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Lung Cancer, Cardiopulmonary Mortality, and Long-term Exposure to Fine Particulate Air Pollution

C. Arden Pope III, PhD; Richard T. Burnett, PhD; Michael J. Thun, MD; Eugenia E. Calle, PhD; Daniel Krewski, PhD; Kazuhiko Ito, PhD; George D. Thurston, ScD

ABSTRACT

Context Associations have been found between day-to-day particulate air pollution and increased risk of various adverse health outcomes, including cardiopulmonary mortality. However, studies of health effects of long-term particulate air pollution have been less conclusive.

Objective To assess the relationship between long-term exposure to fine particulate air pollution and all-cause, lung cancer, and cardiopulmonary mortality.

Design, Setting, and Participants Vital status and cause of death data were collected by the American Cancer Society as part of the Cancer Prevention II study, an ongoing prospective mortality study, which enrolled approximately 1.2 million adults in 1982. Participants completed a questionnaire detailing individual risk factor data (age, sex, race, weight, height, smoking history, education, marital status, diet, alcohol consumption, and occupational exposures). The risk factor data for approximately 500 000 adults were linked with air pollution data for metropolitan areas throughout the United States and combined with vital status and cause of death data through December 31, 1998.

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Main Outcome Measure All-cause, lung cancer, and cardiopulmonary mortality.

Results Fine particulate and sulfur oxide--related pollution were associated with all-cause, lung cancer, and cardiopulmonary mortality. Each 10-μg/m^3 elevation in fine particulate air pollution was associated with approximately a 4%, 6%, and 8% increased risk of all-cause, cardiopulmonary, and lung cancer mortality, respectively. Measures of coarse particle fraction and total suspended particles were not consistently associated with mortality.

Conclusion Long-term exposure to combustion-related fine particulate air pollution is an important environmental risk factor for cardiopulmonary and lung cancer mortality.

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INTRODUCTION

Based on several severe air pollution events,[1-3] a temporal correlation between extremely high concentrations of particulate and sulfur oxide air pollution and acute increases in mortality was well established by the 1970s. Subsequently, epidemiological studies published between 1989 and 1996 reported health effects at unexpectedly low concentrations of particulate air pollution.[4] The convergence of data from these studies, while controversial,[5] prompted serious reconsideration of standards and health guidelines[6-10] and led to a long-term research program designed to analyze health-related effects due to particulate pollution.[11-13] In 1997, the Environmental Protection Agency adopted new ambient air quality standards that would impose regulatory limits on fine particles measuring less than 2.5 μm in diameter (PM$_{2.5}$). These new standards were challenged by industry groups, blocked by a federal appeals court, but ultimately upheld by the US Supreme Court.[14]

Although most of the recent epidemiological research has focused on effects of short-term exposures, several studies suggest that long-term exposure may be more important in terms of overall public health.[4] The new standards for long-term exposure to PM$_{2.5}$ were originally based primarily on 2 prospective cohort studies,[15-16] which evaluated the effects of long-term pollution exposure on mortality. Both of these studies have been subjected to much scrutiny,[5] including an extensive independent audit and reanalysis of the original data.[17] The larger of these 2 studies linked individual risk factor and vital status data with national ambient air pollution data.[16] Our analysis uses data from the larger study and (1) doubles the follow-up time to more than 16 years and triples the number of deaths; (2) substantially expands exposure data, including gaseous copollutant data and new PM$_{2.5}$ data, which have been collected since the promulgation of the new air quality standards; (3) improves control of occupational exposures; (4) incorporates dietary variables that account for total fat consumption, and consumption of vegetables, citrus, and high-fiber grains; and (5) uses recent advances in statistical modeling, including the incorporation of random effects and nonparametric spatial smoothing components in the Cox proportional hazards model.

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METHODS

Study Population

The analysis is based on data collected by the American Cancer Society (ACS) as part of the Cancer Prevention Study II (CPS-II), an ongoing prospective mortality study of approximately 1.2 million adults.[18-19] Individual participants were enrolled by ACS volunteers in the fall of 1982. Participants resided in all 50 states, the District of Columbia, and Puerto Rico, and were generally friends, neighbors, or acquaintances of ACS volunteers. Enrollment was restricted to persons who were aged 30 years or older and who were members of households with at least 1 individual aged 45 years or older. Participants completed a confidential questionnaire, which included questions about age, sex, weight, height, smoking history, alcohol use, occupational exposures, diet, education, marital status, and other characteristics.

Vital status of study participants was ascertained by ACS volunteers in September of the following years: 1984, 1986, and 1988. Reported deaths were verified with death certificates. Subsequently, through December 31, 1998, vital status was ascertained through automated linkage of the CPS-II study population with the National Death Index.[19] Ascertainment of deaths was more than 98% complete for the period of 1982-1988 and 93% complete after 1988.[19] Death certificates or codes for cause of death were obtained for more than 98% of all known deaths. Cause of death was coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*. Although the CPS-II cohort included approximately 1.2 million participants with adequate questionnaire and cause-of-death data, our analysis was restricted to those participants who resided in US metropolitan areas with available pollution data. The actual size of the analytic cohort varied depending on the number of metropolitan areas for which pollution data were available. Table 1 provides the number of metropolitan areas and participants available for each source of pollution data.

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Table 1. Summary of Alternative Pollution Indices*

Air Pollution Exposure Estimates

Each participant was assigned a metropolitan area of residence based on address at time of enrollment and 3-digit ZIP code area.[20] Mean (SD) concentrations of air pollution for the metropolitan areas were compiled from various primary data sources (Table 1). Many of the particulate pollution indices, including $PM_{2.5}$, were available from data from the Inhalable Particle Monitoring Network for 1979-1983 and data from the National Aerometric Database for 1980-1981, periods just prior to or at the beginning of the follow-up period. An additional data source was the Environmental Protection Agency Aerometric Information

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Retrieval System (AIRS). The mean concentration of each pollutant from all available monitoring sites was calculated for each metropolitan area during the 1 to 2 years prior to enrollment.[17]

Additional information on ambient pollution during the follow-up period was extracted from the AIRS database as quarterly mean values for each routinely monitored pollutant for 1982 through 1998. All quarterly averages met summary criteria imposed by the Environmental Protection Agency and were based on observations made on at least 50% of the scheduled sampling days at each site. The quarterly mean values for all stations in each metropolitan area were calculated across the study years using daily average values for each pollutant except ozone. For ozone, daily 1-hour maximums were used and were calculated for the full year and for the third quarter only (ie, July, August, September). While gaseous pollutants generally had recorded data throughout the entire follow-up period of interest, the particulate matter monitoring protocol changed in the late 1980s from total suspended particles to particles measuring less than 10 µm in diameter (PM_{10}), resulting in the majority of total suspended particle data being available in the early to mid-1980s and PM_{10} data being mostly available in the early to mid-1990s.

As a consequence of the new $PM_{2.5}$ standard, a large number of sites began collecting $PM_{2.5}$ data in 1999. Daily $PM_{2.5}$ data were extracted from the AIRS database for 1999 and the first 3 quarters of 2000. For each site, quarterly averages for each of the 2 years were computed. The 4 quarters were averaged when at least 1 of the 2 corresponding quarters for each year had at least 50% of the sixth-day samples and at least 45 total sampling days available. Measurements were averaged first by site and then by metropolitan area. Although no network of $PM_{2.5}$ monitoring existed in the United States between the early 1980s and the late 1990s, the integrated average of $PM_{2.5}$ concentrations during the period was estimated by averaging the $PM_{2.5}$ concentration for early and later periods.

