.*)

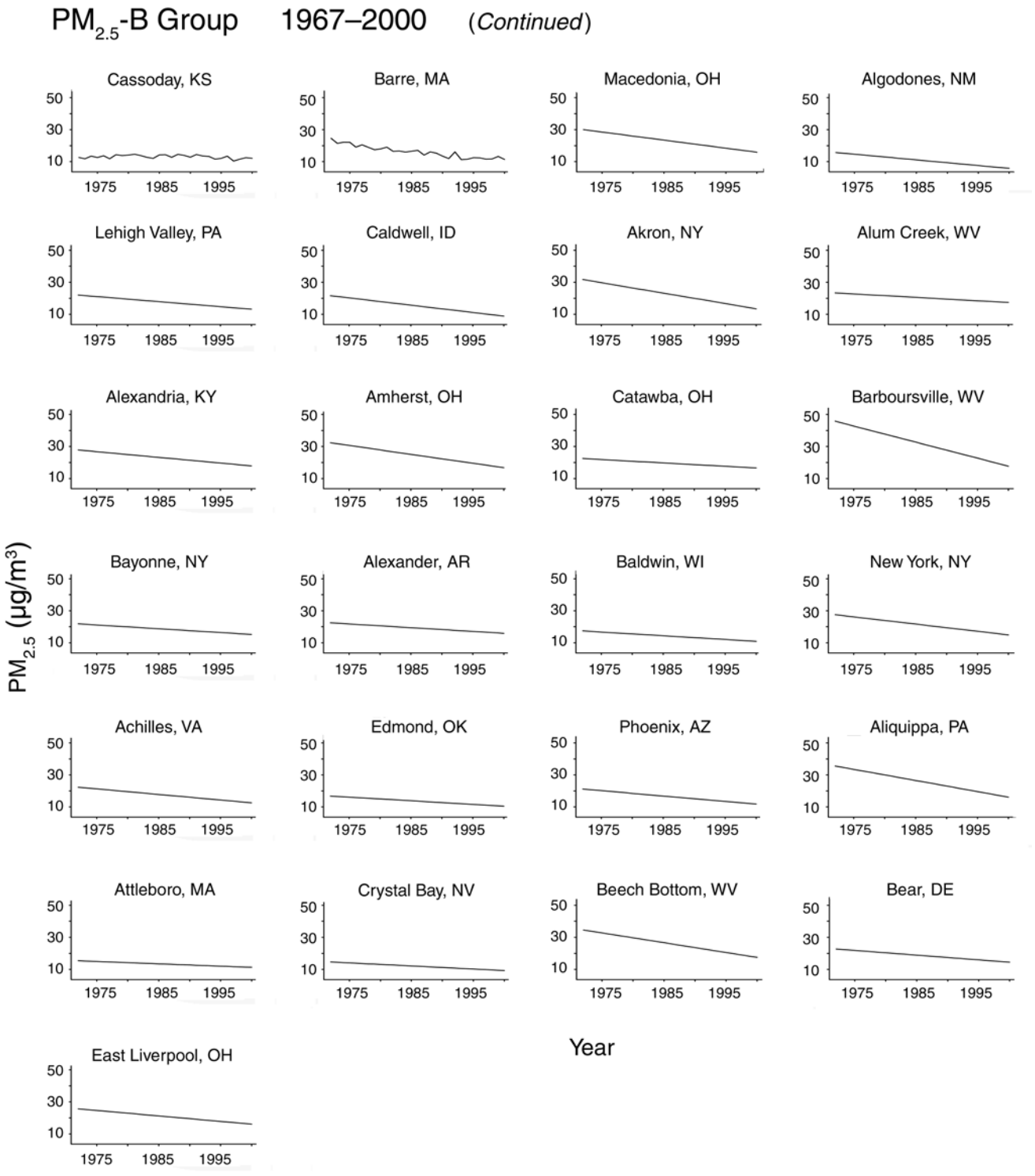

Figure 18 (*Continued*).

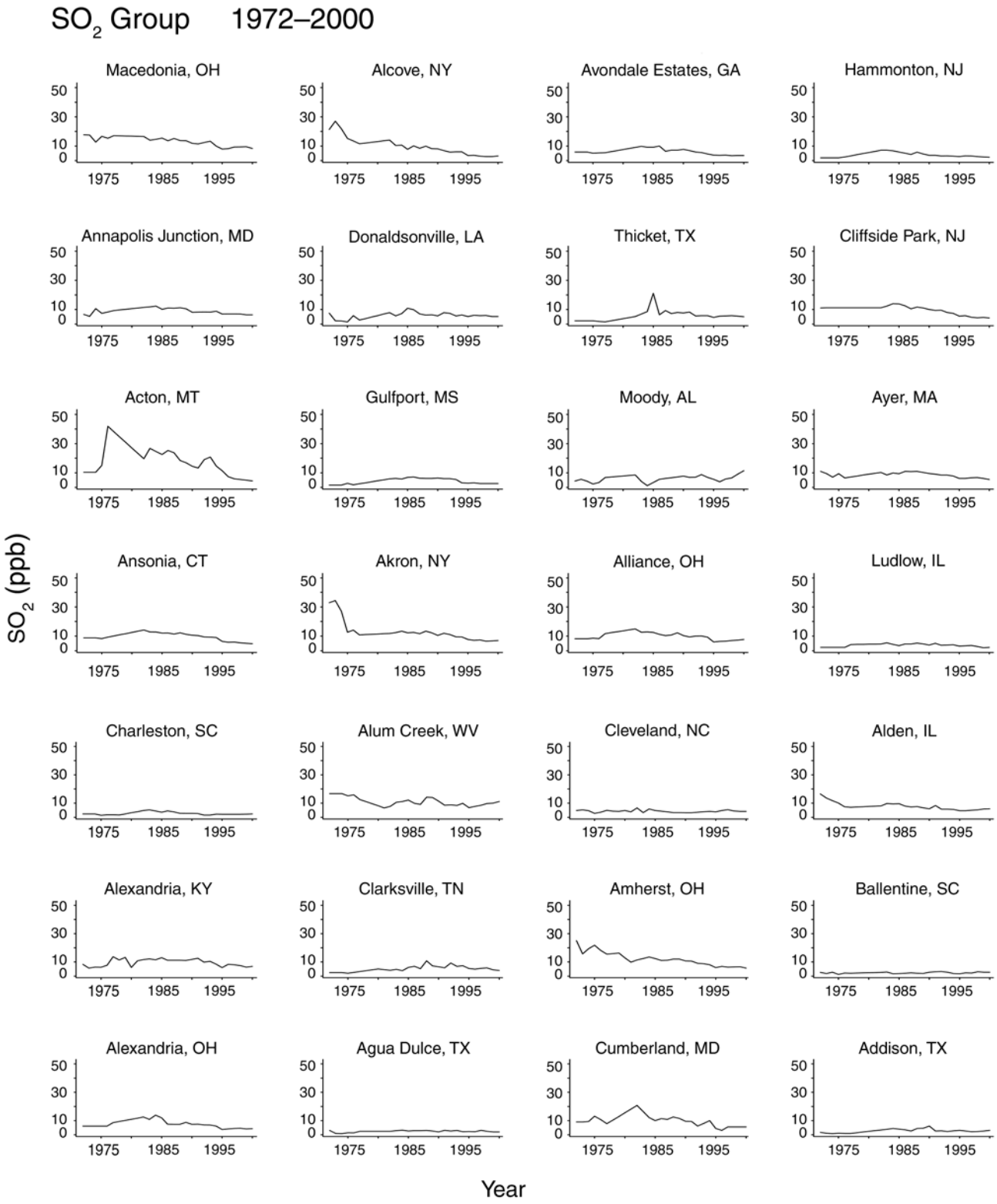

Figure 19. Profile of time trends (1972–2000) in SO_2 concentrations for 120 MSAs. Measured average annual SO_2 data for most of the period were available. Linear interpolation between adjacent time points was used for years in which average annual measurements were missing. (*Figure continues next page.*)

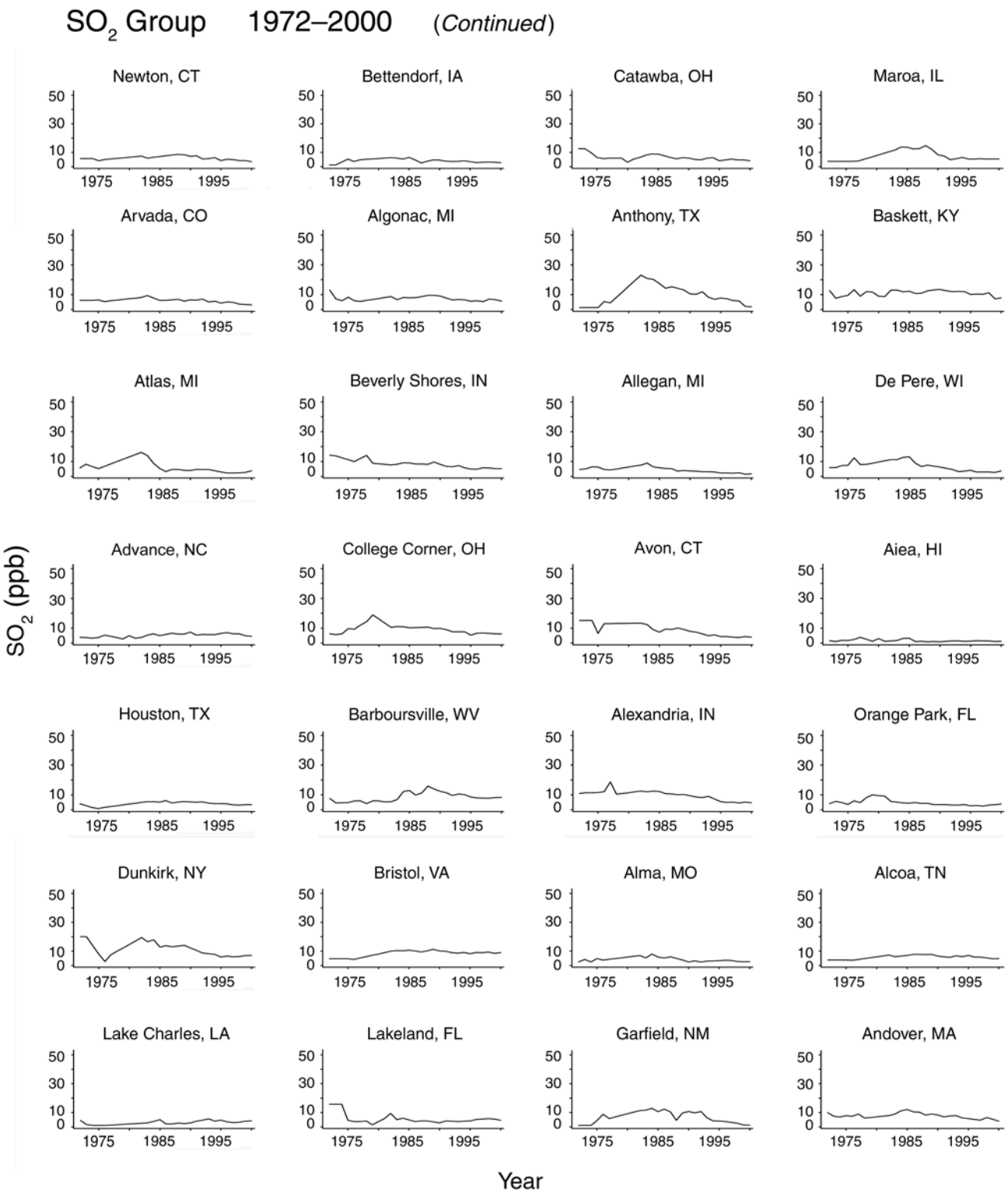

Figure 19 (*Continued*).

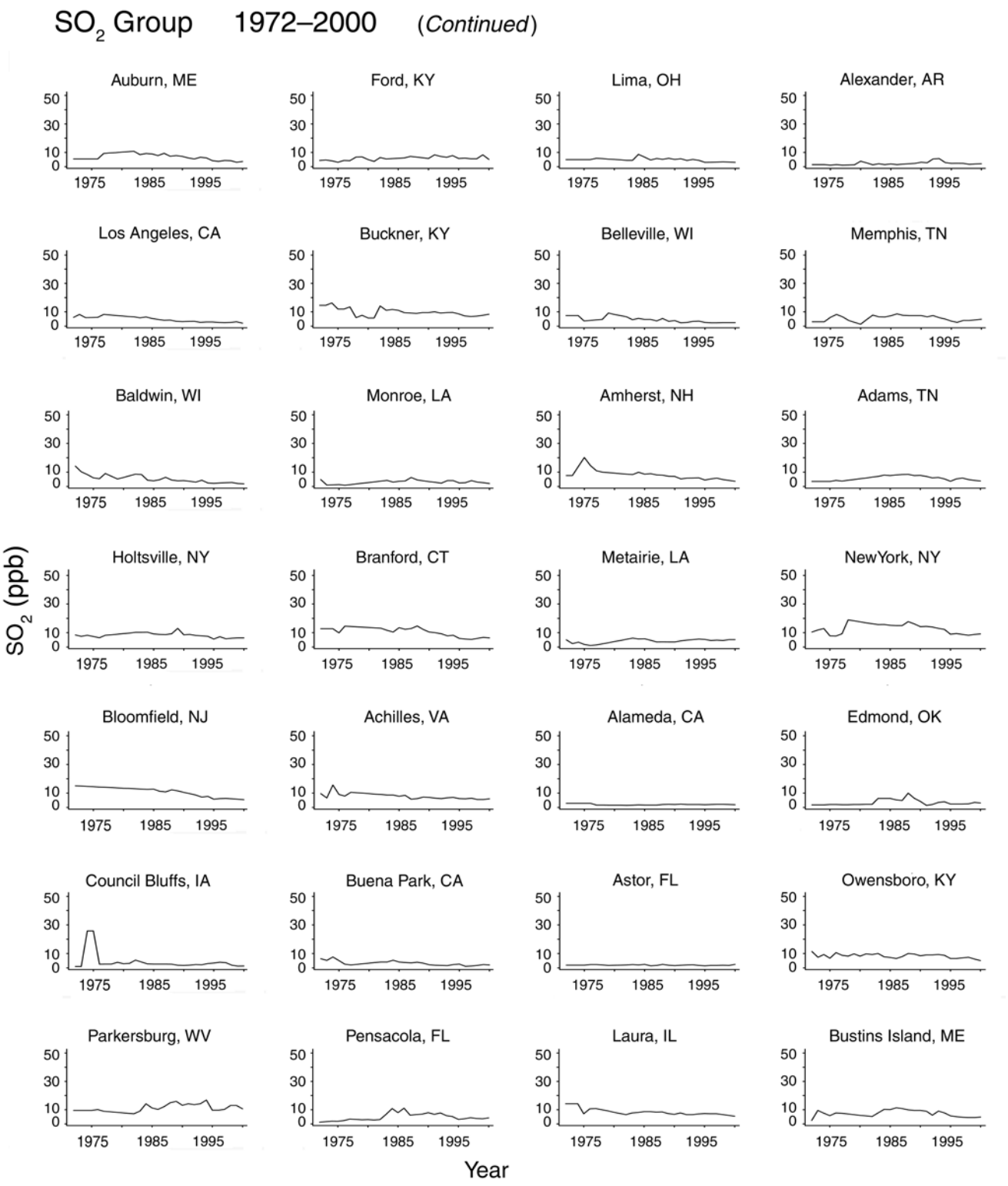

Figure 19 (*Continued*).

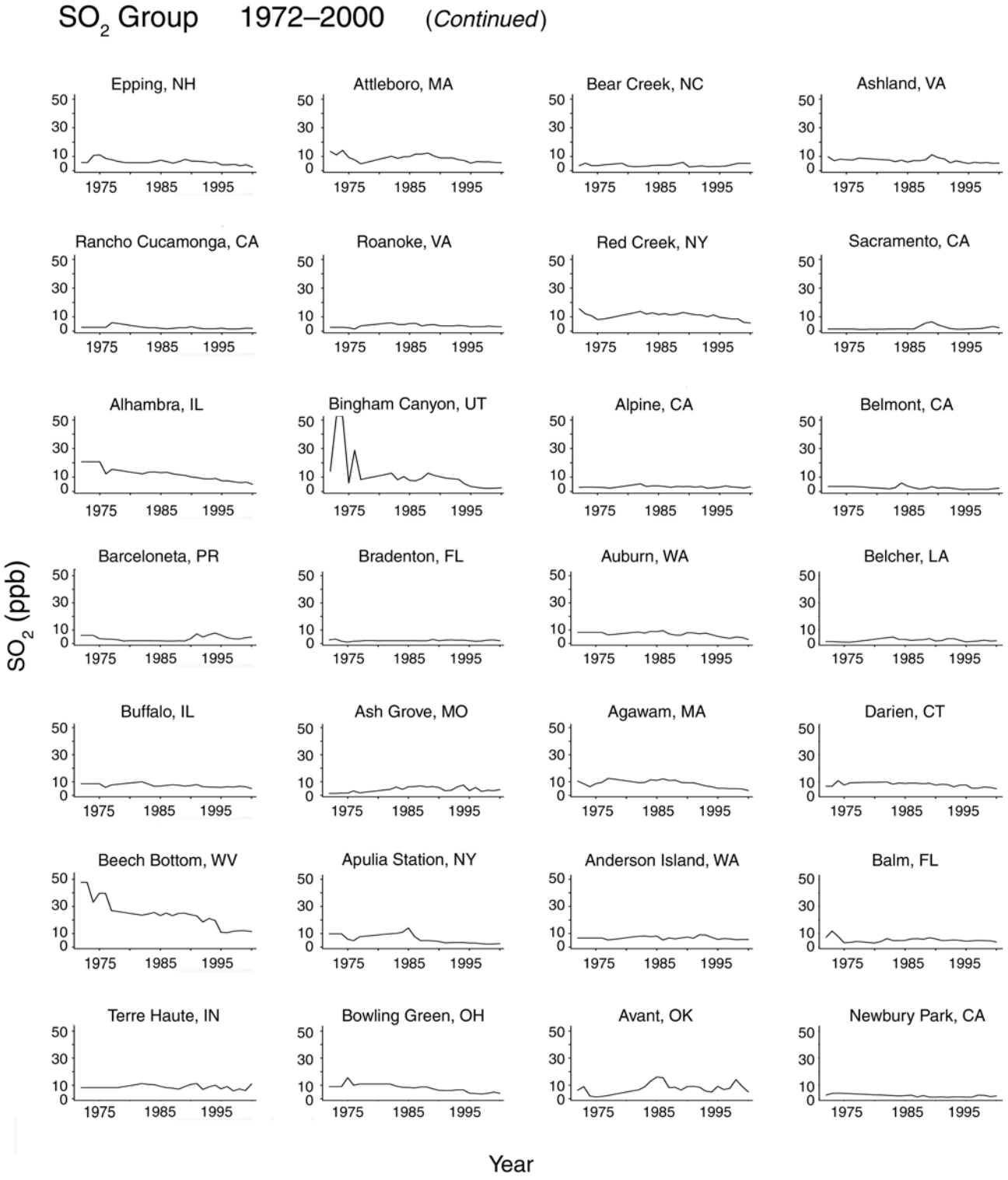

Figure 19 (*Continued*).

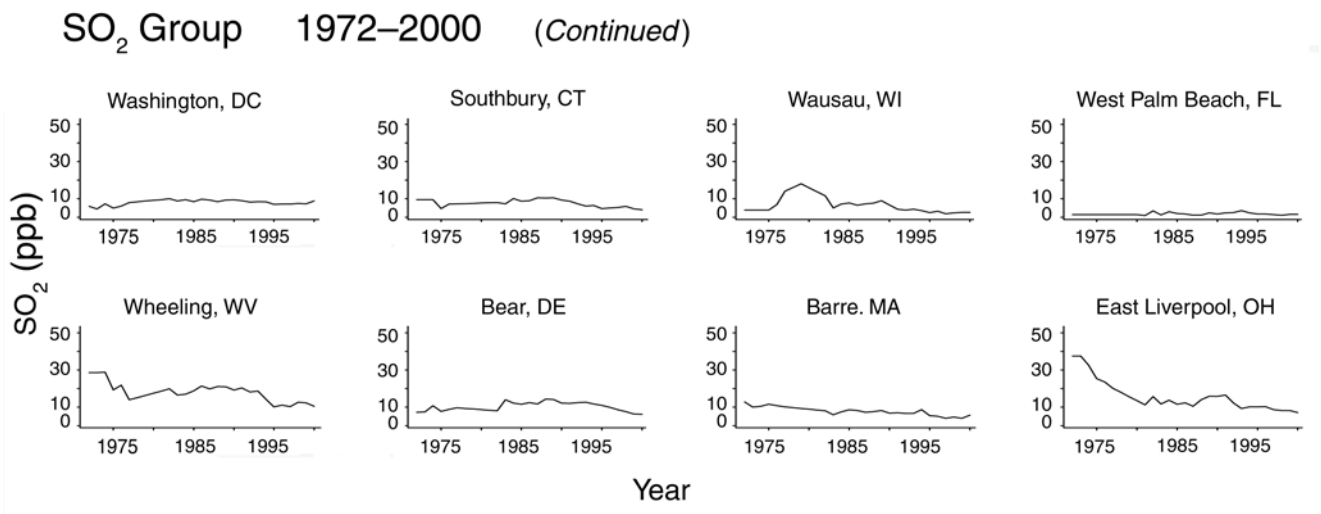

Figure 19 (*Continued*).

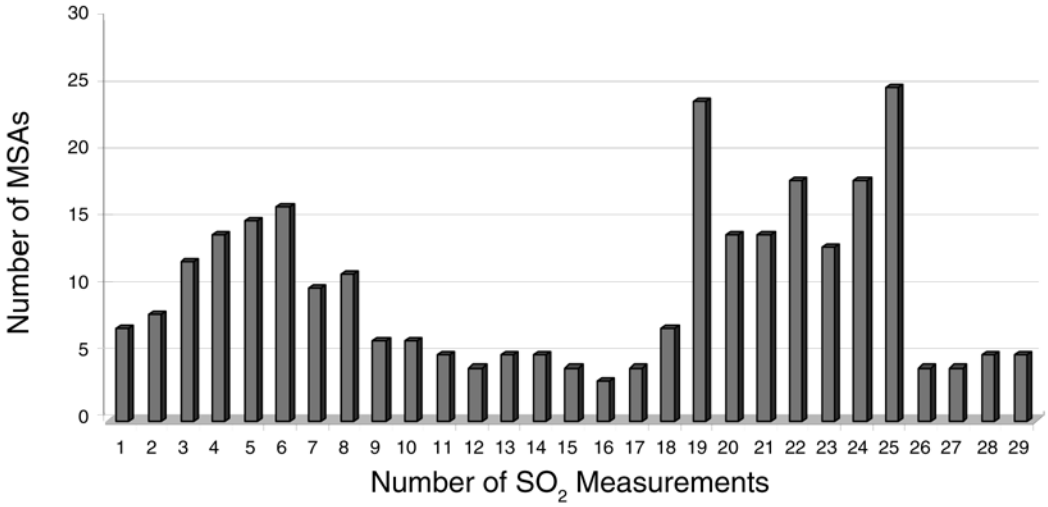

Figure 20. Distribution of measured average annual SO_2 data for 1972–2000. Note that only 5 MSAs had 29 years of SO_2 measurements for which no imputations were needed.

the direction of the effect be the same for each of the three time windows.

Because SAS does not provide a means of fitting the constrained model, we fit the unconstrained model to see if all three fitted effects had the same sign. Unfortunately, this produced a combination of both positive and negative weights making interpretation problematic. For example, two positive effects in the more distant time windows and a negative effect for the most recent time window would imply that current exposure is deleterious only until 5 years have passed, at which time it becomes beneficial. In the absence of established software to fit the correct, constrained model, we were obliged to abandon this line of inquiry.

RESULTS

Tables 25 (15-year time window) and 26 (three separate 5-year time windows) present adjusted HRs (with 95% CIs) and AIC values for all-cause, lung-cancer, and CPD mortality associated with $PM_{2.5}$ or SO_2 exposure. HRs

Table 25. HRs by Cause of Death Associated with a 10-μg/m^3 Change in $PM_{2.5}$ Concentrations or a 5-ppb Change in SO_2 Concentrations Over the 15-Year Time Window[a]

Cause of Death	$PM_{2.5}$-A Group (n = 60,941)	$PM_{2.5}$-B Group (n = 81,466)	SO_2 Group (n = 80,711)
All causes			
Deaths (n)	6,117	81,466	7,702
HR	0.98 (0.92–1.06)	1.01 (0.99–1.02)	0.99 (0.96–1.01)
Lung cancer			
Deaths (n)	599	6,038	763
HR	1.08 (0.87–1.35)	**1.07** (1.02–1.13)	0.96 (0.88–1.05)
CPD			
Deaths (n)	2,478	40,496	3,145
HR	1.00 (0.90–1.11)	**1.05** (1.03–1.07)	1.01 (0.97–1.05)

[a] Model included the 44 individual-level covariates. Baseline hazard function was stratified by age (1-year groupings), sex, and race and was adjusted for smoking, marital status, body mass index, alcohol, occupational exposures, and diet. Bolded values refer to text. HRs are followed by 95% confidence intervals.

associated with $PM_{2.5}$ exposure in several of the 15-year windows were elevated, and significantly so for the $PM_{2.5}$-B cohort group for lung-cancer and CPD mortality. Results for analyses stratified by level of education attainment are presented in Tables 27–29.

An examination of HRs revealed no clear pattern. For $PM_{2.5}$, no one exposure time window stood out as demonstrating the greatest HR; nor was there any clear pattern of a trend in HRs going from most recent to most distant windows or vice versa. For SO_2, the HRs were highest in the most recent time window (1 to 5 years), although none of the HRs was significantly elevated.

Differences in AIC values among the three 5-year exposure time windows were small. For both $PM_{2.5}$ groups the AIC value tended to be lowest (the model with the best fit to the data) in either the most recent time window (1 to 5 years) or the middle time window (6 to 10 years). This was apparent for all three cause-of-death categories in analyses with all subjects (Table 26) and in analyses stratified by education attainment (Tables 28 and 29). The exception was lung cancer in the $PM_{2.5}$-A group (Table 26). For the SO_2 group, AIC values were lowest in the most recent time window for nearly all cause-of-death categories, although differences in AIC values were again small. The exceptions were all-cause and lung-cancer mortality among those with a lower level of education attainment (Table 28).

DISCUSSION AND CONCLUSIONS

Overall, no clear pattern emerged as to which of the time windows of exposure may be most responsible for the $PM_{2.5}$–mortality association. Although for SO_2 exposure, models that used exposure data from the most recent 5 years provided a slightly better fit to available data on mortality from all causes, lung cancer, and CPD, as evidenced by lower AIC values; these differences were small. The HRs for mortality associated with exposure to SO_2 were highest in the most recent time window; however, none of them were significantly elevated.

To be able to identify which exposure time windows are associated with mortality attributable to air pollution, the patterns of exposure among individuals in the cohort need to be sufficiently varied. Variation can be spatial (different exposure profiles experienced by individuals living in different MSAs) and temporal (exposure profiles for a given MSA changing over time). In this data set, both spatial and temporal variations in exposure patterns were limited by the ecologic nature of the exposure measure used. Greater variability in temporal exposure patterns may be expected for individuals who move from one MSA to another during the study period; however, relatively few participants moved during the time span of this analysis.

On average, the spatial (between MSAs) and temporal (within MSAs) variations in exposure patterns were similar for the $PM_{2.5}$-A group (some of whom moved during the study period) and the $PM_{2.5}$-B group (who were assumed to not have moved between enrollment and death). For spatial variation in both groups, the SD around the annual average $PM_{2.5}$ concentrations was 5.0; and for temporal variation it was 3.5 for group A and 3.4 for group B. Spatial variation of within-MSA temporal variation, however, was somewhat higher in the $PM_{2.5}$-B group than in the $PM_{2.5}$-A group as shown by SDs of 1.9 for group B and 1.7 for group A. For the SO_2 group, SDs were 3.7 for spatial variation, 2.6 for temporal variation, and 1.9 for spatial–temporal variation.

Table 26. HRs and AIC Values by Cause of Death Associated with a 10-μg/m^3 Change in $PM_{2.5}$ Concentrations or a 5-ppb Change in SO_2 Concentrations for Three 5-Year Time Windows[a]

Exposure Time Window[b]	$PM_{2.5}$-A Group (n = 60,941)	$PM_{2.5}$-B Group (n = 81,466)	SO_2 Group (n = 80,711)
All Causes			
Years 1–5			
HR	1.01 (0.94–1.08)	1.01 (0.99–1.03)	1.03 (0.97–1.09)
(Rank) AIC	(3) 81,144.310	(1) 933,094.00	(1) 102,074.03
Years 6–10			
HR	0.98 (0.91–1.04)	1.01 (0.99–1.02)	0.99 (0.95–1.03)
(Rank) AIC	(1) 81,143.776	(2) 933,094.94	(3) 102,074.37
Years 11–15			
HR	0.98 (0.92–1.04)	1.01 (0.99–1.02)	0.99 (0.95–1.02)
(Rank) AIC	(2) 81,143.970	(3) 933,095.03	(2) 102,074.19
Lung Cancer			
Years 1–5			
HR	1.12 (0.89–1.40)	1.10 (1.04–1.17)	1.12 (0.94–1.35)
(Rank) AIC	(2) 7,541.342	(1) 67,541.515	(1) 9,661.684
Years 6–10			
HR	1.02 (0.83–1.25)	1.06 (1.01–1.12)	1.03 (0.91–1.16)
(Rank) AIC	(3) 7,542.180	(2) 67,545.732	(2) 9,662.963
Years 11–15			
HR	1.10 (0.91–1.33)	1.05 (1.01–1.10)	0.98 (0.87–1.09)
(Rank) AIC	(1) 7,541.275	(3) 67,546.285	(3) 9,662.990
CPD			
Years 1–5			
HR	1.02 (0.91–1.14)	1.06 (1.03–1.08)	1.06 (0.96–1.17)
(Rank) AIC	(2) 32,234.695	(3) 462,773.21	(1) 40,854.733
Years 6–10			
HR	0.98 (0.89–1.09)	1.05 (1.03–1.07)	0.99 (0.93–1.05)
(Rank) AIC	(1) 32,234.694	(1) 462,771.08	(2) 40,856.150
Years 11–15			
HR	0.99 (0.90–1.09)	1.04 (1.02–1.06)	1.00 (0.94–1.05)
(Rank) AIC	(3) 32,234.791	(2) 462,772.56	(3) 40,856.224

[a] Model included the 44 individual-level covariates. Baseline hazard function was stratified by age (1-year groupings), sex, and race and was adjusted for smoking, marital status, body mass index, alcohol, occupational exposures, and diet. HRs are followed by 95% confidence intervals.

[b] The AIC value is a measure of how well the model fits the available data; the time window with the lowest AIC value (number 1 in rank) best represents the patterns of mortality.

Correlations between exposures assigned to the same subject in different time windows also tended to be high (r ranged from 0.75 to 0.98 for $PM_{2.5}$ and 0.11 to 0.92 for SO_2). These correlations indicate that the amount of independent information available for each time window was somewhat limited.

Two recent studies by Jerrett and colleagues (2007) and Laden and associates (2006) have attempted to examine temporal variation of mortality risk associated with longer-term air pollution exposure in cohort studies. In both studies, relative risk estimates for mortality were found to vary with follow-up time. For the ACS CPS-II cohort, Jerrett and coworkers (2007) reported that the relative risk of mortality from all causes and from CPD associated with SO_4^{2-} exposure declined from the 1980s to the 1990s, possibly due to air quality improvements. In contrast, $PM_{2.5}$ HRs were largest for exposures in more recent time windows, possibly due to changing patterns of $PM_{2.5}$ emissions. Complex patterns of population mobility, individual susceptibility, and exposure measurement error have also been suggested as possible explanations for the observed temporal variation in risk. In contrast, HRs for lung-cancer mortality exhibited an inverted U-shaped pattern over time, possibly reflecting a prolonged multifactorial etiology

Table 27. HRs by Cause of Death Associated with a 10-μg/m^3 Change in $PM_{2.5}$ Concentrations or a 5-ppb Change in SO_2 Concentrations Over the 15-Year Time Window as Modified by Education Attainment[a]

Cause of Death	$PM_{2.5}$-A Group	$PM_{2.5}$-B Group	SO_2 Group
Less than High School	***n* = 2,902**	***n* = 16,479**	***n* = 4,026**
All Causes			
Deaths (*n*)	533	16,479	699
HR	1.13 (0.90–1.42)	1.02 (0.99–1.06)	1.02 (0.94–1.12)
Lung Cancer			
Deaths (*n*)	66	1,199	82
HR	1.30 (0.67–2.52)	1.08 (0.97–1.21)	1.03 (0.78–1.36)
CPD			
Deaths (*n*)	231	9,281	307
HR	1.00 (0.70–1.42)	1.08 (1.04–1.13)	1.03 (0.90–1.18)
High School or More	***n* = 58,039**	***n* = 64,987**	***n* = 76,685**
All Causes			
Deaths (*n*)	5,584	64,987	7,003
HR	0.97 (0.90–1.05)	1.00 (0.99–1.02)	0.98 (0.96–1.01)
Lung Cancer			
Deaths (*n*)	533	4,839	681
HR	1.06 (0.84–1.35)	1.07 (1.01–1.13)	0.95 (0.87–1.04)
CPD			
Deaths (*n*)	2,247	31,215	2,838
HR	0.99 (0.89–1.11)	1.04 (1.02–1.07)	1.01 (0.97–1.06)

[a] Model included 42 individual-level covariates (the two covariates for education attainment were omitted for this analysis). Baseline hazard function was stratified by age (1-year groupings), sex, and race and was adjusted for smoking, marital status, body mass index, alcohol, occupational exposures, and diet. HRs are followed by 95% confidence intervals.

for lung cancer. In a Swedish case–control study, Nyberg and colleagues (2000) reported that NO_2 exposure more than 20 years in the past was most important for lung cancer development compared with more recent exposure.

In an analysis of the Harvard Six Cities Study participants over a follow-up period similar to the one used in the current study, Laden and colleagues (2006) reported that relative risk estimates of mortality associated with $PM_{2.5}$ exposure declined in accordance with a decline in exposure; this was true for overall, cardiovascular, and respiratory mortality but not for lung-cancer mortality. Whether $PM_{2.5}$ exposure was modeled as the annual average in the year of death or as the average over the entire follow-up period, it had similar effects on mortality. The results from the study suggest that since $PM_{2.5}$ exposure may affect sensitive individuals with preexisting conditions and play a role in the development of chronic disease, as exposure declines so may the excess mortality related to it. The importance of the effect of recent air pollution exposure on mortality has also been emphasized in other studies using different modeling approaches (Schwartz and Laden 2004; Roosli et al. 2005). Most recently, Schwartz and associates (2008), in a further analysis of data from the Harvard Six Cities Study, reported that mortality associated with exposure to fine particles was observed largely within 1 to 2 years of exposure.

The purpose of the present analysis was not to provide estimates of the relative risk of mortality associated with air pollution, but rather to examine the relative effectiveness of exposures at different times in the past to affect mortality associated with air pollution in the present. Therefore, these HR estimates for the Nutrition Cohort are not directly comparable with those from previous analyses based on the full ACS CPS-II cohort.

The results of the present study are subject to certain limitations. Whereas the SO_2 concentrations were all measured data, the $PM_{2.5}$ concentrations were predicted from PM_{10} and TSP measurements and are therefore subject to a certain degree of exposure measurement error. For some subjects, $PM_{2.5}$ data were interpolated based on two time points, at baseline (1982) and the end of follow-up (2000); and for the larger $PM_{2.5}$-B group, we extrapolated back from 1972 exposures for models that considered exposures up to 15 years in the past, which sometimes extended to 1967. It is possible that increasingly older air pollution measurements may have been subject to a greater degree of measurement error than more recent measurements; if so,

Table 28. HRs and AIC Values by Cause of Death Associated with a 10-μg/m^3 change in $PM_{2.5}$ Concentrations or a 5-ppb Change in SO_2 Concentrations for Three 5-Year Time Windows for Those with an Education of Less than High School[a]

Exposure Time Window[b]	$PM_{2.5}$-A Group (n = 2,902)	$PM_{2.5}$-B Group (n = 16,479)	SO_2 Group (n = 4,026)
All Causes			
Years 1–5			
HR	1.11 (0.87–1.41)	1.03 (0.99–1.07)	1.00 (0.80–1.24)
(Rank) AIC	(3) 3,930.551	(3) 134,703.47	(3) 5,319.918
Years 6–10			
HR	1.15 (0.93–1.42)	1.03 (0.996–1.06)	1.04 (0.90–1.19)
(Rank) AIC	(1) 3,929.531	(1) 134,702.42	(2) 5,319.643
Years 11–15			
HR	1.10 (0.90–1.33)	1.02 (0.99–1.05)	1.04 (0.92–1.17)
(Rank) AIC	(2) 3,930.464	(2) 134,703.30	(1) 5,319.545
Lung Cancer			
Years 1–5			
HR	1.15 (0.56–2.34)	1.10 (0.97–1.26)	1.12 (0.61–2.04)
(Rank) AIC	(3) 486.585	(1) 9,346.718	(3) 601.746
Years 6–10			
HR	1.33 (0.72–2.46)	1.07 (0.96–1.20)	1.12 (0.74–1.69)
(Rank) AIC	(1) 485.900	(3) 9,347.238	(2) 601.602
Years 11–15			
HR	1.29 (0.72–2.31)	1.07 (0.98–1.17)	1.18 (0.82–1.71)
(Rank) AIC	(2) 486.021	(2) 9,346.887	(1) 601.098
CPD			
Years 1–5			
HR	1.10 (0.76–1.60)	1.09 (1.04–1.14)	1.08 (0.77–1.50)
(Rank) AIC	(1) 1,689.729	(3) 76,074.461	(1) 2,354.605
Years 6–10			
HR	0.99 (0.71–1.38)	1.08 (1.04–1.13)	1.01 (0.82–1.25)
(Rank) AIC	(3) 1,690.004	(1) 76,071.375	(3) 2,354.778
Years 11–15			
HR	0.94 (0.69–1.28)	1.07 (1.03–1.10)	0.97 (0.80–1.17)
(Rank) AIC	(2) 1,689.836	(2) 76,072.491	(2) 2,354.686

[a] Model included 42 individual-level covariates (the two covariates for education attainment were omitted for this analysis). Baseline hazard function was stratified by age (1-year groupings), sex, and race and was adjusted for smoking, marital status, body mass index, alcohol, occupational exposures, and diet. HRs are followed by 95% confidence intervals.

[b] The AIC value is a measure of how well the model fits the available data; the time window with the lowest AIC value (number 1 in rank) best represents the patterns of mortality.

that could result in higher AIC values and a bias of HRs toward the null in more distant exposure time windows.

We may have also misclassified exposure with certain assumptions about individuals' residential histories, such as that the place of residence remained unchanged before 1982. The $PM_{2.5}$-B group was composed entirely of participants who had died and were assumed to have never moved, whereas the $PM_{2.5}$-A and SO_2 groups were composed of self-selected CPS-II participants who had survived until 1992. Although this may introduce some type of a selection bias, we think it does not influence the identification of critical exposure time windows, which are determined by the pathophysiological disease processes.

Updated information for certain demographic and lifestyle covariates have been collected in follow-up surveys for Nutrition Cohort participants. Although data on these covariates were not available for all study participants included in this analysis, most of the covariates do not

Table 29. HRs and AIC Values by Cause of Death Associated with a 10-μg/m^3 Change in $PM_{2.5}$ Concentrations or a 5-ppb Change in SO_2 Concentrations for Three 5-Year Time Windows for Those with an Education of High School or More[a]

Exposure Time Window[b]	$PM_{2.5}$-A Group (n = 58,039)	$PM_{2.5}$-B Group (n = 64,987)	SO_2 Group (n = 76,685)
All Causes			
Years 1–5			
HR	1.00 (0.93–1.08)	1.01 (0.99–1.03)	1.03 (0.96–1.10)
(Rank) AIC	(3) 73,721.769	(1) 722,351.83	(1) 92,415.750
Years 6–10			
HR	0.96 (0.90–1.03)	1.00 (0.98–1.02)	0.99 (0.95–1.03)
(Rank) AIC	(1) 73,720.383	(3) 722,352.50	(3) 92,416.128
Years 11–15			
HR	0.97 (0.91–1.03)	1.00 (0.99–1.02)	0.99 (0.95–1.02)
(Rank) AIC	(2) 73,720.888	(2) 722,352.49	(2) 92,416.016
Lung Cancer			
Years 1–5			
HR	1.12 (0.87–1.42)	1.10 (1.03–1.18)	1.13 (0.93–1.37)
(Rank) AIC	(1) 6,702.496	(1) 52,588.969	(1) 8,620.221
Years 6–10			
HR	0.99 (0.79–1.23)	1.06 (1.00–1.12)	1.04 (0.91–1.18)
(Rank) AIC	(3) 6,703.257	(2) 52,592.574	(3) 8,621.479
Years 11–15			
HR	1.08 (0.88–1.33)	1.05 (0.998–1.10)	0.96 (0.86–1.08)
(Rank) AIC	(2) 6,702.698	(3) 52,593.565	(2) 8,621.350
CPD			
Years 1–5			
HR	1.01 (0.90–1.14)	1.05 (1.02–1.08)	1.06 (0.96–1.18)
(Rank) AIC	(2) 29,075.089	(1) 346,041.73	(1) 36,658.773
Years 6–10			
HR	0.98 (0.88–1.09)	1.04 (1.02–1.07)	0.99 (0.93–1.06)
(Rank) AIC	(1) 29,074.988	(2) 346,042.27	(2) 36,660.093
Years 11–15			
HR	0.99 (0.90–1.10)	1.04 (1.01–1.06)	1.00 (0.95–1.06)
(Rank) AIC	(3) 29,075.102	(3) 346,043.24	(3) 36,660.141

[a] Model included 42 individual-level covariates (the two covariates for education attainment were omitted for this analysis). Baseline hazard function was stratified by age (1-year groupings), sex, and race and was adjusted for smoking, marital status, body mass index, alcohol, occupational exposures, and diet. HRs are followed by 95% confidence intervals.

[b] The AIC value is a measure of how well the model fits the available data; the time window with the lowest AIC value (number 1 in rank) best represents the patterns of mortality.

appreciably affect the air pollution–mortality relationship (education attainment is the major exception) and were not expected to complicate the identification of critical time windows of exposure (Krewski et al. 2000a,b). In the present study, stratification of the analysis by level of education attainment (less than high school versus high school or greater) did not shed light on the question of which time windows might be most important. However, consistent with previous studies that did not account for residential mobility information, we also observed larger mortality HRs among those with a lower level of education attainment. Levels of smoking cessation may have also differed between analytic groups.

Overall, identification of critical exposure time windows, even among large national cohorts, remains a challenge and further research to identify them with other relevant data sets is needed. Such work would improve our understanding of the time frame surrounding the human health benefits from reduced exposure to long-term air pollution.

IMPLICATIONS OF THE FINDINGS

PHASE I

This report provides the results of Phase III of the Particle Epidemiology Reanalysis Project, which began in 1998. Phases I and II together are referred to as the Reanalysis. In Phase I, we validated the data used in the Harvard Six Cities Study (follow-up 1974–1991; Dockery et al. 1993) and the American Cancer Society Study (follow-up 1982–1989; Pope et al. 1995) of long-term exposure to particulate air pollution and mortality and, using the same analytic methods, replicated the numerical results reported by the original investigators. Our findings in Phase I established the integrity of the original data and confirmed, with trivial discrepancies, the original risk estimates (Krewski et al. 2000a; 2003b; 2004; 2005a).

PHASE II

In Phase II, we conducted a detailed sensitivity analysis to assess the robustness of the original findings to alternative analytic approaches (Krewski et al. 2000b). Specific sensitivity analyses focused on the impact on risk estimates of including additional individual-level covariates in the risk models that relate particulate air pollution with mortality; including new ecologic covariates related to demographic factors, socioeconomic indicators, availability of health services, climate variables, characteristics of the physical environment, and gaseous copollutants (Krewski et al. 2000b; 2003a,b); possible confounding due to occupational exposures (Siemiatycki et al. 2003); and population mobility.

These sensitivity analyses produced four main results: (1) Adjusting for most ecologic covariates did not substantially alter mortality risk estimates related to exposure to particulate and gaseous air pollutants. An exception was population change (movement of people from one area of the country to another), which notably reduced the risk estimates for all-cause mortality related to SO_4^{2-} exposure, although the effects of population change were completely attenuated by control for residual autocorrelation. (2) The risk estimates did not vary with adjustment for most individual-level covariates. However, education attainment was found to modify the effect — risk estimates for all causes of death studied decreased with increasing education attainment for both $PM_{2.5}$ and SO_4^{2-} exposures. (3) Adjustment for ambient SO_2 concentrations at the MSA scale markedly

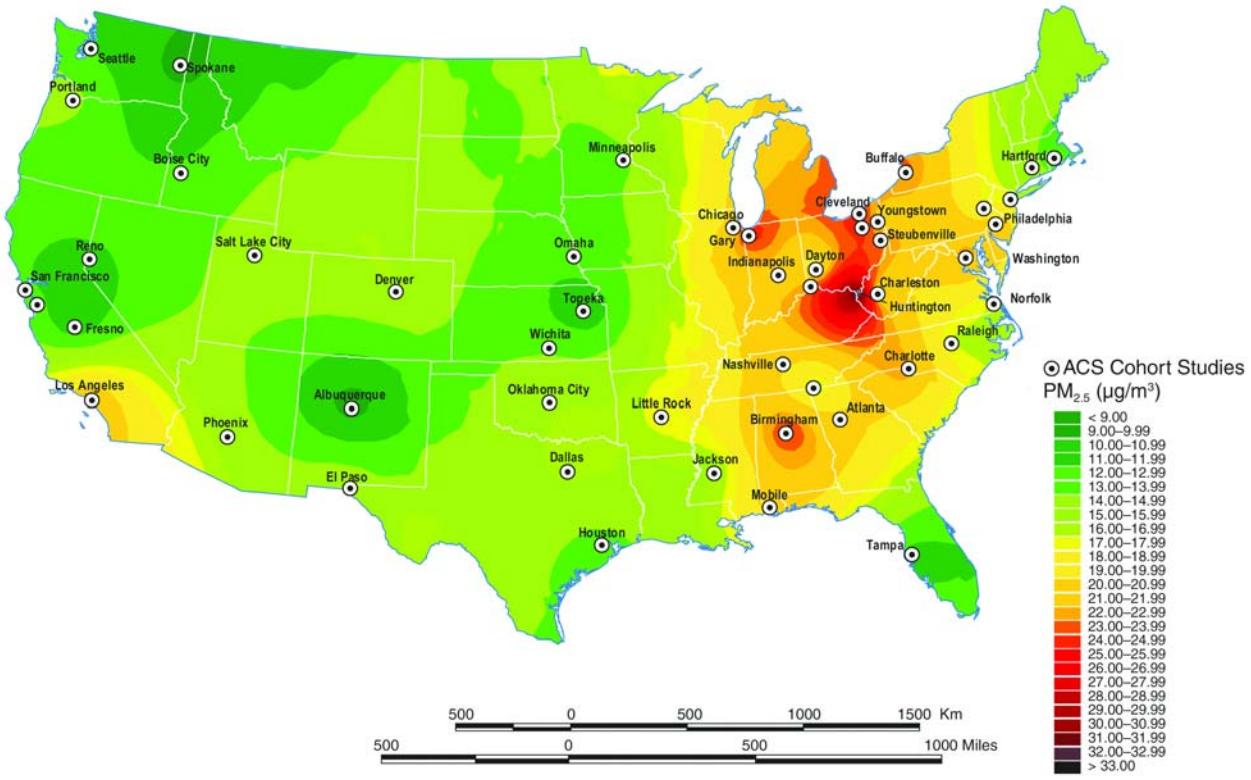

Figure 21. Spatial distribution (kriged) of $PM_{2.5}$ concentrations based on data from 1982–1986. Analysis done in Phase II (Krewski et al. 2000b).

reduced the mortality risk estimates for both $PM_{2.5}$ and SO_4^{2-} exposures. (4) Adjusting for occupational exposures based on an occupational "dirtiness" score and an index of occupational exposure to known lung carcinogens did not materially alter air pollution risk estimates, thereby all but ruling out residual confounding by occupation.

New methods of analysis that take into account spatial patterns in the ACS data were also developed and applied in Phase II (Krewski et al. 2000b; Burnett et al. 2001; Cakmak et al. 2003; Jerrett et al. 2003; Ma et al. 2003). These methods, which consider different patterns of spatial autocorrelation in both mortality rates and air pollutant levels, resulted in slightly higher mortality risk estimates with wider confidence limits compared with those found using standard Cox regression methods based on the assumption of no spatial autocorrelation. The results of flexible exposure–response models indicated that air pollution risk estimates were particularly sensitive to the use of alternate risk projection models (Abrahamowicz et al. 2003). The effects of using ecologic (neighborhood-level) rather than individual-level covariates were also explored (Abrahamowicz et al. 2004); this analysis showed that although biases due to aggregation of individual-level covariates can occur, those biases were unlikely to account for the observed associations between air pollution exposure and mortality.