Mean sulfate concentrations for 1980-1981 were available for many cities based on data from the Inhalable Particle Monitoring Network and the National Aerometric Database. Recognizing that sulfate was artifactually overestimated due to glass fiber filters used at that time, season and region-specific adjustments were made.[17] Since few states analyzed particulate samples for sulfates after the early 1980s, individual states were directly contacted for data regarding filter use. Ion chromatography was used to analyze PM_{10} filters and this data could be obtained from metropolitan areas across the United States. Filters were collected for a single reference year (1990) in the middle of the 1982-1998 study period. The use of quartz filters virtually eliminated the historical overestimation of sulfate. Mean sulfate concentrations for 1990 were estimated using sulfate from AIRS, data reported directly from individual states, and analysis of archived filters.

Statistical Analysis

The basic statistical approach used in this analysis is an extension of the standard Cox proportional hazards survival model,[21] which has been used for risk estimates of pollution-related mortality in previous longitudinal cohort studies.[15-16] The standard Cox model implicitly assumes that observations are statistically independent after controlling for available risk factors, resulting in 2

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concerns with regard to risk estimates of pollution-related mortality.[22] First, if the assumption of statistical independence is not valid, the uncertainty in the risk estimates of pollution-related mortality may be misstated. Second, even after controlling for available risk factors, survival times of participants living in communities closer together may be more similar than participants living in communities farther apart, which results in spatial autocorrelation. If this spatial autocorrelation is due to missing or systematically mismeasured risk factors that are spatially correlated with air pollution, then the risk estimates of pollution-related mortality may be biased due to inadequate control of these factors. Therefore, in this analysis, the Cox proportional hazards model was extended by incorporating a spatial random-effects component, which provided accurate estimates of the uncertainty of effect estimates. The model also evaluated spatial autocorrelation and incorporated a nonparametric spatial smooth component (to account for unexplained spatial structure). A more detailed description of this modeling approach is provided elsewhere.[22]

The baseline analysis in this study estimated adjusted relative risk (RR) ratios for mortality by using a Cox proportional hazards model with inclusion of a metropolitan-based random-effects component. Model fitting involved a 2-stage process. In the first stage, survival data were modeled using the standard Cox proportional hazards model, including individual level covariates and indicator variables for each metropolitan area (without pollution variables). Output from stage 1 provided estimates of the metropolitan-specific logarithm of the RRs of mortality (relative to an arbitrary reference community), which were adjusted for individual risk factors. The correlation between these values, which was induced by using the same reference community, was then removed.[23] In the second stage, the estimates of adjusted metropolitan-specific health responses were related to fine particulate air pollution using a linear random-effects regression model.[24] The time variable used in the models was survival time from the date of enrollment. Survival times of participants who did not die were censored at the end of the study period. To control for age, sex, and race, all of the models were stratified by 1-year age categories, sex, and race (white vs other), which allowed each category to have its own baseline hazard. Models were estimated for all-cause mortality and for 3 separate mortality categories: cardiopulmonary (*ICD-9 401-440 and 460-519*), lung cancer (*ICD-9 162*), and all others.

Models were estimated separately for each of the 3 fine particle variables, $PM_{2.5}$ (1979-1983), $PM_{2.5}$ (1999-2000), and $PM_{2.5}$ (average). Individual level covariates were included in the models to adjust for various important individual risk factors. All of these variables were classified as either indicator (ie, yes/no, binary, dummy) variables or continuous variables. Variables used to control for tobacco smoke, for example, included both indicator and continuous variables. The smoking indicator variables included: current cigarette smoker, former cigarette smoker, and a pipe or cigar smoker only (all vs never smoking) along with indicator variables for starting smoking before or after age 18 years. The continuous smoking variables included: current smoker's years of smoking, current smoker's years of smoking squared, current smoker's cigarettes per day, current smoker's cigarettes per day squared, former smoker's years of smoking, former smoker's years of smoking squared, former smoker's cigarettes per day, former smoker's cigarettes per day squared, and the number of hours per day exposed to passive cigarette smoke.

To control for education, 2 indicator variables, which indicated completion of high school or education beyond high school, were included. Marital status variables included indicator variables for single and other vs married. Both body mass index (BMI) values and BMI values squared were included as continuous variables. Indicator variables for beer, liquor, and wine drinkers and

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nonresponders vs nondrinkers were included to adjust for alcohol consumption. Occupational exposure was controlled for using various indicator variables: regular occupational exposure to asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel engine exhaust, or formaldehyde, and additional indicator variables that indicated 9 different rankings of an occupational dirtiness index that has been developed and described elsewhere.[17, 25] Two diet indices that accounted for fat consumption and consumption of vegetables, citrus, and high-fiber grains were derived based on information given in the enrollment questionnaire.[18] Quintile indicator variables for each of these diet indices were also included in the models.[18]

In addition to the baseline analysis, several additional sets of analysis were conducted. First, to more fully evaluate the shape of the concentration-response function, a robust locally weighted regression smoother[26] (within the generalized additive model framework[27]) was used to estimate the relationship between particulate air pollution and mortality in the second stage of model fitting. Second, the sensitivity of the fine particle mortality risk estimates compared with alternative modeling approaches and assumptions was evaluated. Standard Cox proportional hazards models were fit to the data including particulate air pollution as a predictor of mortality and sequentially adding (in a controlled forward stepwise process) groups of variables to control for smoking, education, marital status, BMI, alcohol consumption, occupational exposures, and diet.

In addition, to evaluate the sensitivity of the estimated pollution effect while more aggressively controlling for spatial differences in mortality, a 2-dimensional term to account for spatial trends was added to the models and was estimated using a locally weighted regression smoother. The "span" parameter, which controls the complexity of the surface smooth, was set at 3 different settings to allow for increasingly aggressive fitting of the spatial structure. These included a default span of 50%, the span that resulted in the lowest unexplained variance in mortality rate between metropolitan areas, and the span that resulted in the strongest evidence (highest P value) to suggest no residual spatial structure. The risk estimates and SEs (and thus the confidence intervals) were estimated using generalized additive modeling[27] with S-Plus statistical software,[28] which provides unbiased effect estimates, but may underestimate SEs if there is significant spatial autocorrelation and significant correlations between air pollution and the smoothed surface of mortality. Therefore, evidence of spatial autocorrelation was carefully evaluated and tested using the Bartlett test.[29] The correlations of residual mortality with distance between metropolitan areas were graphically examined.

Analyses were also conducted of effect modification by age, sex, smoking status, occupational exposure, and education. Finally, models were fit using a variety of alternative pollution indices, including gaseous pollutants. Specifically, models were estimated separately for each of the pollution variables listed in Table 1, while also including all of the other risk factor variables.

RESULTS

Fine particulate air pollution generally declined in the United States during the follow-up period of this study. Figure 1 plots mean $PM_{2.5}$ concentrations for 1999-2000 over mean $PM_{2.5}$ concentrations for 1979-

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1983 for the 51 cities in which paired data were available. The concentrations of $PM_{2.5}$ were lower in 1999-2000 than in 1979-1983 for most cities, with the largest reduction observed in the cities with the highest concentrations of pollution during 1979-1983. Mean $PM_{2.5}$ levels in the 2 periods were highly correlated (r = 0.78). The rank ordering of cities by relative pollution levels remained nearly the same. Therefore, the relative levels of fine particle concentrations were similar whether based on measurements at the beginning of the study period, shortly following the study period, or an average of the 2.

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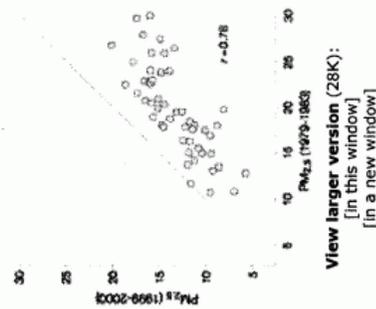- Author information
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Figure 1. Mean Fine Particles Measuring Less Than 2.5 μm in Diameter ($PM_{2.5}$)

Mean $PM_{2.5}$ concentrations in micrograms per meters cubed for 1999-2000 are plotted along with concentrations for 1979-1983 for the 51 metropolitan areas with paired pollution data. The dotted line is a reference 45°-equality line.