In Phase II, we also explored the effect of the geographic unit of scale for spatial analyses, and noted that mortality risk estimates using $PM_{2.5}$ concentrations at the county scale were higher than estimates based on pollutant concentrations at the MSA scale (Willis et al. 2003). Therefore, we explored the MAUP in more detail in Phase III using Intra-Urban Analyses for the Los Angeles and New York City regions.

PHASE III

The Phase III Extended Analysis was intended to further explore the association between ambient air pollution and mortality by using additional follow-up data on vital status in the ACS cohort through 2000, thereby providing 11 more years of follow-up beyond that considered in Phase II.

Additional data on exposure to ambient air pollution was also available for use in Phase III. In Phase II, all air pollution exposure data we considered were related to baseline exposures at the time the ACS cohort was enrolled in 1982 (Figure 21). Levels of air pollution have since changed; Figure 22 presents the spatial distribution of $PM_{2.5}$ in 2000. Part of our team at NYU constructed

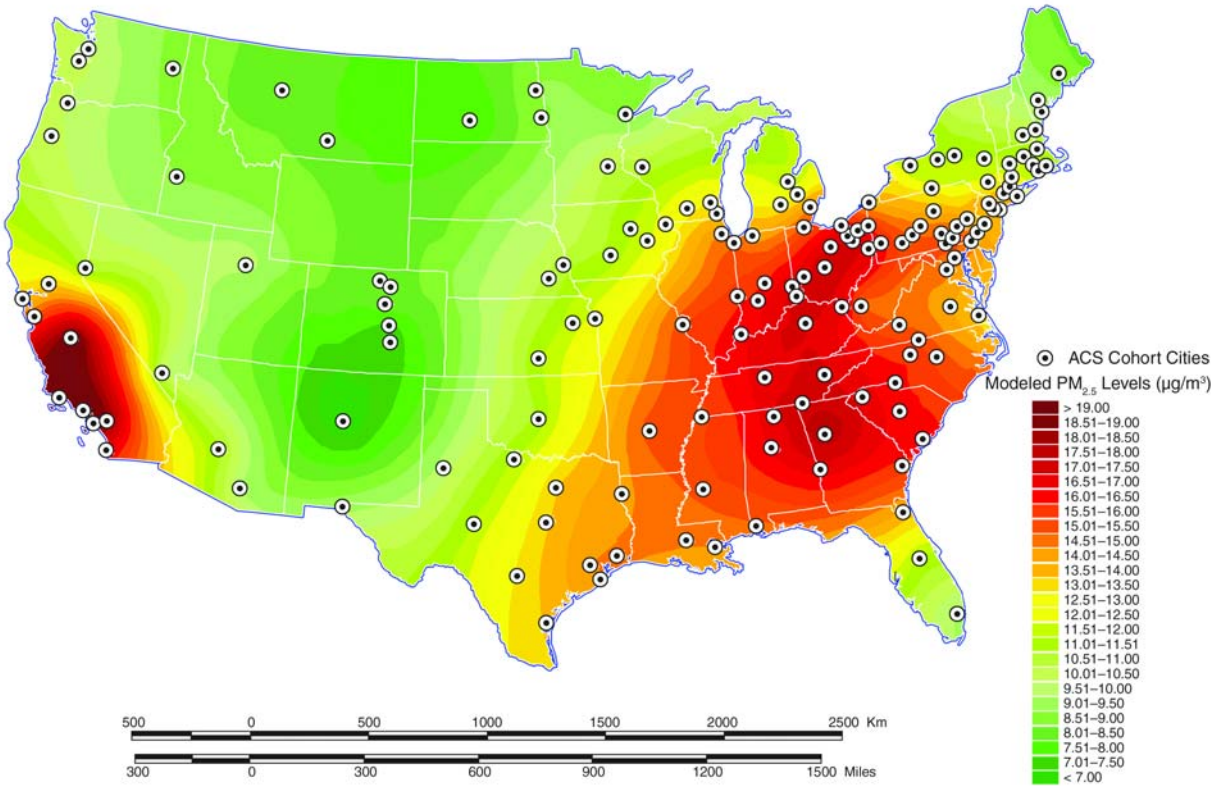

Figure 22. Spatial distribution (kriged) of $PM_{2.5}$ concentrations based on data from 1999–2000. Analysis done in the current project.

annual average estimates of $PM_{2.5}$ concentrations for 1972–2000, and we used them in the analysis of possible critical exposure time windows. Measured annual average SO_2 concentrations were also available from the EPA AIRS database for the same period.

The specific objectives of Phase III were threefold: (1) Do social, economic, and demographic ecologic variables confound or modify the relationship between particulate air pollution and mortality? (2) How can spatial autocorrelation and multiple geographic levels be taken into account within the random effects Cox models? (3) What critical exposure time windows affect the association between air pollution and mortality?

During the course of Phase III, a fourth objective of focusing on Intra-Urban Analyses in the Los Angeles and New York City regions was added. These Intra-Urban Analyses were intended to explore the MAUP by using more geographically refined indicators of air pollution exposure. Specifically, the relatively dense grid of air pollution monitors in both of these large cities permitted an assessment of exposure to ambient air pollution at the ZCA scale.

The extensive series of analyses conducted during the course of Phase III provided a number of important findings concerning the association between exposure to ambient air pollutants and mortality.

SUMMARY OF RESULTS FROM PHASE III

Nationwide Analysis

The first set of analyses focused on further characterizing the relationship between air pollution and mortality using the most recent follow-up data for the ACS cohort.

Nationwide Analysis of the full ACS cohort confirmed that mortality increases with exposure to $PM_{2.5}$; the HR for death from all causes was 1.033 (95% CI, 1.015–1.052), for death from CPD was 1.091 (95% CI, 1.063–1.120), for death from IHD was 1.152 (95% CI, 1.111–1.196), and for death from lung cancer was 1.110 (95% CI, 1.040–1.185) (see Table 3). These risk estimates were based on annual average air pollutant concentrations in 1999–2000 and were calculated based on a 10-$\mu g/m^3$ change in $PM_{2.5}$. (Similar although slightly lower risk estimates were obtained using air pollutant concentrations for 1979–1983.)

The Reanalysis showed stronger and more robust associations between SO_2 exposure and all causes of mortality compared with those observed for $PM_{2.5}$ exposure (Krewski et al. 2000b). A plausible mechanism by which SO_2 could increase mortality risk, however, has not yet been identified. One possibility is that SO_2 may serve as a marker for particulate air pollution formed by the atmospheric transformation of SO_2 into SO_4^{2-} particles. In contrast, the present analysis showed stronger mortality associations for $PM_{2.5}$ than for SO_2 exposure. We did not investigate sources of particles or particle transformation; however, source apportionment is an important avenue for future research.

In analyses conducted at the national level, the largest mortality risk estimates were consistently associated with IHD; a similar result was noted in the Reanalysis Project. Whereas lung-cancer mortality in Phase II was found not to be significantly elevated in relation to $PM_{2.5}$ exposure, the additional number of lung-cancer deaths during the further 11 years of follow-up used for Phase III resulted in a significant association between $PM_{2.5}$ exposure and lung cancer. A significant increase in lung-cancer mortality was also noted in the Updated Analysis of the ACS cohort with follow-up through 1998 (Pope et al. 2002).

We adjusted models for ecologic covariates to account for sociodemographic risks, which would yield less biased mortality risk estimates of air pollution exposure. In nearly all models that adjusted for the seven ecologic covariates simultaneously, the HR tended to increase in comparison to models with no adjustment, although many of the differences were small. The geographic unit of analysis of ecologic covariates (ZCA, MSA, or MSA & DIFF) tended not to make an appreciable difference in influence on HR estimates; however, in many cases HR estimates tended to be highest in models with the ecologic covariates considered at the MSA & DIFF levels simultaneously.

The air pollution–lung-cancer mortality association was also found to vary somewhat by the level of education attainment recorded when subjects were enrolled. Specifically, participants who completed high school or less had a significant increase in risk of lung-cancer mortality of approximately 20% associated with each 10-$\mu g/m^3$ change in $PM_{2.5}$ (as measured in 2000) compared with no association observed for those who completed more than high school.

Intra-Urban Analyses

The Intra-Urban Analyses for the Los Angeles region using the LUR-based exposure assignments resulted in notably larger mortality risk estimates than those found in the Nationwide Analysis. Such differences were suggested by an earlier simulation study of the effects of exposure measurement error in studies of this type conducted by Mallick and associates (2002). Mortality risk estimates using the LUR-based exposure estimates were somewhat smaller than those based on the exposure estimates from the kriging model, but were generally comparable. The HR of mortality due to exposure to $PM_{2.5}$ in Los Angeles from

all causes was 1.143 (95% CI, 1.033–1.266), from CPD was 1.114 (95% CI, 0.968–1.282), from IHD was 1.331 (95% CI, 1.084–1.634), and from lung cancer was 1.392 (95% CI, 0.964–2.010) (see Table 23). These risk estimates are based on $PM_{2.5}$ concentrations in Los Angeles in 1999–2000 and correspond to a change of 10 μg/m^3 $PM_{2.5}$. Mortality was not significantly higher in relation to exposure to O_3 concentrations or with proximity to freeways within the Los Angeles MSA.

The Intra-Urban Analysis for the New York City region produced a somewhat different picture of the association between air pollution and mortality than in Los Angeles. In New York City, the HR of mortality due to exposure to $PM_{2.5}$ from all causes was 0.984 (95% CI, 0.948–1.020), from CPD was 0.953 (95% CI, 0.902–1.007), from IHD was 1.072 (95% CI, 1.003–1.147), and from lung cancer was 0.955 (95% CI = 0.836–1.091) (see Table 15). Whereas in Los Angeles $PM_{2.5}$ exposure was related to all cause-of-death categories, in New York IHD was the only cause of death associated with $PM_{2.5}$ exposure (which is consistent with the mechanistic hypothesis put forward by Pope and associates [2004] in the Updated Analysis). These HR estimates are based on 3-year average $PM_{2.5}$ concentrations from the 28 counties of New York City in 1999–2001 and correspond to a difference of 1.5 μg/m^3 of $PM_{2.5}$ between the highest level of exposure and the lowest. The exposure estimates were based on LUR models, taking into account traffic density, population density, and industrial land use.

Previously, we have used kriging methods to estimate levels of ambient $PM_{2.5}$ concentrations (Jerrett et al. 2005a). Table 30 presents a comparison of HRs obtained from analyses using LUR and kriging exposure assignments in Los Angeles and LUR in New York City. The comparison suggests that the method used for exposure assignment did not affect HR estimates appreciably and was not responsible for differences between the two cities that have been previously observed. The differences in mortality risks may be attributable to fundamental differences in the topographical, geographical, and urban attributes of these two metropolitan areas.

Comparing the mortality risk estimates obtained from the Nationwide Analysis with those from the Intra-Urban Analyses indicates that the Nationwide risk estimates cannot be directly applied to all urban areas within the United States and that mortality risk estimates can vary appreciably among large urban areas with different characteristics.

In an effort to understand the variation in risk estimates between the Los Angeles, New York, and Nationwide Analyses, we compared the subjects' characteristics in the three locations (see Table 31). As shown in the table, few remarkable differences were apparent among the groups of the ACS cohort used for each analysis. (1) The New York City cohort had slightly fewer deaths, largely due to a lower number of CPD deaths. (2) The Los Angeles cohort had fewer subjects who are white. (3) Subjects in Los Angeles had higher education levels, a slightly healthier

Table 30. A Comparison of HRs by Cause of Death Associated with a 10-μg/m^3 Change of $PM_{2.5}$ (Los Angeles) or with an Interdecile Comparison Value of 1.5 μg/m^3 $PM_{2.5}$ (New York City) with Exposure Estimated Using LUR or Kriging[a]

	Los Angeles		New York City
Covariates	LUR	Kriging	LUR
All Causes			
$PM_{2.5}$ only	1.20 (1.08–1.32)	1.24 (1.11–1.37)	1.01 (0.94–1.05)
+ 44 Individual-level	1.14 (1.03–1.27)	1.17 (1.05–1.30)	0.98 (0.95–1.02)
IHD			
$PM_{2.5}$ only	1.42 (1.15–1.74)	1.49 (1.20–1.85)	1.11 (1.04–1.18)
+ 44 Individual-level	1.33 (1.08–1.63)	1.39 (1.12–1.73)	1.07 (1.00–1.15)
CPD			
$PM_{2.5}$ only	1.18 (1.02–1.36)	1.20 (1.04–1.39)	0.98 (0.93–1.03)
+ 44 Individual-level	1.11 (0.97–1.28)	1.12 (0.97–1.30)	0.95 (0.90–1.01)
Lung Cancer			
$PM_{2.5}$ only	1.46 (1.01–2.10)	1.60 (1.09–2.33)	1.04 (0.91–1.18)
+ 44 Individual-level	1.39 (0.96–2.01)	1.44 (0.98–2.11)	0.96 (0.84–1.09)

[a] The $PM_{2.5}$ concentration of 1.5 μg/m^3 for New York City represents the difference between the concentrations at the 90% decile and at the 10% decile in the exposure distribution from the 28-county 3-year model. HRs are followed by 95% confidence intervals.

Table 31. Descriptive Statistics of Risk Factors for the Nationwide, New York City, and Los Angeles Data Sets

Variable	Nationwide[a]	New York City	Los Angeles
Participants (*n*)	488,370	44,056	22,905
Participants died from (%)			
All causes	26.4	24.0	25.6
CPD	13.1	10.5	13.7
Lung cancer	2.0	1.9	1.9
All other causes	11.3	11.1	10.0
Age[b]	56.6 (10.5)	55.3 (10.7)	57.0 (10.6)
Male (%)	56.5	56.3	57.0
White (%)	94.0	95.0	89.1
Education (%)			
< High School	12.1	11.8	8.2
High School	31.2	31.2	22.9
> High School	56.7	57.0	68.9
Current Smoker (%)	21.9	23.5	19.3
Cigarettes per day	22.0 (12.4)	21.8 (12.6)	21.3 (12.6)
Years of smoking	33.6 (11.0)	32.8 (11.0)	34.0 (11.1)
Former smoker (%)	30.3	33.5	33.0
Cigarettes per day	21.6 (14.6)	22.1 (15.1)	20.9 (14.8)
Years of smoking	22.2 (4.1)	25.2 (4.0)	24.7 (4.0)
Age when started smoking (%)			
< 18 yrs (current smoker)	9.3	11.5	8.4
≥ 18 yrs (current smoker)	13.0	12.4	11.3
< 18 yrs (former smoker)	11.8	15.3	12.0
≥ 18 yrs (former smoker)	18.4	18.3	20.8
Hours per day exposed to smoking[b]	3.2 (4.4)	3.6 (4.5)	2.8 (4.2)

Table continues next page

[a] Based on the 116 MSAs for which $PM_{2.5}$ (1999–2000) data were available in the national dataset and follow-up of participants through 2000.

[b] Mean (SD).

[c] Occupational exposure to PM increases with increasing index number.

[d] Dietary fat consumption increases with increasing index number.

[e] Dietary fiber consumption increases with increasing index number.

diet, and higher levels of alcohol consumption. (4) Occupational exposures were slightly lower in Los Angeles and New York than in the national cohort. (5) With the exception of a lower proportion of white subjects, the slight differences of the characteristics in the Los Angeles cohort compared with the New York cohort were likely to increase survival, which would likely decrease susceptibility to air pollution; yet the health effects observed in Los Angeles were generally higher than those observed in either of the other two groups. Based on these comparisons, it appears unlikely that the differences in results observed between the Nationwide Analysis and the two Intra-Urban Analyses are attributable to differences in the underlying characteristics in each cohort group. The possibility of confounding by non-PM effects of mobile sources, such as noise, remains.

Critical Exposure Time Windows

A unique aspect of Phase III was the use of the ACS Nutrition Cohort to examine the time window of exposure that may be primarily responsible for the association between air pollution and mortality. We constructed an individual time-dependent exposure profile for each participant in this large cohort for which population mobility information was available. We evaluated air pollutant exposure concentrations experienced by individuals

Table 31 (*Continued*). Descriptive Statistics of Risk Factors for the Nationwide, New York City, and Los Angeles Data Sets

Variable	Nationwide[a]	New York City	Los Angeles
Marital status (%)			
Married	83.9	83.0	80.9
Separated	3.5	4.5	3.6
Divorced	12.6	12.5	15.5
Body mass index[b]	25.2 (4.1)	25.2 (4.0)	24.7 (4.0)
Occupational exposure to PM index[c] (%)			
Level 1	13.1	13.9	13.1
Level 2	11.3	10.2	12.4
Level 3	4.7	4.5	4.6
Level 4	6.4	4.9	3.8
Level 5	4.2	3.7	4.1
Level 6	1.1	0.6	0.8
Not able to access	8.7	10.1	9.2
Self-reported exposure to dust or fumes (%)	19.9	19.2	19.5
Dietary fat consumption index[d] (%)			
Level 1	15.9	18.2	17.8
Level 2	17.5	18.6	18.3
Level 3	21.4	21.5	21.3
Level 4	30.9	25.2	24.5
Dietary fiber consumption index[e] (%)			
Level 1	19.8	20.0	18.1
Level 2	18.8	19.3	17.4
Level 3	22.8	23.3	22.9
Level 4	22.0	21.2	26.4
Alcohol consumption (%)			
Drink beer	22.9	23.2	22.4
Drink liquor	27.6	30.4	31.3
Drink wine	23.2	29.9	34.2

[a] Based on the 116 MSAs for which $PM_{2.5}$ (1999–2000) data were available in the national dataset and follow-up of participants through 2000.

[b] Mean (SD).

[c] Occupational exposure to PM increases with increasing index number.

[d] Dietary fat consumption increases with increasing index number.

[e] Dietary fiber consumption increases with increasing index number.

dynamically, during three separate exposure time windows reflecting individual exposure 1–5, 6–10, and 11–15 years in the past. Overall, no clear findings emerged for either $PM_{2.5}$ or SO_2. Identification of critical exposure time windows, even among large national cohorts, remains a challenge and further work on identifying them with other relevant datasets — including other cohorts with different exposure circumstances — is needed.

REVISIONS TO THE COX MODELS

An important methodologic contribution from Phase III is the extension of the random effects Cox regression models to handle multiple levels of clustering. The software developed for this purpose in Phase II has been significantly enhanced and allows for a broader class of spatial autocorrelation models. We expect the extended random effects Cox regression model software to find application in a wide variety of research directions outside of the ACS cohort.

Application of the random effects Cox model to the updated ACS cohort data in Phase III tended to modestly increase the air pollution risk estimates over those from the standard Cox model, and to inflate the uncertainty in the estimates, as is reflected in the associated broader confidence limits.

COMPARISON OF DATA SETS AND ANALYTIC METHODS FOR THE THREE FOLLOW-UP TIME PERIODS

We further examined how a variety of analytic factors may influence the estimation of the long-term air pollution–mortality association in the ACS cohort over time. Table 32 provides some descriptive statistics about three major analyses conducted with the ACS cohort data at different points in time.

In the Reanalysis Project (Krewski et al. 2000b), $PM_{2.5}$ exposure data were available for the time period 1979–1983 for 50 MSAs containing 298,825 study participants. Follow-up of participants had been performed through 1989 and had documented a total of 23,180 deaths from all causes, 11,262 from CPD, 2,001 from lung cancer, and 5,968 from IHD.

In the Updated Analysis by Pope and colleagues (2002), the follow-up period had been extended by 9 years until 1998. Additional $PM_{2.5}$ data had been obtained and exposure could be estimated for two time periods (1979–1983 and 1999–2000); these corresponded to a total of 61 and 116 MSAs, respectively. Due in large part to the longer follow-up period, more deaths had occurred; over 80,000 deaths from all causes were recorded among those subjects for whom $PM_{2.5}$ exposure data for 1979–1983 were available.

Finally, for the current Extended Analysis, the ACS follow-up period had been extended by 2 more years, until 2000. Because we examined several additional ecologic covariates at different levels of analysis, the total number of MSAs and participants available for the Nationwide Analysis was slightly lower than the number available for the Updated Analysis by Pope and colleagues (2002). The two additional years of follow-up, however, included more deaths: over 90,000 from all causes among the same group for whom $PM_{2.5}$ exposure data were available for 1979–1983.

Table 33 compares HR estimates for the five main cause-of-death categories using different cohort follow-up periods (until 1989, 1998, and 2000) that correspond with the analytic time periods used for the Reanalysis Project (Krewski et al. 2000a,b), the Updated Analysis (Pope et al. 2002), and the current Extended Analysis. By holding the number of MSAs and study subjects constant, we were better able to examine the independent influence of changing the length of the follow-up period on study findings. The $PM_{2.5}$ (1979–1983) results were obtained using available data for 342,521 subjects residing in 58 MSAs, and the $PM_{2.5}$ (1999–2000) results were obtained using available data for 488,370 subjects residing in 116 MSAs. Results are presented with adjustment for the standard suite of 44 individual-level covariates and with and without adjustment for the seven ecologic covariates examined in the current study.

With models adjusted for individual-level covariates only, estimated HRs associated with exposure to $PM_{2.5}$ (1979–1983) ranged from 1.03–1.05 for all causes, 1.07–1.10 for CPD, 1.12–1.13 for IHD, and 1.05–1.09 for lung cancer. HR estimates were slightly higher for IHD and lung cancer

Table 32. Characteristics of the Analytic Cohorts in the Previous and Current Analyses[a]

Characteristic	Cohort Data Set Used in Reanalysis (2000)	Cohort Data Sets Used in Updated Analysis (2002, 2004)		Cohort Data Sets Used in Current Nationwide Analysis (2009)	
Years of $PM_{2.5}$ exposure data	1979–1983	1979–1983	1999–2000	1979–1983	1999–2000
Years of cohort follow-up	1982–1989	1982–1998	1982–1998	1982–2000	1982–2000
MSAs (*n*)	50	61	116	58	116
Study participants (*n*)	298,825	360,682	499,779[b]	342,521	488,370[b]
Person-years	2,109,750	5,302,337	7,350,011	5,542,998	7,908,283
Deaths (*n*)					
All causes	**23,180**	**80,819**	111,677	**90,783**	**128,954**
CPD	11,262	35,782	49,539	44,866	63,917
Lung cancer	2,001	6,335	8,754	6,827	9,788
IHD	5,968	14,691	20,791	**20,651**	**29,989**

[a] Bolded data refer to text.

[b] For the $PM_{2.5}$ 1999–2000 exposure data, the 116 MSAs used for the Updated Analysis and in the current Nationwide Analysis are the same. The number of study participants differs because several additional ecologic covariates were analyzed in the current study and those data were not available for the full cohort.

associated with the $PM_{2.5}$ (1999–2000) exposure data. With models including ecologic covariates, HR estimates increased to 1.04–1.06 for all causes, 1.09–1.13 for CPD, 1.18 for IHD, and 1.07–1.10 for lung-cancer mortality associated with exposure to $PM_{2.5}$ (1979–1983) over the different follow-up time periods. Overall, there was little change in risk estimates over different periods of follow-up time; those for $PM_{2.5}$ (1979–1983) tended to either remain fairly similar or decrease slightly with increasing follow-up time. An exception was lung-cancer mortality for which HRs increased and were significant when follow-up was extended beyond 1989.

It is possible that there may be increasing exposure misclassification due to population mobility during the 11 years of follow-up from 1989 to 2000. A recent analysis by Jerrett and colleagues (2007) showed that population mobility in the ACS cohort demonstrates that areas of relatively low improvements in air pollution have higher population gains.