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As reported in Table 2, all 3 indices of fine particulate air pollution were associated with all-cause, cardiopulmonary, and lung cancer mortality, but not mortality from all other causes combined. Figure 2 presents the nonparametric smoothed exposure response relationships between cause-specific mortality and $PM_{2.5}$ (average). The log RRs for all-cause, cardiopulmonary, and lung cancer mortality increased across the gradient of fine particulate matter. Goodness-of-fit tests indicated that the associations were not significantly different from linear associations ($P > .20$).

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Table 2. Adjusted Mortality Relative Risk (RR) Associated With a 10-μg/m³ Change in Fine Particles Measuring Less Than 2.5 μm in Diameter

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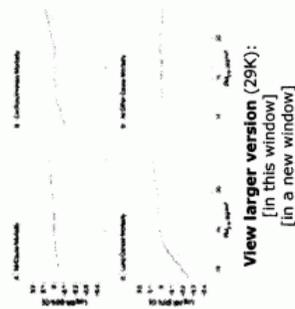
Figure 2. Nonparametric Smoothed Exposure Response Relationship

Vertical lines along x-axes indicate rug or frequency plot of mean fine particulate pollution; $PM_{2.5}$, mean fine particles measuring less than 2.5 μm in diameter; RR, relative risk; and CI, confidence interval.

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The fine particle mortality RR ratios from various alternative modeling approaches and assumptions are presented in Figure 3. After controlling for smoking, education, and marital status, the controlled forward stepwise inclusion of additional covariates had little influence on the estimated associations with fine particulate air pollution on cardiopulmonary and lung cancer mortality. As expected, cigarette smoking was highly significantly associated with elevated risk of all-cause, cardiopulmonary, and lung cancer mortality ($P<.001$). Estimated RRs for an average current smoker (men and women combined, 22 cigarettes/day for 33.5 years, with initiation before age 18 years) were equal to 2.58, 2.89, and 14.80 for all-cause, cardiopulmonary, and lung cancer mortality, respectively. Statistically significant, but substantially smaller and less robust associations, were also observed for education, marital status, BMI, alcohol consumption, occupational exposure, and diet variables. Although many of these covariates were also statistically associated with mortality, the risk estimates of pollution-related mortality were not highly sensitive to the inclusion of these additional covariates.

Figure 3. Mortality Relative Risk (RR) Ratio Associated With 10-μg/m³ Differences of $PM_{2.5}$ Concentrations

Data presented are for 1979-1983 for the different causes of death, with various levels of controlling for individual risk factors, and using alternative modeling approaches. The 3 models with spatial smoothing allow for increasingly aggressive fitting of the spatial structure. Plus sign indicates model included previous variables (ie, smoking included stratification by age, sex, and race); $PM_{2.5}$, mean fine particles measuring less than 2.5 μm in diameter; and CI, confidence interval.

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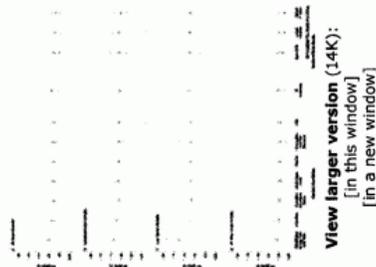[in this window]
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Figure 3 also demonstrates that the introduction of the random-effects component to the model resulted in larger SEs of the estimates and, therefore, somewhat wider 95% confidence intervals. There was no evidence of statistically significant spatial autocorrelation in the survival data based on the Bartlett test ($P>.20$) after controlling for fine particulate air pollution and the various individual risk factors. Furthermore, graphical examination of the correlations of the residual mortality with distance between metropolitan areas did not reveal significant spatial autocorrelation (results not shown). Nevertheless, the incorporation of spatial smoothing was included to further investigate the robustness of the estimated particulate pollution effect. Effect estimates were not highly sensitive to the incorporation of spatial smoothing to account for regional clustering or other spatial patterns in the data.

Figure 4 presents fine particle air pollution–related mortality RR ratios after stratifying by age, sex, education, and smoking status, and adjusting for all other risk factors. The differences across age and sex strata were not generally consistent or statistically significant. However, a consistent pattern emerged from this stratified analysis: the association with particulate pollution was stronger for both cardiopulmonary and lung cancer mortality for participants with less education. Also, for both cardiopulmonary and lung cancer mortality, the RR estimates were higher for nonsmokers.

Figure 4. Adjusted Mortality Relative Risk (RR) Ratio Associated With 10-µg/m^3 Differences of PM$_{2.5}$ Concentrations

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Data presented are for 1979-1983 for the different causes of death stratified by age, sex, education, and smoking status. $PM_{2.5}$ indicates mean fine particles measuring less than 2.5 µm in diameter; CI, confidence interval.
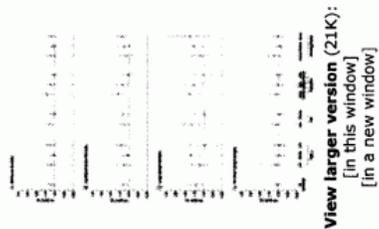
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Figure 5 summarizes the associations between mortality risk and air pollutant concentrations listed in Table 1. Statistically significant and relatively consistent mortality associations existed for all measures of fine particulate exposure, including $PM_{2.5}$ and sulfate particles. Weaker less consistent mortality associations were observed with PM_{10} and PM_{15}. Measures of the coarse particle fraction ($PM_{15-2.5}$) and total suspended particles were not consistently associated with mortality. Of the gaseous pollutants, only sulfur dioxide was associated with elevated mortality risk. Interestingly, measures of $PM_{2.5}$ were associated with all-cause cardiopulmonary, and lung cancer mortality, but not with all other mortality. However, sulfur oxide pollution (as measured by sulfate particles and/or sulfur dioxide) was significantly associated with mortality from all other causes in addition to all-cause, cardiopulmonary, and lung cancer mortality.
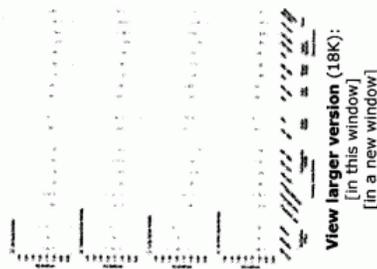
Figure 5. Adjusted Mortality Relative Risk (RR) Ratio Evaluated at Subject-Weighted Mean Concentrations

$PM_{2.5}$ indicates particles measuring less than 2.5 µm in diameter; PM_{10}, particles measuring less than 10 µm in diameter; PM_{15}, particles measuring less than 15 µm in diameter; $PM_{15-2.5}$, particles measuring between 2.5 and 15 µm in diameter; and CI, confidence interval.

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COMMENT

This study demonstrated associations between ambient fine particulate air pollution and elevated risks of both cardiopulmonary and lung cancer mortality. Each 10-μg/m³ elevation in long-term average PM$_{2.5}$ ambient concentrations was associated with approximately a 4%, 6%, and 8% increased risk of all-cause, cardiopulmonary, and lung cancer mortality, respectively, although the magnitude of the effect somewhat depended on the time frame of pollution monitoring. In addition, this analysis addresses many of the important questions concerning the earlier, more limited analysis of the large CPS-II cohort, including the following issues.

First, does the apparent association between pollution and mortality persist with longer follow-up and as the cohort ages and dies? The present analysis more than doubled the follow-up time to more than 16 years, resulting in approximately triple the number of deaths, yet the associations between pollution and mortality persisted.

Second, can the association between fine particulate air pollution and increased cardiopulmonary and lung cancer mortality be due to inadequate control of important individual risk factors? After aggressively controlling for smoking, the estimated fine particulate pollution effect on mortality was remarkably robust. When the analysis was stratified by smoking status, the estimated pollution effect on both cardiopulmonary and lung cancer mortality was strongest for never smokers vs former or current smokers. This analysis also controlled for education, marital status, BMI, and alcohol consumption. This analysis used improved variables to control for occupational exposures and incorporated diet variables that accounted for total fat consumption, as well as for

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consumption of vegetables, citrus, and high-fiber grains. The mortality associations with fine particulate air pollution were largely unaffected by the inclusion of these individual risk factors in the models. The data on smoking and other individual risk factors, however, were obtained directly by questionnaire at time of enrollment and do not reflect changes that may have occurred following enrollment. The lack of risk factor follow-up data results in some misclassification of exposure, reduces the precision of control for risk factors, and constrains our ability to differentiate time dependency.

Third, are the associations between fine particulate air pollution and mortality due to regional or other spatial differences that are not adequately controlled for in the analysis? If there are unmeasured or inadequately modeled risk factors that are different across locations, then spatial clustering will occur. If this clustering is independent or random across metropolitan areas, then the spatial clustering can be modeled by adding a random-effects component to the Cox proportional hazards model as was done in our analysis. The clustering may not be independent or random across metropolitan areas due to inadequately measured or modeled risk factors (either individual or ecological). If these inadequately measured or modeled risk factors are also spatially correlated with air pollution, then biased pollution effects estimates may occur due to confounding. However, in this analysis, significant spatial autocorrelation was not observed after controlling for fine particulate air pollution and the various individual risk factors. Furthermore, to minimize any potential confounding bias, sensitivity analyses, which directly modeled spatial trends using nonparametric smoothing techniques, were conducted. A contribution of this analysis is that it included the incorporation of both random effects and nonparametric spatial smoothing components to the Cox proportional hazards model. Even after accounting for random effects across metropolitan areas and aggressively modeling a spatial structure that accounts for regional differences, the association between fine particulate air pollution and cardiopulmonary and lung cancer mortality persists.

Fourth, is mortality associated primarily with fine particulate air pollution or is mortality also associated with other measures of particulate air pollution, such as PM_{10}, total suspended particles, or with various gaseous pollutants? Elevated mortality risks were associated primarily with measures of fine particulate and sulfur oxide pollution. Coarse particles and gaseous pollutants, except for sulfur dioxide, were generally not significantly associated with elevated mortality risk.

Fifth, what is the shape of the concentration-response function? Within the range of pollution observed in this analysis, the concentration-response function appears to be monotonic and nearly linear. However, this does not preclude a leveling off (or even steepening) at much higher levels of air pollution.

Sixth, how large is the estimated mortality effect of exposure to fine particulate air pollution relative to other risk factors? A detailed description and interpretation of the many individual risk factors that are controlled for in the analysis goes well beyond the scope of this report. However, the mortality risk associated with cigarette smoking has been well documented using the CPS-II cohort.[16] The risk imposed by exposure to fine particulate air pollution is obviously much smaller than the risk of cigarette smoking. Another risk factor that has been well documented using the CPS-II cohort data is body mass as measured by BMI.[30] The Word Health Organization has categorized BMI values between 18.5–24.9 kg/m² as normal; 25–29.9 kg/m², grade 1 overweight; 30–39.9 kg/m², grade 2 overweight; and 40 kg/m² or higher, grade 3 overweight.[31] In the present analysis, BMI

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values and BMI values squared were included in the proportional hazards models. Consistent with previous ACS analysis,[30] BMI was significantly associated with mortality, optimal BMI was between approximately 23.5 and 24.9 kg/m^2, and the RR of mortality for different BMI values relative to the optimal were dependent on sex and smoking status. For example, the RRs associated with BMI values between 30.0 and 31.9 kg/m^2(vs optimal) would be up to approximately 1.33 for never smokers. Based on these calculations, mortality risks associated with fine particulate air pollution at levels found in more polluted US metropolitan areas are less than those associated with substantial obesity (grade 3 overweight), but comparable with the estimated effect of being moderately overweight (grade 1 to 2).

In conclusion, the findings of this study provide the strongest evidence to date that long-term exposure to fine particulate air pollution common to many metropolitan areas is an important risk factor for cardiopulmonary mortality. In addition, the large cohort and extended follow-up have provided an unprecedented opportunity to evaluate associations between air pollution and lung cancer mortality. Elevated fine particulate air pollution exposures were associated with significant increases in lung cancer mortality. Although potential effects of other unaccounted for factors cannot be excluded with certainty, the associations between fine particulate air pollution and lung cancer mortality, as well as cardiopulmonary mortality, are observed even after controlling for cigarette smoking, BMI, diet, occupational exposure, other individual risk factors, and after controlling for regional and other spatial differences.

AUTHOR INFORMATION

Author Contributions: *Study concept and design:* Pope, Burnett, Krewski, Thurston.

Acquisition of data: Thun, Calle, Krewski, Ito, Thurston.

Analysis and interpretation of data: Pope, Burnett, Krewski, Thurston.

Drafting of the manuscript: Pope, Burnett, Ito, Thurston.

Critical revision of the manuscript for important intellectual content: Pope, Thun, Calle, Krewski, Thurston.

Statistical expertise: Pope, Burnett, Krewski.

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Association of Low-Level Ozone and Fine Particles With Respiratory Symptoms in Children With Asthma

Janneane F. Gent, PhD; Elizabeth W. Triche, PhD; Theodore R. Holford, PhD; Kathleen Belanger, PhD; Michael B. Bracken, PhD; William S. Beckett, MD; Brian P. Leaderer, PhD

ABSTRACT

Context Exposure to ozone and particulate matter of 2.5 μm or less ($PM_{2.5}$) in air at levels above current US Environmental Protection Agency (EPA) standards is a risk factor for respiratory symptoms in children with asthma.

Objective To examine simultaneous effects of ozone and $PM_{2.5}$ at levels below EPA standards on daily respiratory symptoms and rescue medication use among children with asthma.

Design, Setting, and Participants Daily respiratory symptoms and medication use were examined prospectively for 271 children younger than 12 years with physician-diagnosed, active asthma residing in southern New England. Exposure to ambient concentrations of ozone and $PM_{2.5}$ from April 1 through September 30, 2001, was assessed using ozone (peak 1-hour and 8-hour) and 24-hour $PM_{2.5}$. Logistic regression analyses using generalized estimating equations were performed separately for maintenance medication users (n = 130) and nonusers (n = 141). Associations between pollutants (adjusted for temperature, controlling for

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same- and previous-day levels) and respiratory symptoms and use of rescue medication were evaluated.

Main Outcome Measures Respiratory symptoms and rescue medication use recorded on calendars by subjects' mothers.

Results Mean (SD) levels were 59 (19) ppb (1-hour average) and 51 (16) ppb (8-hour average) for ozone and 13 (8) $\mu g/m^3$ for $PM_{2.5}$. In copollutant models, ozone level but not $PM_{2.5}$ was significantly associated with respiratory symptoms and rescue medication use among children using maintenance medication; a 50-ppb increase in 1-hour ozone was associated with increased likelihood of wheeze (by 35%) and chest tightness (by 47%). The highest levels of ozone (1-hour or 8-hour averages) were associated with increased shortness of breath and rescue medication use. No significant, exposure-dependent associations were observed for any outcome by any pollutant among children who did not use maintenance medication.

Conclusion Asthmatic children using maintenance medication are particularly vulnerable to ozone, controlling for exposure to fine particles, at levels below EPA standards.