Table 34 shows the influence of (1) the number of MSAs and participants included in the analysis and (2) the choice of statistical method (either the standard Cox model or the random effects Cox model). For these analyses, we either held the number of MSAs and participants constant across the different follow-up periods (using the same number of MSAs and participants as those in the current study) or we allowed the number of MSAs and participants to vary across the different follow-up periods (using the number of MSAs and participants that corresponded with those used in the earlier analyses [Krewski et al. 2000a,b; Pope et al. 2002; see Table 32]). For $PM_{2.5}$ (1979–1983) both the number of MSAs and participants could vary; but for $PM_{2.5}$ (1999–2000), the number of MSAs was

Table 33. HRs by Cause of Death for a 10-μg/m^3 Change in $PM_{2.5}$ Covering Three Follow-Up Time Periods, Using the Same Number of MSAs and Study Participants Within $PM_{2.5}$ Exposure Categories, and With and Without Adjustment for the Seven Ecologic Covariates[a]

Covariates in Model[b]	Follow-Up Through 1989	Follow-Up Through 1998		Follow-Up Through 2000	
$PM_{2.5}$	1979–1983	1979–1983	1999–2000	1979–1983	1999–2000
MSAs (*n*)	58	58	116	58	116
Participants (*n*)	342,521	342,521	488,370	342,521	488,370
All Causes					
44 Individual	**1.048** (1.022–1.076)	**1.031** (1.015–1.047)	1.032 (1.012–1.053)	**1.028** (1.014–1.043)	1.036 (1.017–1.054)
+ 7 Ecologic	**1.061** (1.031–1.091)	1.047 (1.029–1.064)	1.057 (1.033–1.080)	**1.044** (1.028–1.060)	1.057 (1.036–1.079)
CPD					
44 Individual	**1.101** (1.061–1.143)	1.071 (1.048–1.095)	1.092 (1.063–1.123)	**1.070** (1.049–1.092)	1.100 (1.073–1.129)
+ 7 Ecologic	**1.129** (1.084–1.175)	**1.098** (1.073–1.125)	1.134 (1.099–1.170)	1.094 (1.070–1.118)	1.138 (1.106–1.172)
IHD					
44 Individual	**1.122** (1.066–1.181)	**1.130** (1.094–1.166)	**1.143** (1.099–1.190)	**1.133** (1.100–1.167)	**1.155** (1.113–1.199)
+ 7 Ecologic	1.183 (1.119–1.250)	1.183 (1.143–1.225)	1.234 (1.179–1.291)	**1.184** (1.146–1.222)	1.242 (1.191–1.295)
Lung Cancer					
44 Individual	**1.053** (0.963–1.150)	**1.089** (1.031–1.151)	**1.116** (1.041–1.197)	1.075 (1.021–1.132)	**1.109** (1.039–1.185)
+ 7 Ecologic	**1.070** (0.973–1.177)	**1.104** (1.040–1.171)	1.152 (1.065–1.247)	**1.092 (1.033–1.154)**	1.138 (1.057–1.225)
All Other Causes					
44 Individual	0.998 (0.958–1.040)	0.981 (0.957–1.005)	0.953 (0.924–0.982)	0.979 (0.957–1.000)	0.953 (0.927–0.980)
+ 7 Ecologic	0.992 (0.949–1.037)	0.984 (0.958–1.010)	0.953 (0.920–0.988)	0.983 (0.960–1.007)	0.953 (0.923–0.984)

[a] Based on a standard Cox model with the 44 individual-level covariates with and without adjustment for the seven ecologic covariates at MSA & DIFF levels. The baseline hazard function was stratified by age (1-year groupings), gender, and race. All analyses were conducted using the same 58 MSAs (342,521 participants) or 116 MSAs (488,370 participants) that were used in the current analysis. HRs are followed by 95% confidence intervals. Bolded data refer to text.

[b] Data for the 44 individual-level covariates are from the ACS enrollment questionnaire. Data for the seven ecologic covariates were extracted from the 1980 U.S. Census Bureau database for the Nationwide Analysis of the current study.

Table 34. HRs by Cause of Death for a 10-μg/m^3 Change in $PM_{2.5}$ Based on Either a Standard Cox or a Random Effects Cox Model Covering Three Follow-Up Time Periods and Using the Same or Different Numbers of MSAs and Participants[a]

Model and Number of MSAs	Follow-Up Through 1989[b]	Follow-Up Through 1998[c]		Follow-Up Through 2000[d]	
$PM_{2.5}$ data	1979–1983	1979–1983	1999–2000	1979–1983	1999–2000
Same[e]					
MSAs (*n*)	58	58	116	58	116
Participants (*n*)	342,521	342,521	488,370	342,521	488,370
Different[e]					
MSAs (*n*)	50	61	116	58	116
Participants (*n*)	298,825	360,682	499,779	342,521	488,370
All Causes					
Standard Cox					
Same	1.048 (1.022–1.076)	1.031 (1.015–1.047)	1.032 (1.012–1.053)	1.028 (1.014–1.043)	1.036 (1.017–1.054)
Different	1.067 (1.037–1.099)	1.027 (1.012–1.043)	1.028 (1.009–1.048)		
Random Effects Cox					
Same	1.074 (1.028–1.122)	1.046 (1.014–1.080)	1.061 (1.023–1.101)	1.042 (1.012–1.073)	1.063 (1.026–1.102)
Different	1.101 (1.046–1.157)	1.044 (1.011–1.078)	1.058 (1.020–1.098)		
CPD					
Standard Cox					
Same	1.101 (1.061–1.143)	1.071 (1.048–1.095)	1.092 (1.063–1.123)	1.070 (1.049–1.092)	1.100 (1.073–1.129)
Different	1.109 (1.063–1.157)	1.060 (1.036–1.084)	1.079 (1.049–1.111)		
Random Effects Cox					
Same	1.116 (1.055–1.180)	1.075 (1.032–1.120)	1.100 (1.044–1.159)	1.073 (1.031–1.116)	1.105 (1.050–1.162)
Different	1.130 (1.063–1.201)	1.061 (1.018–1.105)	1.081 (1.025–1.141)		
IHD					
Standard Cox					
Same	1.122 (1.066–1.181)	1.130 (1.094–1.166)	1.143 (1.099–1.190)	1.133 (1.100–1.167)	1.155 (1.113–1.199)
Different	1.122 (1.059–1.189)	1.119 (1.081–1.159)	1.141 (1.091–1.193)		
Random Effects Cox					
Same	1.167 (1.062–1.282)	1.160 (1.074–1.252)	**1.198 (1.099–1.305)**	1.155 (1.074–1.124)	1.200 (1.106–1.301)
Different	1.174 (1.064–1.295)	1.140 (1.053–1.235)	**1.192 (1.085–1.310)**		
Lung Cancer					
Standard Cox					
Same	**1.053 (0.963–1.150)**	1.089 (1.031–1.151)	1.116 (1.041–1.197)	1.075 (1.021–1.132)	1.109 (1.039–1.185)
Different	**1.001 (0.907–1.104)**	1.072 (1.017–1.130)	1.117 (1.042–1.197)		
Random Effects Cox					
Same	1.117 (0.979–1.274)	1.102 (1.032–1.177)	1.129 (1.045–1.220)	1.085 (1.019–1.156)	1.124 (1.041–1.213)
Different	1.062 (0.913–1.235)	1.083 (1.014–1.157)	1.126 (1.044–1.214)		
All Other Causes					
Standard Cox					
Same	0.998 (0.958–1.040)	0.981 (0.957–1.005)	0.953 (0.924–0.982)	0.979 (0.957–1.000)	0.953 (0.927–0.980)
Different	1.040 (0.993–1.089)	0.992 (0.971–1.013)	0.971 (0.944–0.998)		
Random Effects Cox					
Same	1.017 (0.960–1.077)	1.001 (0.961–1.043)	0.991 (0.946–1.039)	0.999 (0.962–1.037)	0.963 (0.879–1.055)
Different	1.063 (0.995–1.135)	1.014 (0.975–1.054)	1.010 (0.967–1.055)		

[a] Models included the 44 individual-level covariates. The baseline hazard function was stratified by age (1-year groupings), gender, and race. HRs are followed by 95% confidence intervals. Bolded values refer to text.

[b] Follow-up period used for the Reanalysis Project (Krewski et al. 2000).

[c] Follow-up period used for the Updated Analysis (Pope et al. 2002, 2004).

[d] Follow-up period used for this Extended Analysis.

[e] Rows marked "Same" use the MSAs and participants from the current Nationwide Analysis. Rows marked "Different" use the MSAs and participants included in the earlier analyses (as outlined in Table 32).

the same in both follow-up periods, and only the number of participants varied.

As noted previously, risk estimates obtained with the random effects Cox model were slightly higher than those obtained with the standard Cox model; the comparisons in Table 34 show this pattern fairly consistently.

In results obtained with the standard Cox model, there was only slight variation in the mortality HR estimates comparing calculations with the same number or different number of MSAs and participants. One of the largest changes in the HRs was found for mortality from lung-cancer associated with $PM_{2.5}$ (1979–1983) with follow-up through 1989 with a HR of 1.00 (95% CI, 0.91–1.10) when using data from 50 MSAs ("different" row), which increased to 1.05 (95% CI, 0.96–1.15) when we included the 8 additional MSAs for which $PM_{2.5}$ data had later been obtained ("same" row), although it remained nonsignificant.

A similar pattern was observed with the random effects Cox model. Again, the difference in risk estimates was slight whether using the same number or a different number of MSAs and participants. The largest difference was also observed for mortality from lung cancer associated with $PM_{2.5}$ (1979–1983) with follow-up through 1989 with a HR of 1.062 (95% CI, 0.913–1.235) found when using data from 50 MSAs ("different" row), which increased, although again remained nonsignificant, to 1.117 (95% CI, 0.979–1.274) reported when we included 8 additional MSAs ("same" row).

Table 35 presents a comparison of the modifying effect of education attainment on the association between $PM_{2.5}$ (1979–1983) and mortality over the three follow-up time periods with and without the ecologic covariates examined as part of the Nationwide Analysis. (Note that this set of analyses uses the same 58 MSAs and 342,521 subjects as the current Extended Analysis.) In the two most recent periods (through 1998 and 2000), risk of mortality decreased with increasing level of education attainment for all-cause and cause-specific mortality and, with the exception of IHD, was no longer significant in those with the highest level of education attainment. When the follow-up time period was truncated at 1989, although the decreasing trend was less clear, the lowest risk estimates were also consistently reported in the highest education group. A similar pattern of results was obtained with or without adjustment for the seven ecologic covariates evaluated in the current study.

POLICY IMPLICATIONS

The results of Phase III of the Particle Epidemiology Reanalysis Project have important implications for air quality risk management policy. The extended follow-up of the ACS cohort through 2000 supports earlier findings of a positive association between long-term exposure to $PM_{2.5}$ in ambient air and increased mortality rates in urban centers in the United States. The earlier results have figured prominently in establishing the current National Ambient Air Quality Standard for $PM_{2.5}$ in the United States (U.S. EPA 2004). Although short-term exposures to $PM_{2.5}$ are also associated with higher mortality, one of the effects of long-term exposure (Cohen et al. 2003) is to predispose some people to the effects attributed to short-term exposures (Network for Environmental Risk Assessment and Management [NERAM] 2002; Krewski et al. 2005b).

Particulate air pollution represents a major health issue at the international level as well (Cohen et al. 2005). The World Health Organization (WHO 2002) has estimated that particulate air pollution is responsible for approximately 2% of all deaths worldwide. WHO has assumed a leadership role in global air quality management and has recently updated its air quality guidelines for both $PM_{2.5}$ and O_3 (WHO 2006).

Although the precise magnitude of the risk associated with long-term exposure to air pollution remains subject to some uncertainty, these and earlier results from the ACS cohort have generally demonstrated elevated mortality from CPD, IHD, and lung cancer. Mortality from all causes is also clearly associated with long-term exposure to ambient $PM_{2.5}$ in U.S. urban centers. Phases II and III of the Particle Epidemiology Reanalysis Project have both shown these estimates to be robust to alternative analytic methods and to adjustment for other variables that may impact the association between air pollution and mortality.

In an attempt to address the uncertainty about the actual magnitude of the increase in mortality due to long-term exposure to fine particles, the U.S. EPA has recently conducted an expert elicitation involving leading researchers in the health effects of air pollution, especially those with experience evaluating data from large cohorts including the ACS, the Harvard Six Cities Study (Laden et al. 2006), and the Adventist Health Study of Smog (Abbey et al. 1999). This expert elicitation process demonstrated a clear consensus among the participating scientists that long-term exposure to particulate air pollution is associated with increased mortality (Industrial Economics, Incorporated 2006).

The policy implications of the current body of scientific evidence linking air pollution to morbidity and mortality were recently discussed at the fifth and final NERAM Collo-quium on Air Quality and Health (NERAM 2006). Whereas NERAM I (Cohen et al. 2003), II (Krewski et al. 2005a), and III (Craig et al. 2007) focused more on the

Table 35. Modification by Education Attainment: HRs by Cause of Death for a 10-μg/m^3 Change in $PM_{2.5}$ (1979–1983) Covering Three Follow-Up Time Periods, With and Without Seven Ecological Covariates, and Using the Same Number of MSAs and Study Participants[a]

Level of Education	Follow-Up Through 1989		Follow-Up Through 1998		Follow-Up Through 2000	
Covariates[b]	42 Individual	+ 7 Ecologic	42 Individual	+ 7 Ecologic	42 Individual	+ 7 Ecologic
All Causes						
< High school	1.081 (1.024–1.140)	1.104 (1.042–1.170)	1.074 (1.038–1.112)	1.099 (1.059–1.141)	1.072 (1.038–1.107)	1.095 (1.058–1.134)
High school	1.092 (1.042–1.145)	1.090 (1.036–1.147)	1.050 (1.021–1.079)	1.065 (1.033–1.097)	1.045 (1.018–1.071)	1.057 (1.029–1.087)
>High school	1.007 (0.969–1.046)	1.016 (0.974–1.060)	1.001 (0.979–1.023)	1.011 (0.987–1.036)	1.000 (0.980–1.021)	1.011 (0.989–1.034)
CPD						
<High school	1.103 (1.027–1.185)	1.122 (1.038–1.213)	1.125 (1.074–1.178)	1.154 (1.098–1.213)	1.129 (1.081–1.178)	1.157 (1.104–1.212)
High school	1.153 (1.075–1.236)	1.184 (1.099–1.275)	1.103 (1.060–1.148)	1.132 (1.084–1.182)	1.087 (1.048–1.128)	1.112 (1.069–1.157)
>High school	1.066 (1.007–1.127)	1.089 (1.023–1.158)	1.024 (0.992–1.057)	1.042 (1.006–1.080)	1.029 (1.000–1.060)	1.044 (1.011–1.079)
IHD						
<High school	1.148 (1.040–1.268)	1.189 (1.068–1.324)	1.183 (1.106–1.264)	1.229 (1.144–1.321)	1.182 (1.110–1.260)	1.224 (1.143–1.311)
High school	1.170 (1.064–1.286)	1.232 (1.114–1.362)	1.173 (1.107–1.242)	1.219 (1.146–1.296)	1.153 (1.093–1.216)	1.195 (1.129–1.266)
>High school	1.070 (0.991–1.156)	1.133 (1.041–1.232)	1.073 (1.024–1.125)	1.129 (1.072–1.188)	1.093 (1.047–1.142)	1.149 (1.095–1.205)
Lung Cancer						
<High school	1.095 (0.911–1.317)	1.115 (0.912–1.363)	1.175 (1.034–1.335)	1.186 (1.034–1.360)	1.155 (1.024–1.302)	1.142 (1.004–1.298)
High school	1.196 (1.022–1.400)	1.189 (1.003–1.409)	1.151 (1.047–1.267)	1.163 (1.049–1.288)	1.152 (1.054–1.259)	1.168 (1.061–1.286)
>High school	0.931 (0.815–1.064)	0.992 (0.860–1.144)	1.012 (0.935–1.096)	1.040 (0.954–1.135)	0.993 (0.921–1.070)	1.028 (0.948–1.116)
All Other Causes						
<High school	1.046 (0.954–1.148)	1.085 (0.983–1.198)	0.995 (0.939–1.055)	1.015 (0.952–1.081)	0.987 (0.935–1.042)	1.008 (0.950–1.070)
High school	1.021 (0.949–1.098)	0.989 (0.914–1.070)	0.981 (0.940–1.025)	0.981 (0.936–1.028)	0.986 (0.948–1.026)	0.984 (0.943–1.027)
>High school	0.972 (0.917–1.030)	0.956 (0.896–1.019)	0.978 (0.945–1.011)	0.977 (0.941–1.015)	0.973 (0.943–1.003)	0.975 (0.942–1.009)

[a] Based on a standard Cox model with 42 individual-level covariates. The baseline hazard function was stratified by age (1-year groupings), gender, and race. HRs are followed by 95% confidence intervals. All analyses were conducted using the same 58 MSAs and 342,521 participants used in the current Extended Analysis.

[b] Data for the 42 individual-level covariates are from the ACS enrollment questionnaire. Data for the seven ecologic covariates (at MSA & DIFF levels) were extracted from the 1980 U.S. Census Bureau database for the Nationwide Aanalysis in the current study.

scientific evidence of the adverse health effects of ambient air pollution, NERAM IV (2005) and V (2006) focused on air quality management. The conference statement for NERAM V includes the following policy guidelines:

1. Current scientific evidence on adverse health impacts is sufficient to support air quality management action.
2. Air quality management actions have been shown to be cost-beneficial in a number of circumstances.
3. Although additional scientific evidence will be useful in targeted areas, such as characterizing the effects of traffic-related pollution, air quality management actions are needed now.
4. Successful air quality management requires local, regional, national, international, and global actions.

The results of the present analysis support the call for greater efforts to reduce exposure to air pollution embodied in the NERAM V conference statement. In developing air quality management policy, the following additional elements of the NERAM V conference statement are also relevant.

1. Harmonization of air quality measurement methods and health assessments is desirable.
2. Different air quality management strategies may be needed for developed and developing countries.
3. Air quality and climate change are closely linked.
4. Cross-sectoral strategies (air, climate, transportation, energy, agriculture) based on integrated assessments are needed.
5. Air quality management strategies should support sustainable development.
6. The impact of air quality management interventions needs to be evaluated.

The accountability framework proposed by the HEI Accountability Working Group (2003) provides an excellent basis for addressing the last item.

In conclusion, Phase III of the Particle Epidemiology Reanalysis Project has provided additional support for the development of effective air quality management policies and strategies. The epidemiologic results reported here are consistent with those from other population-based studies, which collectively support the hypothesis that long-term exposure to $PM_{2.5}$ increases mortality in the general population. We also now know mechanisms by which particles can increase mortality from CPD (Pope et al. 2004; National Research Council 2004), which provides a biologic basis for the associations observed.

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APPENDIX A. HEI Quality Assurance Statement

The conduct of this study was subject to independent QA oversight by Drs. W. Cary Eaton, Richard Kwok, and James Flanagan of RTI International (RTI), Research Triangle Park, NC. Dr. Eaton, who led the project, is a chemist with over 35 years of relevant experience in air monitoring and quality assurance and is the supervisor of the Quality Systems Programs at RTI. Dr. Flanagan is also a chemist with a specialization in air quality monitoring, data analysis, and quality assurance. Dr. Kwok is a research epidemiologist with applications to air and water pollution; cardiovascular, cancer, and respiratory outcomes; and quality assurance auditing. Other participants on the RTI QA oversight team included Dr. William Wheaton, a Geographic Information Systems specialist, who participated in a conference call with ACS participants, and Drs. Abhik Das and Breda Munoz, statisticians who reviewed the model code and the final report, respectively.

The QA oversight program that RTI conducted of this project consisted of a single on-site audit at the McLaughlin Centre for Population Health Risk Assessment, Ottawa, ON, Canada, conducted by Dr. Flanagan and Dr. Kwok. The audit included interviews with key project staff, and review of study activities for conformance to the study protocol and operating procedures. The investigators provided written responses to the findings of the audit report, which are included as an appendix in the investigators' final report.

In addition to the on-site audit, QA oversight activities included conference calls to coinvestigators and review of the final report.

DATE AND PHASE OF STUDY AUDITED

June 30–October 1, 2004

The auditors conducted an on-site audit at the University of Ottawa. Staffing and internal quality assurance procedures were reviewed. Audit observations consisted primarily of recommendations for improving study documentation and some data processing and security issues. A copy of code was taken for review with an audit team member, Dr. Abhik Das, who did not participate in the on-site portion.

October 14, 2004

Conference call with NYU collaborators

November 22, 2004

Conference call with collaborators at ACS Atlanta

February 3, 2005

Audit report delivered to HEI with findings based on the above activities.

January–March, 2009

Review of Final Report. At HEI's request, the same RTI personnel who conducted the QA 2004 oversight activities (Kwok, Eaton, and Flanagan) reviewed the investigators' final report for the project. In addition, mathematical details in the report were reviewed by Dr. Breda Munoz of RTI's Genomics, Statistical Genetics, and Environmental Research Group. No serious issues were raised during the review, but a list of minor comments and editorial suggestions was submitted to HEI.

Written reports of each activity were provided to the HEI Project Manager, who transmitted the findings to the Principal Investigator. Responses received from the project team demonstrated that the study was conducted by a highly experienced team of scientists with a high regard for the quality and credibility of their work. The final report appears to be an accurate representation of the study.

James B. Flanagan, Ph.D.
Chemist and Quality Assurance Specialist

Richard Kwok, Ph.D.
Epidemiologist
Auditors

APPENDICES AVAILABLE ON THE WEB

Appendices B and C contain supplemental material not included in the printed report. They are available on the HEI Web site *http://pubs.healtheffects.org*. They may also be requested by contacting the Health Effects Institute at 101 Federal Street, Suite 500, Boston, MA 02110, phone +1-617-488-2300, fax +1-488-2335, or e-mail (*pubs@healtheffects.org*). Please give (1) the first author, full title, and number of the Research Report and (2) the title of the appendix requested.

APPENDIX B. Algorithmic Description of the Cox–Poisson Program

APPENDIX C. Computer Program for Random Effects Cox Model Using the Cox–Poisson Program

ABOUT THE AUTHORS

Daniel Krewski is professor and director of the R. Samuel McLaughlin Centre for Population Health Risk Assessment and holds the Natural Sciences and Engineering Research Council/McLaughlin Chair in Risk Science at the University of Ottawa. Dr. Krewski has also served as adjunct research professor of statistics in the Department of Mathematics and Statistics at Carleton University since 1984. Before joining the Faculty of Medicine at the University of Ottawa in 1998, Dr. Krewski was director of risk management in the Health Protection Branch of Health Canada. While with Health Canada, he also served as acting director of the Bureau of Chemical Hazards and as chief of the Biostatistics Division in the Environmental Health Directorate. Dr. Krewski obtained his Ph.D. in statistics from Carleton University and subsequently completed an M.H.A. at the University of Ottawa. His professional interests include epidemiology, biostatistics, risk assessment, and risk management.

Michael Jerrett, Ph.D., is an associate professor in the Division of Environmental Health Sciences, School of Public Health, University of California–Berkeley. Building on expertise in medical geography, Geographic Information Systems, and spatial analysis, Dr. Jerrett currently assesses air pollution–health associations in the United States, Canada, and Mexico with special reference to social–spatial confounders and intra-urban exposure gradients. He is also engaged in determining the role of the built environment as a contributor to childhood obesity formation. He was awarded the 2004 Dangermond Endowed Speaker in Geographic Information Science honor at the Environmental Research Systems Institute and the University of California–Santa Barbara.

Richard Thomas Burnett received his Ph.D. in 1982 from Queen's University in mathematical statistics. He is a senior research scientist with the Healthy Environments and Consumer Safety Branch of Health Canada, where he has been working since 1983 on issues relating to the health effects of outdoor air pollution. He is an adjunct professor in the Department of Epidemiology and Community Medicine, an affiliate scientist in the Institute of Population Health, and a scientist with the McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, all at the University of Ottawa. Dr. Burnett's work has focused on the use of administrative health and environmental information to determine the public health impacts of combustion-related pollution using nonlinear random effects models and time-series and spatial analytic techniques.

Renjun Ma is an associate professor of statistics in the Department of Mathematics and Statistics and a research fellow in the Canadian Research Institute for Social Policy at the University of New Brunswick. He received his Ph.D. in statistics from the University of British Columbia. His primary research interests lie in the area of latent variables multivariate statistical models for spatial and longitudinal data. He collaborates with epidemiologists on spatial analysis of adverse effects of air pollution and works with social scientists on spatio-temporal analysis of healthy development of children and adolescents.

Edward Hughes received his Ph.D. in mathematics from the University of Wisconsin, and served a term as postdoctoral fellow in the University of British Columbia mathematics department. After several years on the Carleton University faculty, he left academic life and worked for two consulting firms and for the research division of Ontario Hydro. Since 1988, he has operated Edward Hughes Consulting, specializing in statistics and applied mathematics. He has worked with clients in the fields of engineering, economics, accounting, finance, and health research. Current research interests focus on developing efficient algorithms for large-scale epidemiologic computations.

Yuanli Shi is a research associate at the McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa. She received her M.D. in China and has been trained in applied statistics from the University of Reading and the University of Salford, England. Her research interests are in environmental, cancer, and reproductive health epidemiology and risk assessment.

Michelle C. Turner is a Ph.D. candidate in Population Health at the University of Ottawa. She received her M.Sc. in epidemiology from the University of Ottawa. Her research focus is on environmental epidemiology, cancer epidemiology, and risk perception. She is supported with a Canada Graduate Scholarship from the Canadian Institutes of Health Research.