INTRODUCTION

Children with asthma are particularly vulnerable to the adverse health effects of high levels of **air pollution**. Studies of children with asthma living in some of the most highly polluted regions of the world conclude that exposure to levels of ozone or particulate matter (especially particles ≤ 2.5 μm in diameter $[PM_{2.5}]$) regularly in excess of US Environmental Protection Agency (EPA) air quality standards (120 ppb [1-hour average] and 80 ppb [8-hour average] for ozone and 65 $\mu g/m^3$ for 24-hour $PM_{2.5}$) significantly enhances the risk of respiratory symptoms, asthma medication use, and reduced lung function.[1-5]

Studies of children with asthma living in regions with levels of pollution within or near compliance with EPA air quality standards suggest that the current standards do not protect these more vulnerable members of the population.[6-10] Asthma severity, as measured by symptoms, medication use, restrictions in activity, or use of medical services, has been shown to be affected by exposure to ozone (1-hour maximum measurement[6-10] or 8-hour average[6-9]), particles 10 μm or smaller (PM_{10}),[6, 8] or $PM_{2.5}$ (12-hour total).[6]

Of interest in many recent studies of children with asthma are the simultaneous effects of ozone and particulates on asthma severity.[2-3,8] Simultaneous exposure to high levels of both ozone and $PM_{2.5}$ (fine particles)[2] or PM_{10}(coarse particles)[3] found in Mexico City, Mexico, contributed to increased respiratory symptoms among children with asthma. In a region of lower pollution, asthma symptoms were associated with both ozone and course particles.[8] In the current study, we examined the simultaneous

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effects of ozone and fine particles on daily respiratory symptoms and rescue medication use of children with asthma residing in southern New England during spring and summer 2001.

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METHODS

Participants

The study participants were 271 children from a cohort of families living in Connecticut and the Springfield area of Massachusetts who were participating in a study of asthma development.[11-12] From 1997 through 1999, 1002 infants born to families with at least 1 child with physician-diagnosed asthma were enrolled in the original birth cohort. Beginning in 2000, eligible asthmatic siblings (1 per cohort family) were identified and invited to participate in a 1-year prospective study of asthma severity. Eligibility criteria were that the child was younger than 12 years at the time of enrollment and had exhibited respiratory symptoms or used asthma medication within the previous 12 months. Included in the current analysis are subjects enrolled for all or part of the 183-day sampling period (April 1 through September 30, 2001), which includes the summertime, high-ozone pollution months in this region. Of 357 children identified as being eligible for inclusion in the current analysis, 56 refused follow-up, 16 were lost to follow-up, and 14 withdrew before April 1, 2001, leaving a total of 271 (76%). The Human Investigation Committee of Yale University, New Haven, Conn, approved this study, and all respondents (mothers of study subjects) gave informed consent before participation.

Data Collection

Demographic information and medical histories were collected during a home interview with the mother at enrollment. Daily respiratory symptoms (wheeze, persistent cough, chest tightness, shortness of breath) and medication use (maintenance medications, including inhaled or systemic steroids, cromolyn sodium, and leukotriene inhibitors, and rescue medications, including bronchodilators) were recorded on symptom and medication calendars by the child's mother and collected through monthly telephone interviews. Additional information about the previous 12 months was collected at an exit interview (eg, dates the child had been away from the southern New England region during the study year).

Air Quality Assessment

Study subjects resided in a 6691-square mile area in Connecticut and the Springfield area of Massachusetts. All ambient air quality monitoring sites (14 sites for ozone, 10 in Connecticut and 4 in Massachusetts; 4 sites for daily $PM_{2.5}$, 2 in Connecticut and 2 in Massachusetts; 13 temperature sites, 12 in Connecticut and 1 in Massachusetts) were located within a 52.5-mile radius centered at Southington, Conn (14 miles southwest of Hartford). The maximum distance between sites was 105 miles; the minimum distance was 4 miles. The Departments of Environmental Protection (DEPs) of Connecticut and Massachusetts provided measurements for hourly ozone concentrations and temperatures and daily 24-hour $PM_{2.5}$ (total $PM_{2.5}$ accumulated during 24

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hours). Since both ozone and fine particle pollutants, as well as meteorological variables, tend to be regional,[13] the maximum daily 1-hour average (mean over 1 hour) and the 8-hour rolling average (mean over previous 8 hours) for ozone, daily $PM_{2.5}$ concentration, and maximum daily temperature were averaged across monitoring sites. Between-site correlation coefficients (Pearson r) were high for the 4 daily $PM_{2.5}$ sites (median r = 0.91; range, 0.84-0.95) and the 13 temperature sites (median r = 0.97; range, 0.85-0.99). There was more variability among the 14 ozone monitoring sites (median r = 0.83; range, 0.50-0.97 for the 1-hour average; and median r = 0.81; range, 0.47-0.97 for the 8-hour average). For technical details on ambient air quality monitoring, see the Web sites for the Connecticut DEP[14] and the Massachusetts DEP.[15]

Data Analysis

To examine the effects of ozone and $PM_{2.5}$ on children with different degrees of asthma severity, children were divided into 2 groups: those who used any maintenance medication during the 183-day observation period (n = 130) and those who did not (n = 141). Use of maintenance medication was used as a proxy for asthma severity to avoid using the outcome measures (respiratory symptoms and rescue medication use) in the assessment of severity. Logistic regression analyses, using generalized estimating equations (PROC GENMOD with AR1 autoregressive structure in SAS statistical software)[16-18] and adjusted for maximum daily temperature, were used to evaluate the association between levels of ozone and $PM_{2.5}$, with presence or absence of specific respiratory symptoms or rescue medication use. Using a repeated-measures technique permitted each subject to serve as his or her own control; therefore, personal variables (eg, race and other sociodemographic factors) that would not change during the study were not included in the models. Subgroup analysis, which included either 17 160 observations (an average of 132 days of data for 130 users of maintenance medication) or 19 035 observations (135 days for 141 nonusers of maintenance medication), focused directly on the association between exposures and health effects.

Exposure variables were categorized into quintiles, then entered into the model as dummy variables. The reference category for each was the lowest quintile. Both same-day and previous-day levels of ozone and $PM_{2.5}$ were examined. Analyses were performed separately for each severity group and each outcome. In single-pollutant models, a test for linear trend was performed by examining the model when the pollutant was entered as a continuous variable instead of as quintiles. In copollutant models, a test for goodness of fit was performed using the Hosmer-Lemeshow statistic for logistic regression. Significance level for all tests was set at .05.

RESULTS

Descriptive Statistics

Levels of ozone, $PM_{2.5}$, and temperature from April through September 2001 are summarized in Table 1 and Figure 1. The EPA 1-hour standard (120 ppb) was exceeded on 3 days, and the 8-hour ozone standard

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(80 ppb) was exceeded on 10 days of the 183 days of observation. There were no days when the level of $PM_{2.5}$ exceeded the EPA 24-hour standard of 65 μg/m³. There was a strong correlation between ozone and fine particles ($PM_{2.5}$ vs 1-hour average ozone $r = 0.77$ vs 8-hour average $r = 0.74$) (Table 2).

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Table 1. Ozone, Particulate Matter of 2.5 μm or Less ($PM_{2.5}$), and Temperature in Southern New England, April 1 to September 30, 2001

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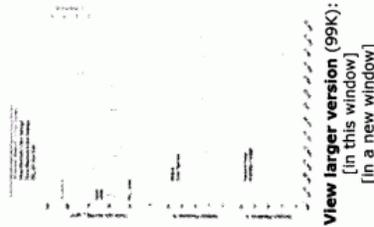
Figure. Daily Levels of Ozone (Both 1-Hour Average and 8-Hour Average), Particulate Matter of 2.5 μm or Less ($PM_{2.5}$), and Daily Maximum Temperature, With Daily Prevalence of Respiratory Symptoms for Users of Asthma Maintenance Medication (n = 130) for Southern New England, April 1 through September 30, 2001

Dotted lines at 80 ppb and 120 ppb indicate Environmental Protection Agency standards for 8-hour average and 1-hour average ozone, respectively. Note that daily exposure levels shown here are the result of averaging over regional monitoring sites (14 ozone, 4 $PM_{2.5}$, and 13 temperature sites).