C. Arden Pope III is the Mary Lou Fulton professor of economics at Brigham Young University. He has a Ph.D. from Iowa State University (1981) where he studied economics and statistics. He has had appointments at Iowa State and Texas A&M Universities and has been an Interdisciplinary Programs in Health fellow and visiting scientist in Environmental Health and Public Policy at the Harvard School of Public Health. He has conducted research dealing with a wide range of natural resource and environmental issues, but over the last 15 years has focused on evaluating health effects of air pollution. He has conducted or collaborated on many of the key, pioneering studies of short-term and long-term effects of air pollution.

George Douglas Thurston is a tenured professor at the New York University School of Medicine's Department of Environmental Medicine. He conducts epidemiologic research into the human health effects of air pollution. Dr. Thurston received his undergraduate degrees in environmental engineering and environmental studies from Brown University, and received his master's and doctorate degrees in environmental health sciences from the Harvard School of Public Health. Dr. Thurston was a contributing author to the most recent U.S. Criteria Document for Particulate Matter (2004) and has testified before the U.S. Congress regarding the human health effects of air pollution in the United States.

Eugenia E. Calle received her Ph.D. (1982) in epidemiology from the Ohio State University. She worked as an epidemiologist at the Oak Ridge National Laboratory in the area of cancer risk assessment (1979–1984) and at the Centers for Disease Control on the Agent Orange projects (1984–1989) before joining the American Cancer Society in 1989. Since 1994, she was the managing director of analytic epidemiology; in that capacity, she oversaw all program activities including data collection, management, and analyses for the Cancer Prevention Study cohorts. Her research was primarily in the areas of breast cancer risk factors, hormone-replacement therapy and cancers in women, and adiposity and cancer incidence and mortality. Dr. Calle retired from the American Cancer Society on January 30, 2009, and died unexpectedly on February 17, 2009.

Michael J. Thun received a B.A. degree from Harvard College, an M.D. from the University of Pennsylvania School of Medicine, and a Master of Science in epidemiology from the Harvard School of Public Health. He has worked for 28 years in epidemiology and disease prevention, first as a medical officer investigating toxic exposures at the New Jersey State Health Department, and then as an epidemic intelligence service officer and staff scientist for the Centers for Disease Control and Prevention at the National Institute for Occupational Safety and Health (1980–1988). In 1989, Dr. Thun became director of analytic epidemiology for the ACS in Atlanta. Since 1998 he has served as vice president of epidemiology and surveillance research, overseeing both cancer surveillance and studies on the causes and prevention of cancer. He is an adjunct professor in the Divisions of Epidemiology and of Environmental and Occupational Health at Emory University, Rollins School of Public Health, and at the Winship Cancer Center.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

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ABBREVIATIONS AND OTHER TERMS

AADT	average annual daily traffic
ACS	American Cancer Society
AIC	Akaike information criteria
AIRS	Aerometric Information Retrieval System
AQS	Air Quality Subsystem
ARB	Air Resources Board
BPM	Best Practice Model
CI	confidence interval
CPD	cardiopulmonary disease
CPS-II	cancer prevention study
DIFF	difference between the ZCA value and the MSA value for an ecologic covariate
EPDC	expected peak daily concentrations
ESRI	Environmental Systems Research Institute
FRM	Federal Reference Method
GIS	Geographic Information System
GPS	global positioning system
Ha	hectare
HR	hazard ratio
ICD-9	International Classification of Diseases, 9th edition
IDW	inverse distance weighting
IHD	ischemic heart disease
IPMN	Inhalable Particle Monitoring Network
LUR	land-use regression
MAPE	mean absolute percentage error
MAUP	modifiable areal unit problem
MCD	minor civil division
MSA	metropolitan statistical area
MSA & DIFF	two levels of data for ecologic covariates analyzed simultaneously
NAAQS	National Ambient Air Quality Standard
NAD	National Aerometric Database
NERAM	Network for Environmental Risk Assessment and Management
NYMTC	New York Metropolitan Transportation Council
NYU	New York University
O_3	ozone
$PM_{2.5}$	particles of 2.5 μm or less in aerodynamic diameter
R^2	coefficient of determination for multivariate analyses
RMSE	root mean squared error
SCAG	Southern California Area Governments
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
TEOM	tapered-element oscillating microbalance
TRAPCA	Traffic Related Air Pollution and Childhood Asthma [study]
TSP	total suspended particulates
USCB	U.S. Census Bureau
U.S. EPA	U.S. Environmental Protection Agency
USGS	United States Geological Survey
USPS	U.S. Postal Service
VIF	variance inflation factor
WHO	World Health Organization
ZCA	Zip Code area

GLOSSARY OF STATISTICAL TERMS

Absolute value The absolute value of a number is its numerical value without regard to its sign. For example, 3 is the absolute value of both 3 and −3.

Bootstrapping A method for estimating the sampling distribution of an estimator by repeatedly *sampling with replacement* from the original set of data or observations. Bootstrapping is most often done with the purpose of deriving robust estimates of standard errors and confidence intervals for the "true" population parameters such as the mean, median, and proportion and when collecting additional data is not feasible. It may also be used for constructing hypothesis tests. See also *jackknifing* and *sample with replacement*.

Census block The smallest geographic unit used by the United States Census Bureau for tabulating data collected from all homes (rather than a sample of homes). Several blocks make up block groups, which make up census tracts.

Centroid The intersection of all straight lines that divide a two-dimensional figure (such as a polygon) into two parts.

Confounder An extraneous or "unmeasured" factor that may be partly or wholly responsible for the observed relationship between the variable and outcome that have actually been measured. A confounder is statistically associated (positively or negatively) with both the exposure of interest and the observed outcome (both the *independent and dependent variables*). For example, regular coffee drinkers are more likely to smoke than people who do not drink coffee. Therefore, any study to link coffee drinking with cancer would need to take participants' smoking habits into account as a possible confounder. A confounder must be accounted for in an analysis so you know if the observed association is not entirely attributable to the confounder.

Construct validity The agreement between the theoretical properties of the object being studied and the properties of the specific measure of that object used.

Dependent and independent variables In an experiment, the dependent variable is the "event" being studied that is expected to change when the independent variable is changed. An independent variable is one whose value is controlled or selected by the experimenter to determine its relationship to the dependent variable. In the current study, the dependent variable is mortality data, and the independent variables are $PM_{2.5}$ exposure data, individual-level covariates, and information about communities.

Explanatory power The ability of a model or theory to account for the observed phenomenon.

Geostatistics Originally applied to problems in geology; it involves statistical procedures to describe and analyze patterns and associations in spatially defined (geographic) data (that is, data whose values are associated with locations in space).

Gini coefficient A measure of statistical dispersion most prominently used as a measure of inequality of income or wealth distribution within a defined area (such as a city, state, or country). It is presented as a ratio with values between 0 and 1: A low value indicates relatively uniform income or wealth distribution and a high value indicates unequal distribution.

Heteroskedasticity In statistics, a sequence of random variables displays heteroskedasticity if the variables have different variances.

Inverse distance weighting (IDW) A process of assigning values to location points for which measured values are unavailable using existing values, usually from a scattered set of known location points. The contribution of existing values to the estimated value are weighted by the inverse of their distance from the estimated location point (that is, closer values receive greater weight); used for multivariate interpolation.

Jackknifing An analytical method that estimates the precision of sample statistics (means, medians, variances, percentiles) using subsets of an available data set with each data point systematically removed and replaced. Jackknifing assesses the sensitivity of calculated statistics to the presence or absence of a single data point. See also *bootstrapping*.

Kernel A mathematical method used to identify the underlying structure of complex data. Nonlinear clustering methods based on kernels provide a common means of resolving patterns in spatially correlated data.

Kriging A family of geostatistical techniques that use the distance between data points and the degree of variation to interpolate or estimate values across a surface (e.g., geographic area) or for unsampled locations.

Manual forward selection process A process of manually adding variables one by one to a regression model, instead of allowing the statistics program to automatically select which variables to add.

Multiple linear regression model A model used to analyze the relationship between a set of *independent variables* and a *dependent variable*.

Nested analysis An analysis that statistically accounts for the effects of the structure of the data, and in which the values for a variable are dependent on the values of the class of variables to which they belong. For example,

health status may be associated with one's neighborhood of residence or city or state; but it may also be related to which neighborhood within the city, and which city within the state, and even to the neighborhood within that city and state together. A nested analysis accounts for these joint effects at different geographic levels.

Orthogonality The quality of being completely independent. When performing statistical analysis, variables that affect a particular result are said to be orthogonal if they are uncorrelated; that is, their statistical relationship is zero.

Orthophoto An aerial photograph that has been geometrically corrected so the scale is uniform; like a map, it lacks distortion. Unlike an uncorrected aerial photograph, an orthophoto can be used to measure true distances, because it is an accurate representation of the earth's surface, having been adjusted for topographic relief, lens distortion, and camera tilt.

Principal component analysis A statistical procedure for reducing the number of variables in an analysis. It combines variables that appear to be correlated into a smaller number of artificial, but uncorrelated, variables called principal components. The resulting principal components may then be included as independent variables in statistical analyses with the expectation that they will account for most of the variance in the dependent or observed variables.

Queen contiguity matrix A matrix in which each element is considered to be the neighbor of another element if it shares a border or vertices with the observation of interest. It is used to characterize spatial contiguity between spatial units (such as a *Thiessen polygon* or a Zip Code area) in which both border and vertices are used to define contiguity.

Random effects Cox model In statistics, many models proceed from the assumption that observed values are independent of one another — that information for any given participant is completely unrelated to information on another. A random effects model does not assume that observations are independent. For example, it does not assume that people living in the same neighborhood or household have completely unrelated dietary or smoking habits, pollution exposures, or health status. See also *standard Cox model*.

Residual (or fitting error) An observable estimate of the unobservable statistical error. For example, if you have a random sample of *n* men whose heights are measured, and the mean of the sample is used as an estimate of the (unobservable) population mean, then:

- the difference between the height of each man in the sample and the unobservable population mean is a statistical error; and
- the difference between the height of each man in the sample and the observable sample mean (predicted height) is a residual.

See also *statistical error*.

Root mean squared error A frequently used measure of the mean of the differences between values predicted by a model or by an estimator and the values actually observed. A measure of fit. See also *residual*.

Sample with replacement A sampling method that involves randomly selecting a specified number of data points for analysis, and returning them to the population before randomly selecting another set of data points. Because these data points are not permanently removed, the population remains intact. If the randomly sampled set of data points had been deleted, the probability for selecting an equivalent set of points in the next sample would be changed.

Semivariogram / variogram A mathematical function used in geostatistics to visualize the spatial or the temporal correlation of data.

Spatial analysis Any of the formal techniques for studying entities using their topological, geometric, or geographic properties.

Spearman rank correlation coefficient A measure of correlation (relationship) between two variables that does not make any assumptions about the shape of the distribution of the observed values. It measures the correspondence between the rankings of observations for each variable in the data and assesses its significance.

Standard Cox proportional-hazards regression model of survival A proportional-hazards model is a subclass of statistical survival models. Survival analysis deals with time until event, death, or failure. Survival models consist of two parts: the underlying hazard function, which describes how hazard (or risk) changes over time; and the effect parameters, which describe how hazard may be affected by other factors, such as the choice of treatment for an illness. The proportional-hazards assumption is that effect parameters multiply hazard in a constant manner over the study follow-up time: For example, if taking drug *X* reduces your hazard by half at time 0, it also does so at time 1, or time 0.5, or at any time *t*. The effect parameter(s) estimated by any proportional-hazards model can be reported as hazard ratios.

Sir David Cox observed that if the proportional-hazards assumption holds (or is assumed to hold), then it is possible to estimate the effect parameter(s) without any consideration of the hazard function. This approach to survival data is referred to as applying the Cox proportional-hazards model (referred to as *standard Cox model* in this report).

Stationarity / nonstationarity Qualities of a random process: the statistical properties (such as mean and standard deviation) of a process that exhibit stationarity do not change over time or across space. If the process exhibits nonstationarity, the statistical properties do change.

Statistical error The amount by which an observation differs from its expected value, which is based on the whole population from which the statistical unit was randomly chosen. The expected value — for example, the mean of the entire population — is typically unobservable. See also *residual*.

Thiessen polygons A type of Voronoi diagram used to analyze spatially distributed data (such as air pollution measurements). A Thiessen polygon defines the area of influence around one of a set of points (e.g., an air pollution monitor). The boundaries of the polygon define the area that is closest to each point relative to all other points. The center of the polygon is called the *centroid*.

Variance The amount of variation among the data measured for one variable. It is a measure of the distribution of values.

Variance inflation factor (VIF) An index that measures how much the variance of a coefficient (square of the standard deviation) is increased because of multicollinearity. Multicollinearity is a statistical phenomenon in which two or more predictor variables in a multiple regression model are highly correlated.

(Glossary prepared by Health Effects Institute)

Research Report 140, *Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality,* D. Krewski et al.

INTRODUCTION

In their report to HEI, Dr. Daniel Krewski and colleagues provide details of Phase III of the Particle Epidemiology Evaluation Project, which summarizes their research with the cohort from the American Cancer Society (ACS*) Cancer Prevention Study II (CPS-II), an ongoing prospective study of mortality among adults residing across the United States and in Puerto Rico. In Phases I and II of their research (referred to here as the Reanalysis Project; Krewski et al. 2000), Krewski and colleagues validated and replicated earlier results from other investigators of associations between exposure to particulate air pollution and mortality and then used their data to try new methods of analysis that incorporated individual-level and ecologic covariates.

Dr. Krewski submitted a preliminary application to HEI in February 2001, requesting funds to conduct a third phase of his analysis of the ACS cohort. Later that year, he submitted a full application, and in February 2002, HEI approved the project.

The HEI Research Committee chose to fund Phase III (referred to here as the Extended Analysis) because they believed it would yield further important information about the effects of long-term exposure to air pollution on mortality. During the Reanalysis Project, Krewski and colleagues had developed new statistical models to incorporate city-level ecologic covariates and control for spatial autocorrelation in the data. For this Extended Analysis, they planned to apply updated statistical methods to new follow-up data (through 2000) for the ACS cohort. This cohort remains a key source of information on the effects of long-term exposure to air pollution on mortality from chronic disease. Among the many uses of the ACS results in U.S., European, and global risk analyses is the use of health risk estimates that resulted from the Reanalysis Project by the U.S. Environmental Protection Agency (U.S. EPA) in the development of the cost–benefit analyses for regulations of emissions from heavy-duty diesel engines. Past results from studies of this cohort along with the Phase III results are also being considered in the current U.S. EPA process for reviewing the National Ambient Air Quality Standard (NAAQS) for fine particles (particulate matter 2.5 μm or smaller in aerodynamic diameter [$PM_{2.5}$]).

BACKGROUND

Epidemiologic studies conducted over several decades have suggested that long-term exposure to elevated ambient levels of particulate air pollution is associated with increased premature mortality. Commentary Table 1 summarizes the details of some key cohort studies that have found and continue to corroborate and further define the relationship between exposure to $PM_{2.5}$ and mortality.

Two U.S. cohort studies became central to the 1997 debate on the NAAQS for $PM_{2.5}$ pollution in the United States: the Harvard Six Cities Study (Dockery et al. 1993), a 20-year prospective cohort study begun in the 1970s, and the ACS study (Pope et al. 1995), a larger retrospective cohort study initiated in 1982 and involving data from 151 cities. Both of these studies estimated exposure to $PM_{2.5}$ based on ambient air monitoring data, and both reported that the risk of death from all causes increased in association with exposure to higher annual average concentrations of $PM_{2.5}$.

Several analyses of these two cohorts were also considered in the EPA review of the NAAQS for $PM_{2.5}$ in 2006. Other important cohort studies that were considered in that review included the Seventh-Day Adventist Health Study of Smog (AHSMOG; Abbey et al. 1999) and the Veterans study (Lipfert et al. 2006; U.S. EPA 2006). Results from the AHSMOG cohort provided some suggestive but less conclusive evidence, and evidence from the Veterans cohort was inconsistent. Nevertheless, looking at all the available evidence, the U.S. EPA concluded that overall the epidemiologic evidence of an association between long-term exposure to $PM_{2.5}$ and mortality was strong (U.S. EPA 2004).

Dr. Krewski's 4-year study, "Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality," began in May 2002. Total expenditures were $425,000. The draft Investigators' Report from Krewski and colleagues was received for review in January 2007. A revised report, received in January 2008, was accepted for publication in June 2008. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and in the Review Committee's Commentary.

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

Commentary Table 1. Key Prospective Long-Term Cohort Studies of Air Pollution and Mortality

Study	Cohort	Exposure Data	Analysis	Results
Studies That Used Data from Cohort Studies Other Than ACS				
Harvard Six Cities (Dockery et al. 1993)	8111 adults in the study of health effects of air pollution; cohort followed prospectively for 14–16 years starting in 1974	Ambient concentrations measured in each community at a centrally located air monitoring station: TSP, SO_2, O_3, suspended SO_4^{2-} for 1977–1985; inhalable and fine particles 1979–1985; SO_4^{2-} particles 1979–1984; aerosol acidity 1985–1988	Adjusted mortality rate ratios for air pollution estimated by simultaneously adjusting for other risk factors in standard Cox model; subjects stratified according to sex and 5-year age group	Adjusted mortality rate ratio for the most-polluted city compared with the least-polluted city was 1.26 (95% CI 1.08–1.47); air pollution weakly associated with death from lung cancer and cardiopulmonary disease; $PM_{2.5}$ and SO_4^{2-} strongly associated with mortality
Seventh-Day Adventist Health Study of Smog (AHSMOG; Abbey et al. 1999)	6338 nonsmokers, white, ages 25–97 years, residents of California, enrolled before 1977	Days per year when PM_{10} exceeded 100 μg/m^3 as measured by California Air Resources Board monitors	Relative risks calculated using standard Cox model, controlled for age, smoking, passive smoke exposure, occupation, diet, body mass index, and family history of chronic disease	Relative risk for an increase of 43 days per year above 100 μg/m^3 PM_{10} and mortality from all natural causes was 1.12 (95% CI 1.01–1.24) for males; for mortality from nonmalignant respiratory disease RR was 1.28 (95% CI 1.03–1.57) for males; no significant associations found for women or for PM_{10} exposure
Veterans' Cohort Mortality Study (Lipfert et al. 2000)	50,000 male U.S. military veterans diagnosed with hypertension in the mid-1970s; average age at recruitment 51 ± 12 years; cohort followed for ~21 years	Pollutant levels averaged by year and county for $PM_{2.5}$, coarse particles, and PM_{15} data from the U.S. EPA IPMN 1979–1984	Standard Cox model controlled for race, smoking, age, blood pressure, body mass index, and "selected ecologic variables" at the Zip Code and county levels	$PM_{2.5}$ was not associated with any significant (positive) excess in mortality risk for any of the models evaluated
Women's Health Initiative (Miller et al. 2007)	65,893 post-menopausal women without preexisting cardiovascular disease in 36 U.S. metropolitan areas; cohort followed 1994–1998	Exposure to $PM_{2.5}$ assessed at monitor nearest to residence	Hazard ratios estimated for the first cardiovascular event or for death from cardiovascular disease; adjusted for age, race, diabetes, hypertension, and hypercholesterolemia	Difference of 10 μg/m^3 $PM_{2.5}$ associated with 24% increase in risk of a cardiovascular event (relative risk 1.24; 95% CI 1.09–1.41) and 76% increase in risk of cardiovascular mortality (RR 1.76; 95% CI 1.25–2.47)
*NLCS-AIR (Beelen et al. 2008; Brunekreef et al. 2009)	120,740 residents of the Netherlands, ages 55–69, enrolled in 1986; cohort followed 1987–1996	Combination of regional, urban, and local exposure (1976–1996 averages) determined from monitoring station data and land-use regression and assigned to participants' residence locations; separate background (urban plus regional) level used with various measures of exposure to traffic	Relative risks calculated using standard Cox model; analyses controlled for personal risk factors, and for community income levels at the local and regional scales	Relative risks for a 10-μg/m^3 change in black-smoke exposure; associated with lung cancer incidence in nonsmokers (RR 1.47; 95% CI 1.01–2.61), mortality from natural causes (RR 1.05; 95% CI 1.00–1.11), and respiratory causes (RR 1.22; 95% CI 0.99–1.50)

Table continues next page

* Study funded by HEI.

Commentary Table 1 (*Continued*). Key Prospective Long-Term Cohort Studies of Air Pollution and Mortality

Study	Cohort	Exposure Data	Analysis	Results
Studies That Used Data from the ACS CPS-II Cohort				
Original ACS CPS-II study (Pope et al. 1995)	552,138 adults enrolled in 1982; included data for individual risk factors; deaths ascertained through 1989	Ambient data for 151 U.S. metropolitan areas in 1980; SO_4^{2-} and $PM_{2.5}$ estimated from national data bases and used as indices of exposure to combustion-source ambient PM	Multivariate analysis used to examine relationships of air pollution with mortality from all causes, lung cancer, and cardiopulmonary disease; analysis controlled for smoking, education, and other risk factors	Increased mortality associated with SO_4^{2-} and $PM_{2.5}$ air pollution at levels commonly found in U.S. cities
*Reanalysis Project (Krewski et al. 2000)	Same cohort data as in the original study but subjected to additional quality control procedures	Same exposure data and assignment to participants as in the original study but with additional quality control procedures and data validation by audit	Phase I — Replication and validation of Harvard Six Cities (Dockery et al. 1993) and ACS CPS-II results Phase II — Sensitivity analysis to compare results from alternative risk models using different hazard functions and spatial factors	Phase I — Mortality association with SO_4^{2-} and $PM_{2.5}$ compared closely with findings from original study Phase II — Positive associations between mortality and pollutants robust to control for confounding, analytic methods used, and adjustment for spatial autocorrelation
Updated Analysis (Pope et al. 2002)	500,000 adults in ACS CPS-II enrolled in 1982; included data for individual risk factors; deaths ascertained through 1998	Mean concentrations of air pollution for metropolitan areas compiled from various primary data sources including EPA AIRS, IPMN, and NAD; extracted from IPMN for 1979–1983 and AIRS for 1999–2000	Adjusted relative risk ratios for mortality estimated using standard Cox model including metropolitan-based random effects component; estimated for mortality from all causes, cardiopulmonary disease, lung cancer, and all remaining causes	$PM_{2.5}$, SO_4^{2-}, and SO_2 pollution associated with mortality from all causes, cardiopulmonary disease, and lung cancer; $PM_{2.5}$ found to be an important environmental risk factor for death from cardiopulmonary disease and lung cancer
Updated Analysis (Pope et al. 2004)	319,000 adults in areas with $PM_{2.5}$ monitoring data for 1979–1983 and 1999–2000; 500,000 adults in areas with $PM_{2.5}$ monitoring data for 1999–2000	$PM_{2.5}$ monitoring data from IPMN for 1979–1983 and from AIRS for 1999–2000 and annual average $PM_{2.5}$ exposure assigned to participants	Standard Cox model used to calculate relative risk ratios per 10-μg/m^3 change in $PM_{2.5}$ for sub-categories of cardiopulmonary disease; controlled for available individual risk factors	Long-term $PM_{2.5}$ exposures most strongly associated with mortality attributed to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest; weak associations with respiratory mortality

* Study funded by HEI.

THE HARVARD SIX CITIES STUDY

As part of the Harvard Six Cities Study, Dockery and colleagues (1993) had prospectively followed a cohort of 8111 adult subjects in the Northeast and Midwest regions of the United States for 14 to 16 years, beginning in the mid-1970s. For these analyses, data from the most-polluted city were compared with those from the least-polluted city and the results were described as being associated with the difference in concentrations between the two cities. A difference of 18.6 $\mu g/m^3$ $PM_{2.5}$ was associated with a 26% increase in mortality from all causes. The same difference in $PM_{2.5}$ was associated with a 37% increase in deaths from cardiopulmonary disease. A follow-up study of this cohort conducted in a period of lower air pollution and including 8 additional years of mortality data showed that associations between pollutant exposure and risk of mortality were also lower (Laden et al. 2006).

THE ACS STUDY

In the past 15 years, the ACS cohort has been the subject of numerous analyses and a primary source of information on air pollution exposure and associated mortality for risk estimates and policy making throughout the world. The various ACS cohort analyses, including those from the study reported here, are listed in Commentary Table 2. (A more detailed description of each study, except the current one, is found in Commentary Table 1.)

In the original ACS study, Pope and colleagues (1995) followed 552,138 adult subjects in 151 U.S. cities from 1982 through 1989. Again, higher ambient levels of $PM_{2.5}$ were associated with increased mortality from all causes and from cardiopulmonary disease in the 50 cities for which $PM_{2.5}$ data were available (data from monitors for 1979 to 1983). Higher ambient SO_4^{2-} levels were associated with increased mortality from all causes, cardiopulmonary disease, and lung cancer in the 151 cities for which SO_4^{2-} data were available (data from monitors for 1980 to 1982). The difference in all-cause mortality between the most-polluted city and the least-polluted city was 17% for $PM_{2.5}$ and 15% for SO_4^{2-} (the difference in the pollutant levels was 24.5 $\mu g/m^3$ for $PM_{2.5}$ and 19.9 $\mu g/m^3$ for SO_4^{2-}).

Although these two cohort studies produced similar results, they differed in design and limitations. Important strengths of the Six Cities Study included the random selection of study subjects; the high response rate of participants enrolling (> 70%); the personal interviews conducted with respondents at the time of enrollment and subsequent follow-up interviews at intervals of 3, 6, and 12 years; lung-function measurements at baseline; and the gathering of residential histories. The air pollution measurements were collected by the research team, who had designed the Six Cities Study to monitor a range of air pollutants that was nearly as large as that used for the ACS study. A limitation was that exposure for each pollutant was represented in each city by one average level for the span of years, so only 6 air pollutant data points were used to estimate the exposure–response function.

Important strengths of the ACS study were the number of cities studied (151); the very large cohort of subjects enrolled; and the extensive information collected for the enrollment questionnaire on health status, demographic characteristics, smoking history, alcohol use, and occupational exposure. One limitation was that these subjects were enrolled by ACS volunteers from among their friends and relatives so the subjects may not be representative of the general population. Another was that the air quality measurements were not designed for this study; they were obtained from monitors set up and maintained by the U.S. EPA.

In 1997, the two studies came under intense scrutiny when the U.S. EPA used the results to support new NAAQS standards for $PM_{2.5}$ and to maintain the standards for particles of 10 µm or smaller in aerodynamic diameter (PM_{10}) that were already in effect. Members of Congress and industry, the scientific community, and others interested in the regulation of air quality scrutinized the studies' methods and their results. Some insisted that any data used in studies that were conducted with federal funding should be made public. Others argued that the individual health and mortality data had been gathered with assurances of confidentiality for the individuals who had agreed to participate. Still others claimed that the concept of public access to federally funded data did not take into account the intellectual property rights of the investigators and their supporting institutions. To address the public controversy, Harvard University, the ACS, Congress, the U.S. EPA, and representatives of the motor vehicle industry requested that

Commentary Table 2. Studies of Air Pollution and Public Health That Used the ACS CPS-II Cohort

Principal Investigator	Publication Year	End of Follow Up[a] (*n* Years)
Pope (Original)	1995	1989 (7)
Krewski[b] (Reanalysis)	2000	1989 (7)
Pope (Updated)	2002	1998 (16)
Pope (Updated)	2004	1998 (16)
Krewski (Current Extended)	2009	2000 (18)

[a] Cohort was enrolled 1982.

[b] Part of the HEI-funded Reanalysis of both the original ACS study (Pope et al. 1995) and the Harvard Six Cities Study (Dockery et al. 1993).

the Health Effects Institute organize an independent reanalysis of the data from these studies. The investigators agreed to provide access to their data to a team of analysts to be selected by HEI through a competitive process. HEI's Board of Directors approved the request. HEI then assembled an Expert Panel to provide scientific oversight of the Reanalysis Project on HEI's behalf and to ensure that the Reanalysis would be conducted by independent and impartial investigators. The Panel recommended that Dr. Daniel Krewski of the University of Ottawa and his team conduct the Reanalysis. The HEI Board of Directors approved the Panel's recommendation of Dr. Krewski in November 1997.

THE REANALYSIS PROJECT

The overall objective of the Particle Epidemiology Reanalysis Project (Krewski et al. 2000) was to conduct a rigorous and independent assessment of the findings of the Six Cities and ACS studies of air pollution and mortality (Dockery et al. 1993; Pope et al. 1995). This objective was met in two phases. In *Phase I: Replication and Validation*, the Reanalysis Team sought to replicate the initial studies through a quality assurance audit of a sample of the original data and to validate the original numerical results. In *Phase II: Sensitivity Analyses*, they tested the robustness of the original analyses to alternative risk models and analytic approaches, including models that used different hazard functions and models that incorporated spatial factors (Krewski et al. 2000). Overall, the Reanalysis confirmed the quality of the original data, replicated the original results, and validated those results using alternative risk models and analytic approaches; none of them substantively altered the original finding of an association between indicators of particulate air pollution and mortality.

THE UPDATED ANALYSIS

After the Reanalysis Project, Pope and colleagues undertook a subsequent set of analyses of the ACS cohort data using an additional 10 years of data (covering 1982 through 1998), thus doubling the follow-up time to more than 16 years and tripling the number of deaths. Exposure data were expanded to include data on gaseous copollutants and new $PM_{2.5}$ data that had been collected since the enactment of the new air quality standards. Recent advances in statistical modeling were incorporated in the analyses, including the introduction of random effects and nonparametric spatial smoothing components into the standard Cox proportional-hazards regression model of survival (referred to as the standard Cox model; see Glossary of Statistical Terms in the Investigators' Report). This Updated Analysis provided the strongest evidence that the long-term exposure to fine particulate air pollution that is common to many metropolitan areas is an important risk factor for death from lung cancer and cardiopulmonary disease (Pope et al. 2002). Each 10-μg/m^3 increase in long-term average ambient $PM_{2.5}$ concentrations was associated with approximately a 4%, 6%, or 8% increase in risk of death from all causes, cardiopulmonary disease, and lung cancer, respectively. There was no evidence of a threshold exposure level within the range of observed $PM_{2.5}$ concentrations. There was also no statistically significant evidence that the survival data were spatially autocorrelated after controlling for fine particulate air pollution and the various individual-level risk factors. Graphic examination of the residual mortality also revealed no significant spatial autocorrelation with distance between metropolitan areas.

In the Updated Analysis of the ACS cohort data published in 2004, Pope and colleagues refined their classification of causes of death within the cardiopulmonary category by separately analyzing ischemic heart disease, dysrhythmias, hypertensive disease, atherosclerosis, chronic obstructive pulmonary disease, pneumonia, and other subcategories of cardiovascular and respiratory causes of death. They found significantly increased risks of death (ranging from 8% to 18% per 10-μg/m^3 increase in $PM_{2.5}$) for the various subcategories of cardiovascular causes of death (ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest) and only nonsignificant associations for all respiratory subcategories. This study demonstrated that the strongest association between $PM_{2.5}$ exposure and mortality within the broadly defined cardiopulmonary category is for death from ischemic heart disease.

THE EXTENDED ANALYSIS

The current study, conducted by Daniel Krewski and colleagues, extends the follow-up period for the ACS cohort through 2000 (18 years). The investigators have continued to produce nationwide estimates of the risk of death from various causes using additional years of data. In addition, this project extended the range of analyses to include the following:

- A Nationwide Analysis integrating control for spatial autocorrelation and socioeconomic covariates at the neighborhood (Zip Code area [ZCA]) and city (metropolitan statistical area [MSA]) scales in a single statistical model;
- Intra-Urban Analyses for the New York City and Los Angeles regions featuring land-use regression (LUR) techniques to refine estimates of exposure from local sources (e.g., traffic and industry); and

- An exploration of Critical Exposure Time Windows through analyzing estimated average exposures for up to 5 years, 6 to 10 years, and 11 to 15 years before death to test whether longer-term or more recent exposures might have a stronger effect on premature mortality.

These refinements of methods and additional analyses were intended to further explore the relationships between air pollution exposure and mortality by incorporating sophisticated controls for known sources of bias and confounding in the statistical models.

STUDY SUMMARY

SPECIFIC AIMS

Phase III of the Particle Epidemiology Reanalysis Project, presented in this report, was designed to further analyze associations between air pollution and mortality in U.S. cities using alternative spatial models and to extend the follow-up of the ACS CPS-II cohort to 18 years. Dr. Krewski and his team proposed to address four key research questions in this study:

1. Do social, economic, and demographic (ecologic) variables confound or modify the relationship between particulate air pollution and mortality?
2. How can spatial autocorrelation and multiple levels of spatial analysis be taken into account within the random effects Cox model?
3. What critical time periods of exposure affect the association between air pollution and mortality?
4. How does refining the exposure gradient to the intra-urban level affect the size and significance of health effects estimates?

To achieve Specific Aims 1 and 2, the investigators performed a Nationwide Analysis of air pollution exposure and mortality using an innovative extension to the standard Cox model. It relaxed the assumption that cohort observations are independent, thus enabling the researchers to include multiple levels of nested variables and control for spatial autocorrelation within a single model (referred to as the random effects Cox model). This method contrasts with earlier two-stage analyses of this cohort that used the standard Cox model to produce city-specific estimates of mortality risk and then calculated a nationwide risk estimate from a regression of these city estimates and ecologic covariates (variables that represent local social, economic, and environmental conditions that are known or suspected to influence mortality).

The researchers addressed Specific Aim 3 (Critical Exposure Time Windows) by calculating average exposure concentrations in 5-year time windows and analyzing their relationship with patterns of mortality in the cohort. The Specific Aim 4 (Intra-Urban Analyses), added in year 2 of the study, was carried out in collaboration with a team of researchers led by Dr. Michael Jerrett. This team built separate LUR models to estimate exposure for the New York City and Los Angeles regions using local land-use and traffic data to supplement ambient monitoring data for $PM_{2.5}$. ACS cohort mortality data for these cities were analyzed with the locally refined exposure assessments using the same methods used in the Nationwide Analysis. Each of these research efforts is described in greater detail below.

SOURCES OF DATA

Study Population

In late 1982, volunteers from the ACS recruited participants in the 50 U.S. states, Puerto Rico, and the District of Columbia for a large prospective cancer prevention study (ACS CPS-II) of 1.2 million adults. The ACS allowed air pollution researchers access to the cohort data for the original study of air pollution and mortality (Pope et al. 1995), the HEI-sponsored Reanalysis Project (Krewski et al. 2000), the Updated Analysis (Pope et al. 2002, 2004), and the current Extended Analysis reported here. For the purposes of air pollution research, the cohort has been restricted to participants who reside in metropolitan areas of the contiguous 48 states and District of Columbia that have adequate air pollution monitoring data for the study period. This yielded approximately 575,000 total participants for the air pollution study, including about 360,000 and 500,000 who resided in areas with adequate $PM_{2.5}$ monitoring information in 1980 and in 2000, respectively.

At enrollment in 1982, participants were at least 30 years of age and were members of households with at least one person 45 years of age or older. Participants filled out an extensive questionnaire that included personal demographic characteristics, personal habits, occupational history and exposures, tobacco and alcohol use, and other factors possibly related to mortality from cancer. These questionnaires provided data for the 44 individual-level covariates (see details in the 44 Individual-Level Covariates sidebar in the Investigators' Report) used in these and other analyses of the cohort. Covariate data are summarized in Table 31 of the Investigators' Report.

The ACS has followed this cohort using volunteers to contact participants in 1984, 1986, and 1988, and to gather data through the National Death Index thereafter. They obtained death certificates for participants who were

known to have died and compiled cause-of-death information. Causes of death analyzed in this study fall into these categories: all causes, cardiopulmonary disease, ischemic heart disease, lung cancer, and all other causes. The original study and the Reanalysis of this cohort contained follow-up information through 1989, the Updated Analysis through 1998, and this Extended Analysis through 2000 — 11 additional years of follow-up that were unavailable for the initial studies.

In addition to the individual-level covariate information from the ACS enrollment questionnaires, Dr. Krewski's research team gathered data for seven ecologic covariates to use in their analyses. Ecologic covariates are intended to represent local neighborhood-level conditions or factors known to or suspected of influencing mortality. For example, poverty, level of education attainment, and unemployment in a person's neighborhood are known to influence an individual's health beyond that predicted by a person's own attributes and situation (e.g., diet and exposure to tobacco smoke). Ecologic covariates are included in health research analyses because of a growing awareness that the possible influences of local neighborhood or urban conditions need to be directly accounted for in a health assessment in order to eliminate them as the primary cause of a health outcome (referred to as control of confounding).

For this study, the researchers enumerated ecologic covariates for both the ZCA and city of residence for each participant based on demographic data from the 1980 U.S. Census. These neighborhood factors included prevalence of air conditioning use, percentage of residents who completed high school, percentage of residents who were not white, unemployment, median household income, relative income disparity (income distributed within neighborhoods and cities), and percentage of persons who live in poverty (see details in the Ecologic Covariates sidebar and Table 2 of the Investigators' Report).

Air Pollutants

Air pollutant exposure was estimated from data gathered by several air pollution monitoring systems throughout the continental United States. These networks are run either by the U.S. EPA or by state and local organizations in conjunction with the U.S. EPA. Pollutants and the distributions of exposure to them appear in Table 1 of the Investigators' Report.

$PM_{2.5}$ data were obtained for cities in the Inhalable Particle Monitoring Network (IPMN) and the Aerometric Information Retrieval System (AIRS). Long-term exposure variables were constructed to study how exposure early and late in the follow-up years might have affected the association between particulate exposure and mortality and to compare results from the Nationwide and Intra-Urban Analyses: $PM_{2.5}$ and PM_{15} levels for 1979–1983 were averaged from IPMN data, and $PM_{2.5}$ levels for 1999–2000, which were averaged from AIRS data. Dr. Krewski's team constructed similar variables for long-term exposure to other pollutants of interest from single-year (1980) averages: total suspended particles (TSP) from National Aerometric Database (NAD) data, and ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) from AIRS data. Additional O_3 data for April through September of 1980 represented the peak seasonal average exposure, which was calculated from third-quarter 1980 AIRS data. SO_4^{2-} levels for 1980–1981 were averaged from IPMN and NAD data and SO_4^{2-} levels for 1990 were supplied by the New York University investigators.

METHODS FOR EACH ANALYSIS

NATIONWIDE ANALYSIS (SPECIFIC AIMS 1 AND 2)

In order to address Specific Aim 1 (Do social, economic, and demographic [ecologic] variables confound or modify the relationship between particulate air pollution and mortality?), Dr. Krewski's team used pollutant data for MSAs and ecologic covariate data at both the ZCA and MSA scales.

As shown in Table 1 of the Investigators' Report, the number of MSAs with sufficient monitoring data for exposure assessment and the resulting total number of CPS-II participants varied for the different pollutants. For each monitor site, averages of measurements for each pollutant for each of the years of interest were computed and averaged to obtain a summary concentration for the monitor. If a metropolitan area included more than one monitor, the mean concentration of each pollutant from all available monitoring sites was calculated in order to obtain the exposure level to assign to each participant who lived in the MSA (see also Pope et al. 2004).

For ecologic covariates, the research team encountered difficulties extracting information from the 1980 U.S. Census database at the ZCA scale. Zip Codes are used by the U.S. Postal Service to simplify the delivery of mail and are not necessarily areas with well-defined boundaries. The U. S. Census Bureau has therefore defined ZCAs to approximate the land areas covered by Zip Codes. Some Zip Codes were for post office boxes and commercial areas, not for residences, and others could not be matched to Census ZCAs, paper maps, or private data sources. Despite these difficulties, approximately 10,000 of the nearly 12,000 Zip Codes listed for CPS-II participants in 1982 were successfully connected with ZCAs listed for the 1980 Census.

For each ecologic covariate, ZCA-scale data from the U.S. Census Bureau files were averaged to obtain a value

for each MSA. The difference between the ZCA value and the MSA value for each ecologic covariate is referred to as DIFF. The DIFF values represent the variability of the ecologic covariates at the ZCA level within their MSA. Because the MSA value and ZCA values are highly correlated by definition (the MSA value is the mean of ZCA values), statistical instability might arise from using the MSA and the ZCA values together if the ZCA values were not adjusted for the MSA value.

Survival analyses are frequently used in long-term cohort studies of air pollution exposure and mortality. In this survival analysis, a fixed number of participants are followed over time; mortality data are collected as members die, and no new members are recruited. Groups of participants are classified according to exposure level, and subgroups are compared with each other to understand how levels of exposure may affect the number of cohort members who die and the causes of death over the life of the cohort. Risk analyses are typically adjusted for age, smoking status, sex, and other variables known to affect longevity that could confound the relationship between pollutant exposure and death. The resulting comparisons yield a hazard ratio (HR) or a relative risk of mortality based on exposure to the pollutant of interest.

Dr. Krewski's team chose the standard Cox model to calculate hazard ratios for the various causes of death associated with the levels of air pollution exposure experienced by the cohort. They used two variations of this model for their statistical analysis: the standard Cox model and the random effects Cox model.

The standard Cox model assumes that the mortality experience of individuals in the study is independent (after adjusting for covariates), even for participants living in the same household or neighborhood. However, it is possible that mortality experience for people in the same community will be more similar than that for people in different communities, even after controlling for all available risk factors. Lack of statistical control for these factors can bias the estimate of air pollution's effect on health. Despite these limitations, the researchers used the standard Cox model to test each of the pollutant and cause-of-death combinations of interest in the Nationwide Analysis to find those with the strongest associations. They then explored the selected pollutant–cause of death combinations with the far more computationally powerful random effects Cox model, which allowed them to account for spatial autocorrelation and include multiple levels of spatially defined covariates (Specific Aim 2).

The random effects Cox model relaxes the assumption that every participant's mortality experience is independent of that of his or her neighbors. It permits the researcher to account for (1) the statistical similarity in the risk of mortality often found in persons living near each other (also known as spatial autocorrelation), and (2) the joint effects of neighborhood-level and city-level variables. Dr. Krewski and colleagues developed the random effects Cox model as an extension to the standard Cox model specifically to analyze the complex spatial patterns of risk in the CPS-II data.

INTRA-URBAN ANALYSES (SPECIFIC AIM 4)

In order to address Specific Aim 4 (How does refining the exposure gradient to the intra-urban level affect the size and significance of health effects estimates?), the research team collaborated with investigators in New York City and Los Angeles, two very large metropolitan areas that have extensive pollution monitoring networks. Their goal was to estimate mortality risks associated with exposure to $PM_{2.5}$ in urban areas and compare them with those obtained from the Nationwide Analysis. In the Intra-Urban Analyses, however, they would use land-use data to estimate exposure locally and comprehensively, whereas in the Nationwide Analysis, they had assigned exposure according to metropolitan area averages. These analyses differed from the Nationwide Analysis in the following ways:

- Exposure was restricted to $PM_{2.5}$ in a single large metropolitan area.
- Additional monitoring data were available at local levels.
- A variety of markers of emissions (most notably nearby vehicle emissions) and local exposures were used to estimate participants' exposures.
- Kriging and LUR statistical methods were used to estimate and assign local exposures to participants rather than assigning the same MSA average value to everyone.

New York City Analysis

The investigators used New York City data on pollutants and the CPS-II cohort mortality data that were used for the Nationwide Analysis. A total of 43,930 CPS-II participants lived in the New York City region at enrollment in 1982, and a total of 10,525 deaths had been recorded for this group during the 18 years of follow-up (1982 through 2000). The team chose to analyze mortality from all causes, ischemic heart disease, cardiopulmonary disease, lung cancer, endocrine disorders, diabetes, digestive cancers and disorders, and accidents.

To estimate pollutant levels, the research team calculated 3-year averages for each monitor from daily monitoring data collected for the U.S. EPA's Air Quality Subsystem (AQS) for 1999 through 2001. In addition, they

used LUR, a relatively new statistical process that estimates pollutant exposures at specific locations by incorporating air pollution monitoring data, road and traffic data, land-use information (e.g., population density, industry, vegetation), and data on emissions from local sources. The ultimate goal was to be able to explain the variations in local exposures over a broad area. In New York City, land use was assessed using traffic counting systems, roadway network maps, satellite photos, and local government planning and tax-assessment maps.

Developing a LUR model requires evaluating land use around pollution monitors using different types of land-use variables to find which ones best predict monitored pollutant levels. Data for a selected set of monitors were used to develop the model, and then the model was used to predict pollutant concentrations at the remaining monitors that had not been used. When the predicted value was compared with the actual measured value at a validation site, the team could assess how accurately the model predicted pollutant exposure at locations without monitors but with similar land-use characteristics. The final LUR model for New York City predicted 66% of the variation in monitored $PM_{2.5}$ concentrations across the study area ($R^2 = 0.66$).

Three LUR models were created for the New York City region: two covering 28 counties (one using a 3-year exposure average and one using only winter exposure averaged over 1 season) and one covering 9 counties using a 3-year exposure average. Only the 28-county models were used in the mortality analysis; the 9-county model was used only for testing methods.

The LUR model results were compared with the results of a spatial interpolation of measured values known as kriging. Using kriging, the investigators produced estimates of exposure for the entire study area by interpolating data from the 62 pollution monitoring sites in the 28-county area. The LUR and kriging models produced similar estimates of pollution levels in cross-validation studies in which data from one monitor were removed from the data set and data from the other monitors were used to estimate exposure at the "missing" monitor's location (the procedure was repeated for each monitor in turn). The authors still chose to use their LUR model to assign exposure to participants (for analyzing mortality) because the LUR was more likely to account for highly local variations in exposure due to traffic patterns and land use in the areas where participants actually resided, whereas kriging relied only on data from nearby pollution monitors.

As with the Nationwide Analysis, the investigators used both the standard Cox and random effects Cox models for analyzing pollutant exposure and mortality. They incorporated the 44 individual-level covariates from the ACS enrollment questionnaire as well as data for the seven ecologic covariates at the ZCA and MSA scales. Even in the 28-county winter-2000 model, the team chose to include the percentage of homes with air conditioning as an ecologic covariate because (1) the availability of air conditioning is a good proxy for the type of home construction; and (2) buildings with air conditioning typically have a relatively low level of infiltration of outdoor air into the structure (and therefore less exposure to outdoor ambient air pollution) in the winter as well as in the summer.

Los Angeles Analysis

The Intra-Urban Analysis in the Los Angeles region included 22,905 ACS CPS-II participants in 267 ZCAs covering five counties; 5,856 deaths had been recorded at the end of 2000. As with the New York City Analysis, associations between exposure and mortality were analyzed for mortality from all causes, ischemic heart disease, cardiopulmonary disease, lung cancer, endocrine disorders, diabetes, digestive cancers and disorders, and accidents. In addition, the Los Angeles Analysis included other cancers and all remaining causes. The investigators used both LUR and kriging methods to estimate exposure concentrations at the center of each ZCA. The standard Cox and random effects Cox models were used to calculate exposure–mortality associations; they included the 44 individual-level covariates (from the ACS enrollment questionnaire) and seven ecologic covariates. Unlike the New York City Analysis, the Los Angeles researchers did not include a seasonal (winter-only) model and they did not construct a test model for a smaller portion of the study area; they did, however, control for O_3 concentrations.

In their attempt to model fine geographic variations in pollutant exposure, the team led by Dr. Jerrett assembled data from a wide variety of sources. For the LUR and kriging models, they started with air monitoring data from several sources including the California EPA database for 23 $PM_{2.5}$ monitors and the California Air Resources Board 42 sites that monitor O_3. Although $PM_{2.5}$ was of primary interest, the Los Angeles Analysis included O_3 concentrations as a copollutant in the health analyses.

To develop the LUR models, the team used data for digital land use, mapped road networks, road classes and speed limits, traffic counts, population, and topography (elevation). The investigators constructed a LUR model for the Los Angeles area that predicted 69% of the variation in local $PM_{2.5}$ concentrations when evaluated using regression diagnostics (as described in the Investigators' Report). Primary predictors of exposure in the LUR model were traffic volume, industrial areas, and government areas (as a proxy for traffic intensity around major destinations such

as schools, government service offices, and hospitals). They do note, however, that this model tended to predict excessively high values in certain high-pollution areas, including several freeway intersections with heavy traffic and the Long Beach area near the port facilities for Los Angeles and Long Beach.

As with the New York City Analysis, the team led by Dr. Jerrett built a kriging model based on data from the 23 $PM_{2.5}$ monitors in the Los Angeles metropolitan area. The results lacked much of the local-area variation in concentrations found with the LUR model. The investigators expected this difference because the monitors had been placed for purposes of federal and state regulatory compliance and did not specifically monitor sources of pollution, such as nearby industry and traffic, or pollutant concentrations in residential areas. A brief comparison of the associations (hazard ratios) for death from various causes and $PM_{2.5}$ exposures modeled using both kriging and LUR for Los Angeles and LUR for New York City is presented in Table 30 of the Investigators' Report and in Commentary Table 3.

The investigators also built two kriging models for exposure to O_3 using data from the 42 monitors. One model mapped the interpolated exposure values based on an average of the four highest 8-hour concentrations for each monitor in 2000. The second one mapped the interpolated values for the expected peak daily concentrations (based on the average daily concentration for each monitor for 1999 through 2001).