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Table 2. Pearson Correlation Coefficients for Same Day and Previous Day Levels of Ozone and Particulate Matter of 2.5 μm or Less ($PM_{2.5}$)

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There were no significant differences between the users (n = 130) of maintenance medication and nonusers (n = 141) for mean (SD) age of study subjects (age on April 1, 2001, for users, 8.8 [2.0] years [range, 2.4-12.7 years]; age of nonusers, 8.3 [2.2] years [range, 2.0-12.6 years]; t test $P = .71$) or mean days of participation (mean participation for users, 132 [48] days [range, 3-183 days]; mean participation for nonusers, 135 [51] days [range, 5-183 days]; t test $P = .50$). Sex and ethnicity did not differ by medication use. Nearly two thirds of each group were male (users, 64.6%; nonusers, 64.5%; x^2 test $P = .99$), and most

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children in each group were white, with smaller numbers of black and Hispanic children (users, 80.0%, 8.5%, and 11.5%, respectively; nonusers, 70.9%, 11.4%, and 17.7%, respectively; x^2 test P = .22). Compared with nonusers of maintenance medication, users had significantly more days of all respiratory symptoms and rescue medication use: 50% of this group experienced approximately 1 week of persistent cough or wheeze, had 2 to 3 days of chest tightness or shortness of breath, and used rescue medication for nearly 3 weeks during the 26-week study period. At least half of all nonusers experienced no symptoms and did not use rescue medication during this same period (Table 3). Daily prevalence of symptoms for users of maintenance medication is shown in Figure 1. With the exception of somewhat higher rates of symptoms in the early spring and late summer when the temperatures tended to be lowest, there was overall conformity of reporting all 4 symptoms across the observation period.

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Table 3. Rates of Respiratory Symptoms and Rescue Medication Use for Study Subjects Stratified by Use of Maintenance Medication (Southern New England, April 1-September 30, 2001)*

Single-Pollutant Models for Users of Maintenance Medication

Ozone (1-Hour Average). An ozone concentration of 51.6 ppb or higher (the top 3 quintiles of the distribution of the maximum 1-hour average) on the same day as the reported symptom was the only exposure variable associated with an increased likelihood of wheeze (by 16%, 16%, and 22%, respectively) (Table 4, model 1). A 4% increase in bronchodilator use was also associated with same-day levels of ozone (51.6-58.8 ppb) (Table 4, model 1). Previous-day levels of maximum 1-hour average ozone were associated with increased likelihoods of persistent cough (16% increase for levels ≥72.7 ppb), chest tightness (by 21%, 30%, and 37% for levels ≥51.6 ppb), and shortness of breath (by 22% and 30% for levels ≥58.9 ppb) (Table 4, Model 2). The effects of previous-day levels on chest tightness and shortness of breath were significant in an exposure-dependent way: for each 50-ppb increase in previous-day, 1-hour ozone levels, the likelihood of these symptoms increased by 26% (odds ratio [OR], 1.26; 95% confidence interval [CI], 1.0-1.48) and 22% (OR, 1.22; 95% CI, 1.02-1.45), respectively.

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Table 4. Odds Ratios From 6 Single-Pollutant Logistic Regression Models of Respiratory Symptoms or Rescue Medication Use of Maintenance Medication Users (n = 130) (Southern New England, April 1 to September 30, 2001)*

Ozone (8-Hour Average). An ozone concentration of 63.3 ppb or higher, measured as the maximum 8-hour average on the same day as the reported symptom, was associated with a 30% increase in chest tightness (Table 4, model 3). Previous-day levels of 52.1 ppb or higher were associated with increased chest tightness, persistent cough, and shortness of breath (Table 4, model 4). As was the case with 1-hour ozone levels, the associations with the symptoms of chest tightness and shortness of

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breath were exposure dependent: a 50-ppb increase in previous-day, 8-hour ozone level increased the likelihood of chest tightness (OR, 1.33; 95% CI, 1.09-1.62) and shortness of breath (OR, 1.30; 95% CI, 1.05-1.61).

PM$_{2.5}$. Increased likelihood of chest tightness was associated with same-day levels of PM$_{2.5}$ from 12.1 to 18.9 µg/m^3 (Table 4, model 5). Previous-day levels of 19.0 µg/m^3 or higher were associated with persistent cough, chest tightness, and shortness of breath (Table 4, model 6).

Copollutant Models for Users of Maintenance Medication

In logistic regression models of both ozone and fine particles for children taking maintenance medication, an increased likelihood of respiratory symptoms was associated with levels of ozone on the same day, previous day, or both; and increased bronchodilator use was associated with the highest level of same-day ozone. Neither respiratory symptoms nor bronchodilator use were associated with level of fine particles.

Ozone (1-Hour Average) and PM$_{2.5}$. Increased likelihood of wheeze was associated with same-day levels of 1-hour average ozone of 43.2 ppb or higher in an exposure-dependent manner (Table 5). When ozone is entered into this same model as a continuous variable, a 50-ppb increase in same-day ozone increases the likelihood of wheeze by 35% (OR, 1.35; 95% CI, 1.11-1.65). None of the exposure variables was associated with an increased likelihood of persistent cough, and only 1-hour average ozone levels between 43.2 and 51.5 ppb were associated with a decreased likelihood of cough (OR, 0.88; 95% CI, 0.78-0.99). The likelihood of chest tightness was significantly increased by same-day (≥58.9 ppb) and previous-day (≥51.6 ppb) levels of ozone in an exposure-dependent way. The likelihood of chest tightness increases by 47% (OR, 1.47; 95% CI, 1.18-1.84) for each 50-ppb increase in same-day levels of ozone, and by 42% (OR, 1.42; 95% CI, 1.14-1.78) for each 50-ppb increase in previous-day levels. Shortness of breath and ozone were similarly associated; likelihood of the symptom was increased by same-day levels of 72.7 ppb or higher and previous-day levels from 58.9 to 72.6 ppb (by 32%). Increased likelihood of bronchodilator use was associated with same-day levels of 72.7 ppb or higher (Table 5).

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Table 5. Odds Ratios From the Copollutant Logistic Regression Model for Same-Day and Previous-Day Levels of Ozone (1-Hour Average) and Particulate Matter of 2.5 µm or Less (PM$_{2.5}$) Related to Each Respiratory Symptom or Rescue Medication Use of Maintenance Medication Users (n = 130) (Southern New England, April 1 to September 30, 2001)*

Ozone (8-Hour Average) and PM$^{2.5}$. For 8-hour average ozone levels, the likelihood of chest tightness was increased by same-day (OR, 1.64; 95% CI, 1.23-2.17) and previous-day (OR, 1.45; 95% CI, 1.10-1.92) levels of 63.3 ppb or higher. Shortness of breath was similarly associated; likelihood of the symptom was increased by same-day (OR, 1.45; 95% CI, 1.10-1.91) and

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previous-day (OR, 1.31; 95% CI, 1.00-1.71) levels of 63.3 ppb or higher. As seen for the highest 1-hour ozone level, increased bronchodilator use was associated with same-day levels of 63.3 ppb or higher for 8-hour ozone measurements (OR, 1.09; 95% CI, 1.02-1.17).

Nonusers of Maintenance Medication

Single-Pollutant Models. Similar analyses for nonusers of maintenance medication revealed no significant associations among the top 3 concentration quintiles for the exposure variables and respiratory symptoms or bronchodilator use. For example, chest tightness was not significantly associated with same-day, 1-hour ozone levels of 72.7 ppb or higher (OR, 0.92; 95% CI, 0.68-1.25), same-day, 8-hour ozone levels of 63.3 ppb or higher (OR, 1.17; 95% CI, 0.72-1.92), or previous-day, 8-hour ozone levels of 63.3 ppb or higher (OR, 0.99; 95% CI, 0.74-1.35). The only significant association was an increased likelihood of wheeze (OR, 1.20; 95% CI, 1.00-1.43) in the presence of previous-day, 8-hour average ozone between 39.1 and 45.8 ppb (the second quintile).

Copollutant Models. For the children who were not users of asthma maintenance medication, neither fine particles nor 1-hour average ozone levels were associated with increased likelihoods of respiratory symptoms in copollutant models. Increased bronchodilator use was associated with previous-day fine particle concentrations between 9.0 and 12.0 µg/m³ in the model with 1-hour ozone levels (Table 6) and with these same levels in the model with 8-hour ozone (OR, 1.30; 95% CI, 1.02-1.65). An increase in the likelihood of wheeze was associated with 8-hour ozone, but only for concentrations between 39.1 and 45.8 ppb on the same day (OR, 1.33; 95% CI, 1.00-1.77) or the previous day (OR, 1.31; 95% CI, 1.05-1.63) and between 52.1 and 63.2 ppb for same-day levels (OR, 1.35; 95% CI, 1.00-1.81).

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Table 6. Odds Ratios From the Copollutant Logistic Regression Model for Same-Day and Previous-Day Levels of Ozone (1-Hour Average) and Particulate Matter of 2.5 µm or Less (PM$_{2.5}$) Related to Respiratory Symptoms and Rescue Medication Use of Maintenance Medication Nonusers (n = 141) (Southern New England, April 1 to September 30, 2001)*

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COMMENT

In models controlling for ambient fine particle concentration and typically at levels below EPA air quality standards, daily ambient ozone was found to be significantly associated with increased risk of respiratory symptoms and increased use of rescue medication among children with asthma severe enough to require maintenance medication. Study strengths include frequent telephone follow-up to collect information on daily calendar-recorded symptoms and medication use; absence of reporting bias between symptoms and

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regionally collected ambient air quality data; the use of both the maximum 1-hour average (sensitive to spikes in concentration) and 8-hour average (a measure of short-term, cumulative exposure) to assess daily ambient ozone levels; use of $PM_{2.5}$ levels measured daily; and examination of the simultaneous effects of ozone and $PM_{2.5}$ at levels near or below current EPA ambient standards. Our results contribute to the limited literature examining the simultaneous effects of ozone and suspended particles on daily respiratory symptoms for a sensitive subpopulation in models adjusted for daily temperature.

One potential limitation of the study is that ambient ozone and particle concentrations were represented as means over regional sites. For the 14 ozone sites on any particular day, the mean (SD) ratio of maximum to minimum reading was 1.70 (0.50), which is similar to the mean ratio of upper to lower limit of each quintile of the summer ozone distribution of 1.38 (0.30) from our study. This suggests that the analysis using quintiles of the ozone distribution captures the variability that exists in the study region. Variability among $PM_{2.5}$ sites was less, but a potential limitation is that there were only 4 sites with daily measurements. However, a comparison between readings from these 4 sites and readings from the 10 sites with $PM_{2.5}$ readings every 3 days revealed good agreement. For the 61 days all sites had in common, the 10-site mean (SD) was 13.8 (8.2) compared with 12.8 (7.7) $\mu g/m^3$ for the 4 sites, and the Pearson correlation was 0.97.

Another potential limitation is the lack of personal variables (eg, race) in the regression models. However, by taking advantage of the repeated measurements we had for each subject, we were able to use each subject as his or her own control. The sample of 271 children contributed 36 195 person-days of observations to the analyses. Our within-subjects analytic approach permitted a strong test of the associations between ambient **air pollution** and health outcomes, and personal variables, since they would not vary within subjects, could be excluded from the models.

In this study, we did not consider medical care utilization as an outcome. Since this was not a clinic-based study, we did not have access to records to confirm medical visit dates. However, medical records are not necessarily more objective than reports of symptoms and medication use, since a number of factors unrelated to symptom severity also influence utilization. Symptoms and medication use vary from day to day and may be a more sensitive indicator of the effects of daily changes in **air pollution** on respiratory health, since not all symptoms result in a physician visit.

In our copollutant models, ozone but not fine particles significantly predicted increased risk of respiratory symptoms and rescue medication use among children using asthma maintenance medication. We found an immediate (same-day) effect of ozone on wheeze (with the 1-hour ozone metric), chest tightness, and shortness of breath (with both the 1-hour and 8-hour ozone metrics). We also found that previous-day levels of ozone (both metrics) were significantly associated with increased risk of chest tightness and shortness of breath. Goodness-of-fit tests for copollutant models suggest that the models with significant findings (wheeze, chest tightness, and shortness of breath) are reasonably good fits to the data. There were no systematic patterns to the lack of fit for models for persistent cough and bronchodilator use. However, because of repeated measurements, observations were not independent in any of the models, which may affect the interpretation of the Hosmer-Lemeshow statistic. It is possible that the

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more frequently reported events of persistent cough and bronchodilator use may be associated with ambient **air pollution** in combination with other factors (eg, activity level) not included in the current study.

Effects of 1-hour ozone among children using asthma maintenance medication, especially the association of same-day ozone with wheeze and previous-day ozone with chest tightness, appear to be more exposure dependent than the effects of small particles. In copollutant models for wheeze and chest tightness, a 50-ppb increase in same-day, 1-hour ozone level increased the likelihood of wheeze by 35% and chest tightness by 47%. However, since particles and ozone were positively correlated, it is difficult to separate their effects in the copollutant models. In the single-pollutant model for chest tightness, a 50-ppb increase in previous-day levels of 1-hour ozone resulted in a 26% increase in the likelihood of having the symptom. When same-day levels of 1-hour previous-day, 1-hour ozone level increased the likelihood of chest tightness by 42%. Levels of $PM_{2.5}$ happened to be relatively low and never exceeded EPA standards for the duration of the study period, which likely contributed to the lack of significant particle effects observed in the copollutant models. For our region, an examination of the association between symptoms and particle levels in winter months when ozone is not a factor would help us better understand the role of exposure to small particles on respiratory health.

There is little doubt that children with asthma are especially vulnerable to high levels of **air pollution**. Among a group of asthmatic children (n = 71) living in Mexico City, where levels of ozone have regularly exceeded the EPA standard, multivariate regression analyses of same-day ambient **air pollution** and separate models of previous-day pollution all revealed significant effects of ozone and fine particles on the likelihood of cough (an increase of 8% for each 50-ppb increase in ozone on either the same day or previous day; an increase of 6% or 8% for each 10-μg/m³ increase in $PM_{2.5}$ on the same day or previous day) and lower respiratory tract illness (by 7% for each pollutant on the same day or previous day).[2] The effects seen for $PM_{2.5}$ in Mexico City, but not in our study, could be explained by the large difference between the mean (SD) 24-hour concentration of $PM_{2.5}$ in Mexico City (85.7 [30.2] μg/m³), which was above the EPA standard of 65 μg/m³ and was well above the mean of 13.1 (7.9) μg/m³ observed in the current study. In addition, the chemical composition of the fine particles in each region may be different.[2,10] The larger effect of 1-hour ozone that we found could be explained in part by the fact that we stratified our analysis by asthma severity, thereby observing a consistent pattern of increased likelihood of some symptoms of more than 40% in the group with more severe disease and no significant effects among the group with less severe disease.