The team led by Dr. Jerrett applied the same standard Cox and random effects Cox models used for the Nationwide and New York City Analyses of mortality and exposure concentrations to the Los Angeles region. Unlike the other analyses, Dr. Jerrett's team also included covariates for O_3 exposure because it is sufficiently high in the Los Angeles Basin to be a potential confounder of the relationship between $PM_{2.5}$ exposure and mortality.

CRITICAL EXPOSURE TIME WINDOWS ANALYSIS (SPECIFIC AIM 3)

To address Specific Aim 3 (What critical time periods of exposure affect the association between air pollution and mortality?), Dr. Krewski's team performed an analysis of how exposure to pollutant concentrations in different time intervals might be associated with mortality patterns. This analysis was designed to address hypotheses about long-term exposures — that some time periods of exposure may be more critical than others to possible health outcomes — and whether more recent exposures to air pollution are more or less associated with mortality than exposures much further in the past. The researchers selected three time periods to investigate: 1 to 5 years, 6 to 10 years, and 11 to 15 years before a participant died.

The investigators used the same CPS-II data set used for the Nationwide Analysis to analyze critical time windows of exposure, but with some important distinctions. For one exposure group, they selected participants in the Nutrition Cohort, a subcohort of the CPS-II, to analyze the effect of relocation on exposure and mortality. The Nutrition Cohort was formed in 1992–1993 and composed of 189,194 CPS-II

Commentary Table 3. Selected Hazard Ratios from the Nationwide and Intra-Urban Analyses[a]

	Nationwide[b]	Intra-Urban New York City[c]		Intra-Urban Los Angeles[b]	
Exposure estimation method	MSA Average	LUR		LUR	Kriging
		28-County 3-Year Model	28-County Winter-2000 Model[d]		
Cause of death					
All causes	1.04 (1.03–1.06)	0.87 (0.67–1.13)	0.97 (0.82–1.13)	1.14 (1.03–1.27)	1.17 (1.05–1.30)
Ischemic heart disease	1.18 (1.15–1.22)	1.47 (1.00–2.00)	1.56 (1.21–1.97)	1.33 (1.08–1.63)	1.39 (1.12–1.73)
Cardiopulmonary disease	1.09 (1.06–1.11)	0.67 (0.33–1.07)	1.08 (0.85–1.36)	1.11 (0.97–1.28)	1.12 (0.97–1.30)
Lung cancer	1.09 (1.03–1.15)	0.73 (0.00–1.60)	0.72 (0.26–1.31)	1.39 (0.96–2.01)	1.44 (0.98–2.11)

[a] Results are from random effects Cox models, stratified by age (1-year groupings), sex, and race; adjusted for the 44 individual-level covariates; and adjusted for seven ecologic covariates at the MSA & DIFF levels. HRs are followed by 95% confidence intervals.

[b] HRs for the Nationwide and Los Angeles analyses were calculated for a 10-μg/m^3 change in $PM_{2.5}$.

[c] For easier comparison with Nationwide and Los Angeles results, HRs for the New York City analyses were calculated for a 10-μg/m^3 change in $PM_{2.5}$ converted from data reported for a 1.5-μg/m^3 change in $PM_{2.5}$ for the 28-county 3-year model and from data reported for a 3.9-μg/m^3 change in $PM_{2.5}$ for the 28-county winter-2000 model.

[d] Based on data for January, February, and March 2000.

participants who were between the ages of 50 and 74 years and resided in one of 21 states with population-based cancer registries. These subcohort members completed follow-up questionnaires with detailed questions on diet, physical activity, and other individual-level factors not covered in the initial 1982 enrollment questionnaire and provided updated information in 1997–1998, 1999–2000, and every 2 years thereafter.

From the Nutrition Cohort, the investigators identified approximately 61,000 participants who resided in 106 MSAs with enough available average $PM_{2.5}$ monitoring data; of those, 8181 were known to have moved to another MSA during follow-up. This group is referred to as the $PM_{2.5}$-A group.

A second analysis group (81,466 members in 53 MSAs) was formed from members of the full CPS-II cohort who were not in the Nutrition Cohort and who died while residing in the same MSA in which they were enrolled in 1982; they were assumed to have lived continuously in that MSA from enrollment until death. This group is referred to as the $PM_{2.5}$-B group; the $PM_{2.5}$-B group and the $PM_{2.5}$-A group are mutually exclusive.

A 15-year exposure profile for each member of the $PM_{2.5}$-A and $PM_{2.5}$-B groups was constructed from $PM_{2.5}$ concentrations for the MSA of residence for the three time periods (1 to 5 years, 6 to 10 years, and 11 to 15 years) before his or her death. For participants who were known to have moved, exposures in the new MSAs of residence were also used to create the exposure profiles. For this purpose, $PM_{2.5}$ levels were derived by Lall and colleagues (2004) from average annual measured TSP and PM_{10} concentrations for 1972 through 2000.

A third group included 80,711 Nutrition Cohort participants in 120 MSAs for which at least 20 years of annual average SO_2 measurements were available; 5762 (7.1%) participants moved at least once during the exposure period. Similar exposure profiles for SO_2 were constructed for each participant based on the MSA of residence for 1972 through 2000.

As with all other analyses, the investigators used the standard Cox model to analyze the data, with stratification and adjustment for the 44 individual-level variables from the ACS 1982 enrollment questionnaire. In this set of analyses, however, they used the three 5-year time-period exposure variables instead of the exposure averages for 1980 or 2000. Only one exposure window (1 to 5 years, 6 to 10 years, or 11 to 15 years) was analyzed at a time because the model was designed to avoid statistical complications that would arise if two or more were included together. The $PM_{2.5}$-A and $PM_{2.5}$-B groups were also analyzed separately because they were distinct risk groups.

Dr. Krewski's research team considered the time window with the best-fitting model to be the period during which pollution could have had the strongest influence on mortality. The best-fitting model was judged by the HRs and CIs and by the Akaike information criterion [AIC], a statistical measure of how well a model fits the available data; the lowest AIC value indicates the time window most strongly connected with the pattern of mortality. For example, in Table 26 of the Investigators' Report, the combination of the $PM_{2.5}$-B group, all causes of death, and average exposure 1 to 5 years before death shows an AIC of 933,094.00; for exposure 6 to 10 years in the past, the AIC is 933,094.94; and for exposure 11 to 15 years in the past, the AIC is 933,095.03. The investigators thus ranked the exposure window 1 to 5 years before death as potentially more important than earlier exposure periods, although both the AIC values and HRs were sufficiently close as to be inconclusive.

KEY FINDINGS

NATIONWIDE ANALYSIS

The researchers investigated a suite of U.S. EPA criteria pollutants using the standard Cox model. The primary focus of this project, however, was to extensively evaluate the analytic results for exposure to $PM_{2.5}$ and mortality obtained from the random effects Cox models that were adjusted for ecologic covariates and spatial autocorrelation.

Generally speaking, use of the random effects Cox model leads to somewhat different results than the standard Cox model, most notably small increases in the hazard ratios and slightly wider confidence intervals (CIs). Results of standard Cox and random effects Cox models for the associations of $PM_{2.5}$ with various causes of death are presented in Commentary Table 4.

For the standard Cox models that included the 44 individual-level covariates, the associations between average $PM_{2.5}$ concentrations for both 1979–1983 and 1999–2000 and all listed causes of death (except "all other causes") were statistically significant. When random effects Cox models were used with controls for ecologic covariates (in addition to the 44 individual-level covariates included in the standard Cox models), the effect estimates increased and remained significant; the largest hazard ratio (1.24; 95% CI, 1.19–1.29) was noted for ischemic heart disease. Additional controls for these ecologic covariates at the MSA and ZCA scales appeared to remove some confounding effects, even as the switch to the random effects model, with its relaxed

Commentary Table 4. Associations Between Various Causes of Death and Long-Term Exposure to $PM_{2.5}$ in Two Time Periods from the Nationwide Analysis[a]

Cause of Death	Standard Cox Model	Random Effects Cox Model[b]
HR per 10-μg/m^3 Change in $PM_{2.5}$ Exposure Level (Average for 1979–1983)		
All causes	1.03 (1.01–1.04)	1.04 (1.03–1.06)
Ischemic heart disease	1.12 (1.09–1.16)	1.18 (1.15–1.22)
Cardiopulmonary disease	1.06 (1.04–1.08)	1.09 (1.06–1.11)
Lung cancer	1.08 (1.03–1.14)	1.09 (1.03–1.15)
HR per 10-μg/m^3 Change in $PM_{2.5}$ Exposure Level (Average for 1999–2000)		
All causes	1.03 (1.01–1.05)	1.06 (1.04–1.08)
Ischemic heart disease	1.15 (1.11–1.20)	1.24 (1.19–1.29)
Cardiopulmonary disease	1.09 (1.06–1.12)	1.13 (1.10–1.16)
Lung cancer	1.11 (1.04–1.18)	1.14 (1.06–1.23)

[a] Analyses with the standard Cox model were stratified by age (1-year groupings), sex, and race and were adjusted for the 44 individual-level covariates. Analyses with the random effects Cox model were also adjusted for the 7 ecologic covariates at the MSA & DIFF levels. HRs are followed by 95% confidence intervals. Values are from Tables 3 and 6 in the Investigators' Report.

[b] Results are for the MSA & DIFF combination of ecologic covariates. The DIFF value for each ZCA is the ZCA-specific value minus the MSA mean. This model allowed nested ecologic information to be analyzed.

assumptions, resulted in decreased certainty for some estimates.

Although conventional statistical models, including the standard Cox model, assume that all data points are independent of one another, it is unlikely that individuals who live in the same household or neighborhood are independent with respect to measured and unmeasured factors that affect health and mortality. A number of sensitivity analyses were conducted to allow for nonindependence of observations for CPS-II participants living close together. The results demonstrate relatively unchanged estimates of risk with widened confidence intervals (see Table 9 in the Investigators' Report). This pattern suggests that some clustering of mortality is not explained by the ecologic covariates for MSAs and ZCAs.

Results for some pollutants other than $PM_{2.5}$ are worth noting. In the Reanalysis Project (Krewski et al. 2000), the research team had investigated whether the relationship between $PM_{2.5}$ exposure and mortality changed when O_3 was included in the model and had found little effect. Therefore, the investigators did not repeat those combinations and analyzed O_3 in single-pollutant models. Summer O_3 levels (calculated from concentrations measured from April to September in 1980) were significantly associated with mortality from all causes (HR = 1.02; 95% CI, 1.01–1.03) and from cardiopulmonary disease (HR = 1.03; 95% CI, 1.02–1.04). O_3 exposure has recently been linked with mortality from pulmonary causes (Jerrett et al. 2009), whereas $PM_{2.5}$-related mortality has been shown to be dominated by cardiovascular causes (Pope et al. 2002). This implies that exposure to O_3 does not confound the association between $PM_{2.5}$ and mortality. Dr. Krewski's team did not construct a random effects Cox model for O_3 with ecologic covariates, nor did they compare mortality from respiratory causes with mortality from other causes of death. They have recently published the results of further analyses of O_3 exposure and death from pulmonary causes in this cohort (Jerrett et al. 2009).

Hazard ratios for exposure to SO_4^{2-} and SO_2 were significantly elevated for all analyzed causes of death in the standard Cox models (Table 3 of the Investigators' Report); the research team did not analyze them with random effects Cox models because of the project's limited computing resources and their focus on $PM_{2.5}$ analyses. Because SO_2 concentrations have been reduced across the United States during the follow-up years, however, SO_2 was evaluated separately for possible critical periods of exposure, described below.

Level of education attainment has been identified as a possible surrogate indicator of socioeconomic status and occupational exposure. In the Reanalysis Project (Krewski et al. 2000) and some parts of the Updated Analysis (Pope et al. 2002, 2004), the education level of the cohort members appeared to modify the effect of exposure on mortality: Participants with less than a high school education had substantially higher estimates of risk, and those with more than a high school education had no apparent increase in risk. In the current analysis, with substantial additional follow-up data, there is a moderate suggestion of this same trend (most notably for mortality from lung

cancer), but the hazard ratios for participants with more than a high school education were positive for all evaluated causes of death. For ischemic heart disease, the trend seemed to be reversed — those with higher education had the highest risk. Full results for the analyses of effect modification by education attainment are presented in Table 8 of the Investigators' Report.

INTRA-URBAN ANALYSES

The Intra-Urban Analyses produced very different hazard ratios and confidence intervals for New York City and Los Angeles. Commentary Table 3 presents hazard ratios by cause-of-death category for different methods of estimating and assigning exposure levels to participants: the New York City 28-county LUR-based models for the 3-year (1999–2001) and winter-2000 pollutant levels, and the Los Angeles models with exposure estimated by kriging and LUR. For easier comparison with the hazard ratios for the Los Angeles and Nationwide Analyses, hazard ratios for the New York City Analysis have been converted to a 10-μg/m^3 change in exposure from a 1.5-μg/m^3 change for the 3-year model and from a 3.9-μg/m^3 change for the winter-2000 model. The results for the fully adjusted Nationwide Analysis are included for comparison.

Even though the New York City and Los Angeles Analyses share common theoretical and methodologic approaches, the results of LUR models for assigning exposure and the estimates of attributable health effects are strikingly dissimilar. The hazard ratios are much higher for Los Angeles than for New York City, except for ischemic heart disease. Possible reasons for this difference may be the range of $PM_{2.5}$ exposures derived for the Los Angeles area and the relative uniformity of exposures in the New York City region. Annual averages of measured $PM_{2.5}$ concentrations from air monitors in the Los Angeles region ranged from 9.5 to 28 μg/m^3, and annual average exposure values predicted by the LUR at high-exposure locations such as freeway interchanges were in excess of 125 μg/m^3. In contrast, the interdecile (10th to 90th percentile) range of exposure for the New York City region was 1.9 μg/m^3 for the 3-year model and 3.9 μg/m^3 for the winter-2000 model. These differences may stem, in part, from the different LUR models constructed for the two cities because LUR models are inherently driven by land-use factors that predict exposure and are specific to each urban environment.

CRITICAL EXPOSURE TIME WINDOWS ANALYSIS

This analysis was an innovative start at understanding how the timing of exposure may influence health outcomes. Unfortunately, it did not yield conclusive results. Some interesting contrasts were noted between the $PM_{2.5}$-A group, composed of Nutrition Cohort participants, and the $PM_{2.5}$-B group, made up of CPS-II cohort members who were assumed to have died without moving from their 1982 MSAs of residence. Table 26 in the Investigators' Report details the results for $PM_{2.5}$ and SO_2 exposure in 5-year segments.

Overall, differences in model-fit statistics and in the hazard ratios and confidence intervals for combinations of two exposures, two cohorts, and three 5-year time periods of exposure are modest and demonstrate no definitive patterns. However, some possible trends can be discerned. Deaths from cardiopulmonary disease were most strongly associated with SO_2 exposure 1 to 5 years before death and with $PM_{2.5}$ exposure 6 to 10 years before death. Associations between exposure to $PM_{2.5}$ and mortality from lung cancer showed some interesting patterns for all time windows for both $PM_{2.5}$-A and $PM_{2.5}$-B groups, and some associations for the $PM_{2.5}$-B group were significant. Lung cancer is known to be a disease of long latency (typically 15 to 30 years) and yet the strongest statistical association with PM exposure was reported for the time window 5 to 10 years before death.

DISCUSSION

The Extended Analysis was a complex and important project that addressed several research questions including (1) statistical issues related to confounding and modification of effects by community-level covariates, (2) improved models to accommodate spatial autocorrelation in the data, and (3) within a subcohort with detailed residential data, methods of investigating critical time periods of exposure. Because this project included more years of follow-up and more deaths than previous analyses, it further consolidates existing knowledge about mortality risks in this cohort. Although the intra-urban associations obtained using kriged exposure data for Los Angeles have been published previously (Jerrett et al. 2005), this report describes more refined methods of exposure assessment. The results for the New York City region are entirely new.

NATIONWIDE ANALYSIS

Study Design

The broad study design for this Extended Analysis of the nationwide database was the same as that used in the previous Updated Analysis of this cohort (Pope et al. 2002) and fully appropriate for the task. We have no reason to believe

that limitations in the ascertainment of outcomes would have had any important impact on the study results. The additional years of follow-up added substantially to the data available at the time of the original study (Pope et al. 1995) and the Reanalysis (Krewski et al. 2000), and modestly to the Updated Analysis (Pope et al. 2002, 2004).

Statistical Methods

The model that underlay all mortality analyses was the standard Cox model, which was appropriate for addressing the study's specific aims. The influence of risk factors on which information had been collected through the ACS enrollment questionnaire (including age, sex, diet, education attainment, and occupational exposures) could be controlled at the individual level by including the factors in the model. When an air pollutant variable was considered, the investigators could assume that including these 44 individual-level covariates would substantially control confounding that could arise if one of these risk factors were associated with the pollution variable (for example, if diets are generally poorer where exposures are higher).

The standard Cox model has two major limitations that the investigators addressed in innovative ways: ecologic confounding and spatial autocorrelation. Ecologic covariates are risk factors for mortality that are measured at the neighborhood level rather than at the individual level. Typically, in spatial studies of health, such variables are found to predict mortality even when — as here — adjustment is made for individual-level risk factors. Ecologic confounding arises when such variables are associated with air pollution levels — a matter of particular concern here, because air pollution was estimated at the larger MSA scale. In this study, the ecologic covariates included were aggregate measures derived from the 1980 U.S. Census; they included measures of income, unemployment, availability of air conditioning, and race. This information was collected at the smaller ZCA scale rather than the MSA scale, although MSA-scale values were calculated from ZCA-scale values and included in the analysis.

The inclusion of ZCA-level covariates made the evaluation of ecologic confounding more refined in this Extended Analysis than for the Reanalysis (for which only MSA-scale ecologic covariates were considered). However, not all previously considered ecologic covariates were included in this analysis. In particular, population migration and ambient temperature had both been shown to be determinants of mortality with some evidence of confounding in the Reanalysis and were not further evaluated in this project.

Spatial autocorrelation is the tendency for variables to have similar values for people or areas that are geographically (spatially) close. Experience with spatial analysis of health data generally has led us to expect this pattern, even when individual and ecologic covariates are controlled. Spatial autocorrelation is of particular concern with respect to the mortality data used in this study because the Reanalysis documented that air pollution levels are spatially autocorrelated. Spatial autocorrelation has two types of effects that might be relevant here: Its presence suggests the existence of determinants of mortality otherwise unaccounted for in the model, which might (though need not) confound the association between air pollution and mortality; and its presence distorts (and usually exaggerates) the precision of the estimates.

In this and previous analyses of the ACS study data, the investigators incorporated spatial components into the statistical model in order to reduce such adverse impacts of spatial autocorrelation. The spatial models in this analysis differed from those used in the Reanalysis and in the Updated Analysis by Pope and coworkers (2002). Both of those studies used a variety of approaches; in particular, they included a regional fixed effect; and they fitted a spatially smooth surface to mortality that was unexplained by covariates in the models (Pope et al. 2002). The model used in the current Extended Analysis includes (1) random effects at the ZCA, MSA, and state scales, and (2) correlation between adjacent ZCAs, MSAs, and states (although only two levels could be incorporated in the model simultaneously). (In the Nationwide Analysis section Statistical Methods and Data Analysis, the investigators note that the degree of correlation can, alternatively, be assumed to depend on distance; but results for distance-based models are not presented.)

Technical problems in fitting such spatial models have previously prevented their use in complex formulations such as those used here. The investigators are to be congratulated on overcoming these technical complexities to produce what in many ways is a more comprehensive representation of spatial structure in these data. It remains very difficult, however, to be sure that the range of models considered is broad enough that all of the adverse impacts described above are controlled by the incorporation of spatial patterns of mortality due to unmeasured risk factors. In particular, though the models used seem well formulated to capture local spatial patterns, it is less obvious that they captured larger-scale patterns. For example, the Reanalysis found important residual variation in mortality across regions and incorporated regional terms (as fixed and random effects) in the model. There does not appear to have been any analogous direct representation of larger-scale patterns in this Extended Analysis, although allowing for correlation between adjacent states may have done this to some

extent. One also wonders what the impact would be of allowing for the effects of latitude or longitude, which were not considered.

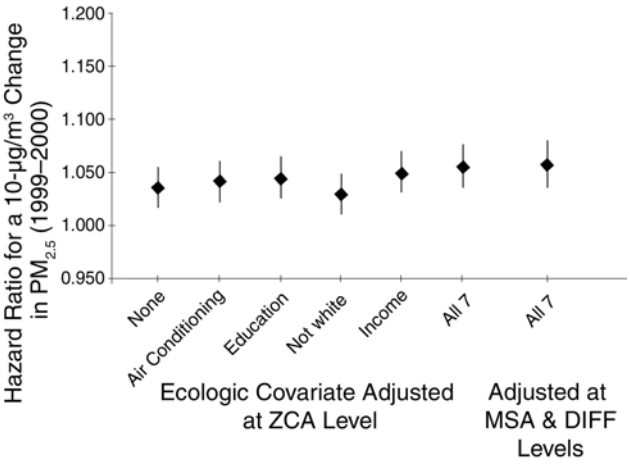
In summary the approach used to allow for spatial autocorrelation in these analyses was technically innovative and provided quite comprehensively for patterns at the local scale. However, the absence of any investigation of larger-scale spatial patterns due to factors other than air pollution makes it impossible to rule out an impact of such factors on results.

Results

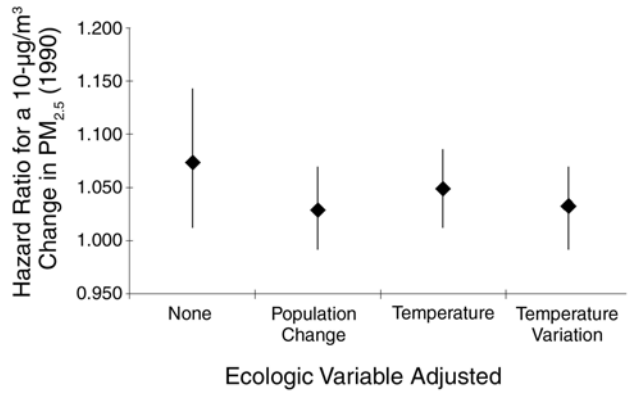
We agree with the investigators that including ecologic covariates (social and economic factors) — measured at the ZCA scale for the first time in this study — changed the risk estimates relatively little (Commentary Figure 1). This lack of strong effect adds to the reassurance provided in previous reports on this cohort that the effects on health of these variables did not bias the risk estimates. However, as noted above, not all ecologic covariates considered in previous analyses were assessed in this study. Some variables not considered in this study — population change and climate (temperature) — did have an impact on pollution risk estimates in some previous analyses (Commentary Figure 2). Although we do not know that including them would have had a similar influence in the current analyses, omitting them amplifies the uncertainty due to possible residual confounding by ecologic covariates that were not included in the models.

We also agree with the investigators that key results were robust when spatial autocorrelation in mortality was incorporated in the statistical models (Commentary Figure 3). This is reassuring, particularly because the spatial autocorrelation models developed in the course of this work represent a refinement of those used previously. However, such reassurance cannot be absolute. It remains possible that spatial patterns in mortality due to unmeasured risk factors could bias estimates of risk. In particular it is unclear to what extent the models used allowed for large-scale geographic patterns, such as those presented in the Reanalysis by fitting regional effects (Krewski et al. 2000). However, an analysis of semivariance presented in a follow-on study of O_3 (Jerrett et al. 2009) using the same individual and ecologic covariates showed no indication of important residual spatial autocorrelation of the O_3 and mortality relationship in this same data set when individual and ecologic covariates were included.

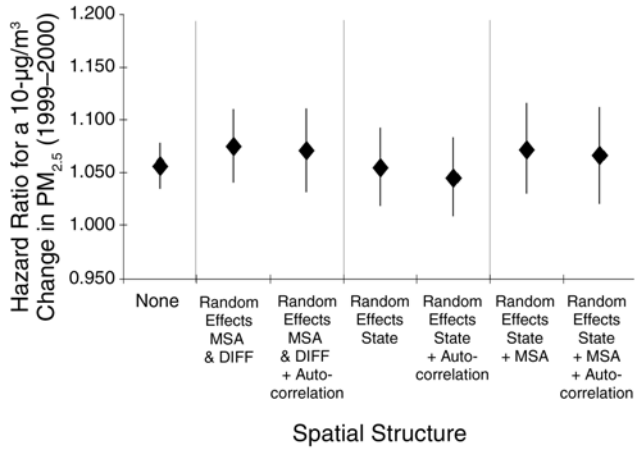
In this Extended Analysis the research team adhered to the practice in early reports of combining deaths from cardiovascular and respiratory causes. This is important for reasons of continuity, but it can be questioned from a biomedical point of view. Although there may well be overlap



Commentary Figure 1. Adjustments to control confounding by ecologic covariates for mortality from all causes related to $PM_{2.5}$ exposure.



Commentary Figure 2. Ecologic variables found to influence the relationship between $PM_{2.5}$ exposure and mortality from all causes in the Reanalysis (data are Independent Observations from Table 46 in Krewski et al. 2000).



Commentary Figure 3. Adjustment for spatial autocorrelation with different statistical methods. Random effects Cox models were used with covariates clustered at ZCA, MSA, and state levels with and without spatial autocorrelation. HRs are shown for $PM_{2.5}$ exposure and mortality from all causes.

of International Classification of Disease codes between the two categories, it would be more prudent to present them separately, as well as in combined categories, until more is known about the biologic mechanisms involved in the effects. The recent report from a Dutch cohort study (Brunekreef et al. 2009) stated that, depending on the exposure metric used, risks tended to be higher for respiratory than for cardiovascular mortality.

The current study, although focused on particles, reports the emergence of a relationship between O_3 and cardiopulmonary mortality that recently has been further analyzed by examining causes of cardiovascular and respiratory mortality separately. The more recent analysis (Jerrett et al. 2009) found an association between O_3 exposure and respiratory but not cardiovascular mortality, which further supports the desirability of presenting results for the two categories separately. Similarly, the Health Review Committee would have liked to see the results for other categories of cardiovascular disease, such as stroke and heart failure, presented alongside those for ischemic heart disease. As more cohort studies are conducted, separate presentation (of these categories) would facilitate meta-analysis.

The Investigators' Report singled out the associations between $PM_{2.5}$ and ischemic heart disease; although other cardiovascular causes of death were not presented, mortality from ischemic heart disease appears to be the category of cardiovascular disease where much of the association between cardiovascular mortality and air pollution exposure is concentrated, as reflected in previous investigations with this cohort (Pope et al. 2004). The investigators referred to this association as having "high biologic plausibility," but the Review Committee thought that the existing limited epidemiologic and mechanistic evidence, though suggestive, does not justify such a strong assertion.

Given that the Reanalysis (Krewski et al. 2000) had extensively tested the potential for the gaseous pollutants to confound the relationship between exposure to $PM_{2.5}$ and mortality and had not found any significant confounding (other than by SO_2), it is understandable that the current investigators chose to focus their limited resources on the extensive exploration of spatial autocorrelation in a series of one-pollutant models. In this case, including gasses such as NO_2 and SO_2 as copollutants would have presented some challenges in a model with $PM_{2.5}$ because (1) levels of NO_2 recorded at central monitoring stations do not reflect the fine scale on which these gases vary; (2) NO_2 and SO_2 are generated by some of the same sources that generate $PM_{2.5}$ (NO_2 from traffic; SO_2 from power plants) and their levels will be correlated with those of $PM_{2.5}$; and (3) the gases are important precursors to components of fine nitrate and SO_4^{2-} particles. Still, it is always reassuring if two-pollutant analyses can be conducted. Further analyses of O_3 and respiratory mortality that were completed recently by members of Dr. Krewski's team included a two-pollutant analysis for $PM_{2.5}$ and O_3 (Jerrett et al. 2009).

INTRA-URBAN ANALYSES

Study Design

Epidemiologically, the design for the two Intra-Urban Analyses (in the New York City and Los Angeles regions) was essentially the same as that for the Nationwide Analysis, from which the data for these two analyses were selected. The differences and methodologic innovations lie in the methods of exposure assessment.

The Nationwide Analysis compared MSAs across a wide range of air shed regions; and because some cities have a common regional background (e.g., New England cities), this study compared effects of air pollution between cities and between air sheds. By contrast, the Intra-Urban Analyses primarily investigated variations in local exposures added to common regional and urban background exposures. Spatial variations within urban areas are driven more by local near-source emissions such as traffic, industry, and residential space heating; the resulting analyses can tell us little about the health effects of chronic exposure to the background pollutant levels.

Statistical Methods

The statistical analysis for these studies had two components. The LUR analysis, used to estimate exposures, will be discussed below. The epidemiologic analysis, designed to estimate the effects of air pollution after controlling for the influence of ecologic covariates, followed essentially the same methods as those used in the Nationwide Analysis, with some differences due to the local scale (e.g., state-level components of the Nationwide Analysis were not relevant to assessing the impact of spatial autocorrelation). For this set of analyses, as for the Nationwide Analysis, the Review Committee considered these methods very appropriate and probably adequate to control most potential confounding. Climate is more homogeneous in these Intra-Urban Analyses, and possible unmeasured determinants of large-scale spatial confounding are not an issue, so residual confounding from these sources is much less of a concern than in the Nationwide Analysis.

Exposure Assessment

Both Intra-Urban Analyses used LUR and kriging techniques to predict exposure at each ZCA centroid (the central point in a ZCA); this is clearly described for the Los Angeles model in the Investigators' Report, but less clearly

stated for the New York City model. These studies are among the first to use LUR to predict $PM_{2.5}$ concentrations at the local level. Unlike NO_2 and elemental carbon, which remain localized near their sources, $PM_{2.5}$ has a large regional component and a smaller local-source component (e.g., traffic emissions), which make it challenging to estimate the contribution of local sources to air pollution exposure. Including specific land uses in the assessment may help make local estimates more precise.

The LUR models differed substantially between the two cities in several important ways, including the number of ambient monitoring sites used (23 in Los Angeles, 62 in New York City); the size of the buffers surrounding each monitoring site (50 m to 5000 m) for determining which land-use variables were significant predictors of monitored levels; and the sources of information available for constructing the independent variables of traffic, land use, and population for each location. In addition, the New York City model used county-wide emissions inventory data to estimate $PM_{2.5}$ emissions for certain types of industrial point sources. In developing the New York City models, the investigators considered about 30 variables, whereas for the Los Angeles model they considered over 140. The three final models for New York City (Table 14 of the Investigators' Report) included single indicators for traffic (within 500 m of each monitor for the 3-year 28- and 9-county models and within 300 m for the 28-county winter-2000 model), total population (within 1000 m for all three models), industrial land use (within 300 m for the 3-year 28- and 9-county models), and vegetation land use (within 1000 m for the 28-county winter-2000 model). The New York City models were able to explain 60% to 64% of the variation in local $PM_{2.5}$ measurements. The final Los Angeles model also included three variables: traffic within 300 m, industrial area within 5000 m, and government area within 5000 m of each monitor; it explained 63% of the variation.

Despite the substantial differences in how the LUR models were constructed and the probable quality of available data, the New York City and the Los Angeles Analyses were both successful in explaining about two-thirds of the variability in $PM_{2.5}$ concentrations at the ZCA scale. Each model is unique to the area where it was developed and is not likely to be transferable to other metropolitan areas.

In addition to the number and spatial distribution of the air-quality monitoring sites, the type of independent variables selected, and the quality of the available data, a number of additional factors need to be considered when assessing the applicability of LUR for providing better spatial estimates of $PM_{2.5}$ concentrations. The ranges of average annual monitored $PM_{2.5}$ concentrations were moderately different between Los Angeles (9.5–28 $\mu g/m^3$) and New York City (10–20 $\mu g/m^3$) and suggest that the $PM_{2.5}$ levels in New York City were more strongly influenced by regional transport than by local emissions. The models reflected this difference. The intercepts in the New York City models varied between 12.3 and 13.2 $\mu g/m^3$, whereas the intercept in the Los Angeles model was 2.3 $\mu g/m^3$. It is difficult to compare coefficients for the independent variables between cities, particularly for traffic, since the variables were constructed from different forms of land-use and traffic data.

LUR has the potential to provide a better estimate of $PM_{2.5}$ levels on a finer spatial scale than simple spatial averaging using central-site air pollution monitors; thus it is somewhat disappointing that the LUR models in validation studies have only slightly outperformed kriging models. For a regional pollutant such as $PM_{2.5}$, it is not clear that there are substantial benefits in using LUR models, compared with spatial averaging models, in extending the analysis of data from regional air pollutant monitors to a finer spatial scale.

Two additional issues arise in using LUR models. As the authors report, the LUR method may include hidden or unmeasured factors that relate to health care, socioeconomic status, or mortality risks and can confound the estimated exposure. This means that although LUR may be good at predicting exposure, confounding may occur if the LUR-derived exposure estimate is then used in a health-assessment model that contains the same or similar factors as variables. (For example, population density may be independently associated with both mortality and air pollution.) This issue deserves further attention.

It is reassuring that the results from the random effects Cox model for Los Angeles obtained using LUR-based exposure assignments were similar to those obtained using kriging. Residential location data for the ACS cohort were available only at the ZCA scale, thus LUR-modeled exposures were appropriate for the central point of the ZCA, but not necessarily for where residences were likely to be located throughout a ZCA. If data for the independent variables were to be applied at the residential addresses of the participants, the modeled exposures might be very different from exposures assigned to the ZCA of residence.

Results

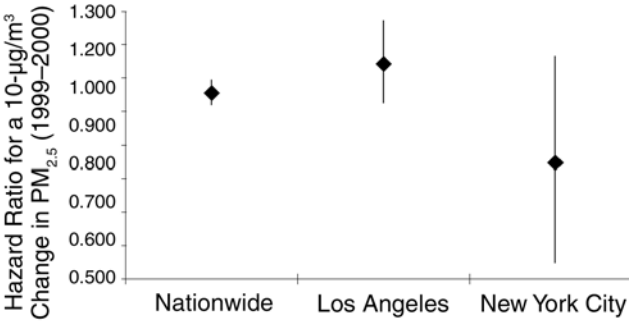
The Intra-Urban results for the two cities were very different. Whereas for Los Angeles there was a strong positive and statistically significant association between $PM_{2.5}$ exposure and mortality from cardiopulmonary disease, the result of the corresponding analysis for New York City was negative and not significant. The confidence intervals were,

however, quite wide for both Intra-Urban Analyses (although more so for New York City), and when the results are compared for the same exposure range, they are both consistent with the Nationwide Analysis result and with one another (Commentary Figure 4). One explanation for the differences could be the play of chance. Other explanations are offered by the authors. In the case of Los Angeles, they suggest that the higher estimate is due to less error in estimating exposure, although this assertion can be questioned. In the case of New York City, the investigators suggest that there was too little heterogeneity in the $PM_{2.5}$ estimates to detect differences in the mortality patterns at high and low ends of the range of exposures; this statement is consistent with our comments on the width of confidence intervals. The authors further suggest that differences between the Los Angeles and New York City Analyses lie in the underlying geographic distribution of social and economic factors in the population relative to exposure levels. For example, in New York City, pollution appears to be worst in areas where people are wealthier and are likely to be in better overall health, whereas pollution in Los Angeles tends to be worst in areas of low socioeconomic status.

Both the Los Angeles and New York City results showed significant associations between $PM_{2.5}$ exposure and mortality from ischemic heart disease, in line with the results of the Nationwide Analysis. The Review Committee noted, however, that the ranges of results for cause-specific mortality that are presented differ among the three analyses, making comparisons more difficult. The Committee also noted that there was a strong and robust association between $PM_{2.5}$ exposure and deaths from endocrine disorders (but not diabetes) in Los Angeles, but not New York City. This comparison is intriguing; it would be helpful to see the corresponding results from the Nationwide Analysis.

In the section Implications of the Findings / Summary of Results from Phase III / Intra-Urban Analyses, the investigators advance the hypothesis that the impact of exposure measurement error on the results of PM–mortality regression coefficients will be less in small-scale spatial studies than in large-scale studies. This suggests that the hazard ratios calculated for the Intra-Urban Analyses would be less subject to the statistical effects of measurement error than the hazard ratios from the Nationwide Analysis would be. There is an intuitive plausibility to this suggestion; but it is not persuasive for reasons elaborated below.

Two types of statistical error are important to this analysis: classical measurement error, which biases coefficients toward the null; and Berkson error, which does not bias coefficients appreciably, though it increases standard errors, widening confidence intervals. It is thus important to identify which type of measurement error was operating to what extent in the Intra-Urban and the Nationwide Analyses.



Commentary Figure 4. Comparison of results from Nationwide and Intra-Urban Analyses. The New York City data were adjusted from a 1.5-µg/m^3 change in $PM_{2.5}$ to a 10-µg/m^3 change to match the scale of the other analyses. HRs are shown for $PM_{2.5}$ exposure and mortality from all causes.

In this context, Berkson error is that due to differences in individual true exposures and in the true means for the areas used in analysis. Zeger and colleagues (2000) explored this concept for time-series studies; the principle is the same for geographic studies. Thus, though using larger spatial units will increase Berkson error, Berkson error does not cause bias in coefficients; therefore this source of error would lead us to expect coefficients to be less biased in small-scale studies.

In this context, classical error, which does bias coefficients downwards, is that due to differences between the true mean exposures for the areas and the values actually used in the regression. Zeger argued that for ecologic time-series studies, classical error will have less variance than Berkson error, and similar arguments seem likely to lead to the same conclusion for geographic studies. That these observed means will be less precisely measured as areas get bigger has some plausibility, though the presumption is much weaker than for the increase in Berkson error in larger-scale studies. Furthermore, if bias due to measurement error in the coefficients based on MSAs in the Nationwide Analysis is compared with that in an analysis based on ZCAs in one region (Los Angeles or New York City), one also has to allow for the greater variation in (true) exposures across the nation, as compared with the variation in one region. The bias due to classical error is (to a reasonable approximation) a function of the ratio of the standard deviation of the error to the standard deviation of the true exposure (Armstrong 1998). It is not at all clear that this ratio is bigger for MSAs nationally than for ZCAs in Los Angeles or New York City. Thus, we should not expect that measurement error bias due to classical error will be greater in small-scale studies than in large-scale studies.

In summary, we saw no persuasive argument that bias due to random measurement error would be expected to be less in the Los Angeles or New York City Analysis than in the Nationwide Analysis. The extent of bias in each remains

an open question, as does the reason for the differences between New York City and Los Angeles observations. Overall, the divergent results argue for caution in applying or extrapolating the results from any such analysis of only one city to any other city.

CRITICAL EXPOSURE TIME WINDOWS ANALYSIS

Study Design

The epidemiologic design (specifically, the selection of study subjects) for the analyses of critical time periods of exposure was more complex than the selection for the Nationwide Analysis, which considered only single estimates of exposure. For this set of analyses to explore exposure over time, the investigators needed to have participants with residential histories, and those were available for only the Nutrition Cohort, a subset of the full ACS study. Therefore, the $PM_{2.5}$-A group comprised some of the participants for whom information was available on changes in residence since enrollment in 1982. Dates of moving were approximate, and no information was available for before 1982, so these sources of approximation are likely to have resulted in misclassification of exposures in specific time windows.

The $PM_{2.5}$-B group is the most unusual epidemiologically. This group comprised subjects who were not in the Nutrition Cohort (and for whom ongoing residential information was therefore not available) but who had died and were assumed to have lived continuously in the same MSA in which they had been living at enrollment in 1982. The investigators reasonably inferred that it was most likely that these subjects did not move in the intervening time, and their time-specific exposures could therefore be assumed to be those determined for the MSA in which they resided in 1982 and in which they died. However, a usual epidemiologic principle for cohort studies is that a subject's presence in the cohort (his or her person-time at risk) should not depend on subsequent death. Because persons who did not die were not included, this group did not adhere to this principle. Though it is not obvious that the nonstandard nature of the group would have caused bias in this context, the validity of the analysis cannot be deduced from the usual "guarantees" of standard cohort analyses.

Statistical Methods

Although fitting a standard Cox model with time-dependent exposures is not as typical as is fitting the model with time-fixed exposures, it is well established (notably for occupational epidemiology), and the approach used by the investigators seemed to fall within the established methods. It is understandable that the compounded complexity of handling both time-dependent exposures and random effects (to reflect spatial autocorrelation) proved to be too much of a technical challenge, and we concur with the investigators that this is a minor limitation here.

The investigators' use of AIC values to compare models for different time windows of exposure is broadly reasonable, though it is curious that more was not made of comparisons of deviance statistics, for which the magnitude as well as the direction of difference between models can be interpreted. Happily, however, because the number of parameters in the models compared is the same, differences in AIC values are the same as differences in deviance and may be interpreted as such.

The Review Committee was somewhat disappointed that the investigators did not present results for "multi-window" models, which would be analogous to multi-pollutant models. The investigators discuss using such models, but they decided that the resulting estimation of negative coefficients for some time windows precluded their useful interpretation. It seemed to the Review Committee that the use of such multi-window models (well established in occupational epidemiology) in conjunction with single-window models would provide the best basis for assessing the evidence for the independent effects of each window (for example, using likelihood ratio tests in nested models). The investigators favored "constrained" multi-window models, in which all coefficients are constrained to be non-negative. Such models are of interest, but, particularly because the technical difficulty in fitting them was apparently insurmountable, unconstrained multi-window models would also be of interest.

For the purposes of formulating and evaluating air pollution policy, it is very important to know whether more recent exposure has a greater effect on risk than earlier exposure. However, the Review Committee thought that the evidence presented was not substantial enough for any conclusions to be drawn from these analyses. This view is mainly based on the extremely small differences in AIC values between the time windows for each pollutant and group. For example, for $PM_{2.5}$ exposure, the three AIC values for the models with exposure in windows 1 to 5, 6 to 10, or 11 to 15 years before death differed by little more than 1 for the $PM_{2.5}$-A group and for the $PM_{2.5}$-B group (Table 26 in the Investigators' Report). As noted above, differences in AIC values for these models will closely approximate differences in deviance, and differences of less than 3.84 (the 5% point of the chi-squared distribution with 1 degree of freedom) can easily be explained by chance.

In only one of the comparisons were differences in AIC large enough to show any more than very weak, suggestive evidence for the greater importance of one time window

over another. The exception was for lung cancer and $PM_{2.5}$ exposure for the $PM_{2.5}$-B group; the AIC value (9346.729) for the time window of 1 to 5 years was 0.515 lower than that for the window of 6 to 10 years (9347.244). However, the direction of the difference (showing that recent exposure is the better predictor) does not correspond with expectations for lung cancer (a disease with a latency of 20 years or longer); therefore, as one "significant" pattern among many results, it cannot be considered as strong evidence.

When the group was restricted to participants who died in the same city where they lived in 1982 ($PM_{2.5}$-B group), no attempt was made to adjust for the effects of exposure earlier or later than the time period of interest. Given the potentially high correlations among exposures 1 to 5, 6 to 10, and 11 to 15 years before death within each city, differences among the effect estimates reported for each separate time window cannot be accepted as meaningfully different from the others.

Patterns of risk estimates across time windows also showed only very weak evidence for the superior predictive value of one window over another, though the width of the confidence intervals indicated that the precision of the study — despite its size — was not sufficient to conclusively determine if there were statistically significant differences.

Exposure Assessment

Average exposures were calculated for each of the deceased participants in 5-year windows of exposure proceeding back from the date of death and are based on previously published work (Lall et al. 2004). Because there were no comprehensive exposure monitoring data available before 1973, cohort members who died before 1987 had data for 1973 substituted for 1967 through 1972 in the calculations of the earliest exposure time window. This practice has the potential to introduce uncertainty in exposure estimations for the most distant time window for the earliest decedents because those estimates may or may not reflect actual exposure concentrations for 1967 through 1972.

CONCLUSIONS

The current Extended Analysis, described in the Investigators' Report, represents a broadly sound and thorough analysis of extended follow-up of an already important cohort study, with several innovative features. The results of the Nationwide Analysis presented in this report will be of great importance worldwide. This is the case because coefficients from earlier analyses (Pope et al. 2002) have been central to the calculation of burden-of-disease estimates, policy evaluation, and comparison of policy options not only in the United States, but in countries and regions throughout the world (e.g., for organizations such as Global Burden of Disease; Clean Air for Europe; U.K. Department for Environment, Food, and Rural Affairs; U.S. EPA). The ACS study remains paramount owing to its size and the richness of the data.

The results presented in this report consolidate earlier findings by showing that the application of state-of-the-art statistical approaches to controlling confounders and spatial autocorrelation does not materially change risk estimates; important residual confounding (by climate and possibly other unmeasured determinants of large-scale spatial variation) cannot be excluded, however, particularly in the Nationwide Analysis. In analyzing the extended follow-up data for mortality, the report also provides new risk estimates, including — for the first time — an estimate for O_3 and premature mortality.

Previous analyses of this ACS cohort have identified subjects with lower education attainment (and probably lower socioeconomic status) as having a higher risk of mortality associated with exposure to $PM_{2.5}$, although this trend was not as consistent in the ACS study as it was in the Harvard Six Cities Study (Krewski et al. 2000). In this Extended Analysis, effect modification by level of education attainment was considerably less marked than it was in the Reanalysis (Krewski et al. 2000); for ischemic heart disease, however, increasing levels of education had the reverse effect (i.e., the association of mortality with air pollution exposure increased as education attainment increased). The Review Committee thought that this recent evidence suggests that effect modification by education is probably not as important as was previously thought and that some of the associations may have been at least partly due to chance. Nonetheless, it is interesting that the recent report on the Netherlands Cohort Study of diet and cancer found some indication that lower education attainment was associated with higher risk (Brunekreef et al. 2009).

The Review Committee's Commentary for the Reanalysis Report mentioned that no single study can be the basis for accepting the existence of a causal relationship between air pollution and mortality. With this in mind, the Committee thought that — with the emergence of new cohort evidence from the United States and Europe — the similarities and differences among the results of the various studies need to be examined closely. Nevertheless, the size and character of the ACS cohort makes it likely that it will remain preeminent.

The number of intra-urban studies is growing along with increased interest in the potential effects of exposure to pollutants from local sources. It is important to recognize,

however, that such studies address the effects of a different pattern of exposure from that addressed in intercity studies, such as those conducted with the national ACS cohort, and that they employ different exposure-assessment techniques. Although the results of the Los Angeles and New York City Intra-Urban Analyses contribute to this body of evidence, their precision is limited.

Information on the time period of exposure that might be critically associated with illness and mortality from various causes, if any, remains elusive in the absence of cohort data with better residential histories. Since very few cohorts are as large as the ACS cohort to begin with, future attempts to find and track a sufficiently large subpopulation to document critical periods of exposure while accounting for the separate effects of earlier or later exposure periods will require careful statistical design and power calculations at the inception. Although many questions remain about the timing of exposures in terms of the development of diseases associated with air pollutants (e.g., the relationship between actions to improve air quality and subsequent improvement in health), this Extended Analysis serves to underscore the difficulty of assessing the relative importance of the timing of exposure in a cohort study, even with a large base population.

The results from this Extended Analysis will likely be very influential in the coming years, despite the limitations discussed in this Commentary. Dr. Krewski and his colleagues have successfully designed, constructed, and implemented advanced statistical methods that include nested random effects variables and control for autocorrelation in a single model of survival. Furthermore, they have confirmed our understanding that exposure to $PM_{2.5}$ is associated with increased mortality and have again validated earlier findings. These results also bolster earlier reports of increased risk of lung cancer associated with long-term exposure to $PM_{2.5}$. For the first time, the association between long-term O_3 exposure and mortality has been identified with a standard Cox model; in further, more recent analyses, the same association was evident with a random effects Cox model (Jerrett et al. 2009).

The Intra-Urban Analysis for Los Angeles suggests that mortality risks associated with $PM_{2.5}$ exposure may be elevated when there is a strong local component of exposure. When the New York City and Los Angeles Analyses are taken together, however, they underscore the important point that cities differ markedly in their local exposure conditions and emphasize the variable importance of the contributions of local sources to the overall risk of mortality associated with $PM_{2.5}$ exposure. These divergent results argue for caution in extrapolating from such studies in any one metropolitan area to other areas.

In summary, the additional follow-up years and methodologic developments used in the Nationwide Analysis have confirmed with remarkable consistency the association of mortality and exposure to $PM_{2.5}$ reported in previous studies of the ACS data starting 15 years ago. In addition to consolidating evidence for a causal association, the new analyses have added precision, especially for the evidence that ischemic heart disease is a cause of death particularly affected by exposure. The lack of support for previous findings of greater risks of mortality for underprivileged population groups adds importantly to evidence on this topic, though no doubt the debate will continue. The Intra-Urban Analyses in Los Angeles and New York City advance methods for such studies; the differences between results from the two cities could be explained by chance, but we must be careful about overgeneralizations, given the very local nature of each study. The search for greater precision on critical periods of exposure was well conducted, but power limitations preclude clear conclusions. The richness of these latest findings from the ACS cohort confirms the vital role of such large, ongoing epidemiologic studies in assessing and protecting human health in relation to air pollution.

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