Our results are consistent with recent studies[7,10] that suggest exposure to lower levels of ozone is associated with respiratory symptoms in children with asthma. Children with asthma who attended a week-long asthma summer camp (a total of 166 children during three 1-week periods compared with our 183-day observation period) in the Connecticut River Valley (the same geographic area as the current study) were exposed to levels of ozone somewhat higher than the current study (mean [SD] 1-hour average, 84 [38] ppb; range, 20-160 ppb). In single-pollutant models, daily levels of same-day ozone were significantly associated with increased chest symptoms, β-agonist use, and decreased lung function.[10] These associations did not change when same-day

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levels of sulfate (a primary constituent of $PM_{2.5}$ in this region) were added to the model. In a recent study[7] of 846 children with asthma living in 8 urban areas around the country, ozone at levels comparable to those observed in the current study (mean 8-hour average of 48 ppb compared with our mean of 51 ppb with <5% of the days exceeding the EPA standard of 80 ppb in both studies) was associated, in single-pollutant models, with morning respiratory symptoms (wheeze, cough, or chest tightness). Although the data were not shown, the authors of each study also noted that adding copollutants to their models did not appreciably confound the effect of ozone. Both studies concluded that ozone, even at levels lower than current EPA standards, is strongly associated with adverse respiratory health effects in children with asthma.

Previous environmental chamber studies[19-21] of adults with asthma exposed to ozone for 1 to a few hours have shown relatively little effect on symptoms or lung function. On the other hand, short-term exposure to elevated levels of ozone and particulates in children under ambient exposure conditions in areas of lower pollution suggests that the more prolonged exposures associated with summertime ozone produce a greater stimulus than chamber exposures, that asthmatic children are more susceptible than asthmatic adults, that effects are delayed and not captured by short-term chamber studies, or that coexposures to other unidentified constituents of ambient air enhance the response to ozone. A recent study supporting this view examined the impact of traffic-reducing changes in Atlanta, Ga, during the 1996 summer Olympic Games.[24] Significant reductions in ozone and particles were associated with significant reductions in acute asthma care events (physician, clinic, or hospital visits) among children aged 1 to 16 years. In analyses including days before, during, and after the Olympics, an increase in daily acute asthma events was associated with levels of 1-hour ozone concentrations beginning at 60 to 89 ppb. Our findings indicate that comparable levels were associated with an increased likelihood of wheeze (≥58.9 ppb), chest tightness (≥58.9 ppb), shortness of breath, and rescue medication use (≥72.7 ppb).

In our study, we defined 2 levels of asthma severity based on maintenance medication use. We reasoned that since we were examining the association of **air pollution** and symptoms, we did not want to use symptoms to define severity. Instead, we used maintenance medication as a proxy for disease severity even though medication use and symptoms will be related. Maintenance medication users had significantly more wheeze, persistent cough, chest tightness, and shortness of breath than the nonusers and used rescue medication significantly more often. Our results strongly suggest that this definition of asthma severity divides the group into 2 levels of vulnerability to **air pollution**.

Our study is a unique combination of a sample of asthmatic children with detailed symptom and medication use followed for a long period and well-measured daily ambient copollutants. These results add to others that suggest that, even at low levels of ambient ozone and controlling for ambient fine particle concentration, children with severe asthma are at a significantly increased risk of experiencing respiratory symptoms.

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Research Article

Ambient Air Pollution and Atherosclerosis in Los Angeles

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Abstract
Associations have been found between long-term exposure to ambient air pollution and cardiovascular morbidity and mortality. The contribution of air pollution to atherosclerosis that underlies many cardiovascular diseases has not been investigated. Animal data suggest that ambient particulate matter (PM) may contribute to atherogenesis. We used data on 798 participants from two clinical trials to investigate the association between atherosclerosis and long-term exposure to ambient PM up to 2.5 μm in aerodynamic diameter ($PM_{2.5}$). Baseline data included assessment of the carotid intima-media thickness (CIMT), a measure of subclinical atherosclerosis. We geocoded subjects' residential areas to assign annual mean concentrations of ambient $PM_{2.5}$. Exposure values were assigned from a $PM_{2.5}$ surface derived from a geostatistical model. Individually assigned annual mean $PM_{2.5}$ concentrations ranged from 5.2 to 26.9 μg/m^3 (mean, 20.3). For a cross-sectional exposure contrast of 10 μg/m^3 $PM_{2.5}$, CIMT increased by 5.9% (95% confidence interval, 1-11%). Adjustment for age reduced the coefficients, but further adjustment for covariates indicated robust estimates in the range of 3.9-4.3% (p-values, 0.05-0.1). Among older subjects (≥ 60 years of age), women, never smokers, and those reporting lipid-lowering treatment at baseline, the associations of $PM_{2.5}$ and CIMT were larger with the strongest associations in women ≥ 60 years of age (15.7%, 5.7-26.6%). These results represent the first epidemiologic evidence of an association between atherosclerosis and ambient air pollution. Given the leading role of cardiovascular disease as a cause of death and the large populations exposed to ambient $PM_{2.5}$, these findings may be important and need further confirmation. _Key words:_ air pollution, atherosclerosis, particulate matter. _Environ Health Perspect_ 113:201-206 (2005). doi:10.1289/ehp.7523 available via http://dx.doi.org/ [Online 22 November 2004]

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Introduction

A large body of epidemiologic evidence suggests associations between ambient air pollution and cardiovascular mortality and morbidity (Peters and Pope 2002; Pope et al. 2004). All of these studies focus on events occurring at a late stage of vascular disease processes. The impact of air pollution on the underlying preclinical conditions remains poorly understood.

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We hypothesize that current levels of ambient particulate matter (PM) up to 2.5 μm in aerodynamic diameter ($PM_{2.5}$) may contribute to atherosclerosis, leading to subclinical anatomical changes that play a major role in cardiovascular morbidity and mortality later in life. Animal studies support our hypothesis by showing that inhalation of ambient PM promotes oxidative lung damage, including alveolar and systemic inflammatory responses (Becker et al. 1996; Dye et al. 2001; Fujii et al. 2002; Goto et al. 2004; Suwa et al. 2002; van Eeden et al. 2001).

We investigated the association between residential ambient $PM_{2.5}$ and carotid artery intima-media thickness (CIMT) using prerandomization baseline data from two recent clinical trials conducted in Los Angeles, California (Hodis et al. 2002). CIMT is a well-established quantitative measure of generalized atherosclerosis that correlates well with all of the major cardiovascular risk factors, with coronary artery atherosclerosis, and with clinical cardiovascular events (Mack et al. 2000). It is an established tool for investigating the contribution of long-term exposures such as smoking or passive smoking to subclinical stages of atherosclerosis at any given age (Diez-Roux et al. 1995; Howard et al. 1994, 1998). This is the first study to assess the association of atherosclerosis with air pollution.

Materials and Methods

Population and health assessment. We used baseline health data from two randomized, double-blind, placebo-controlled clinical trials conducted at the University of Southern California Atherosclerosis Research Unit (Hodis et al. 2002). The Vitamin E Atherosclerosis Progression Study (VEAPS) investigated the effects of vitamin E on the progression of atherosclerosis measured by CIMT. The B-Vitamin Atherosclerosis Intervention Trial (BVAIT) focused on the effect of vitamin B supplements on the progression of atherosclerosis (trial in progress). Baseline assessment in both trials included CIMT measured between 1998 and 2003 using the same standardized methods (Hodis et al. 2002; Selzer et al. 1994, 2001). Recruitment of volunteers occurred over the entire Los Angeles Basin, covering a geographic area of approximately 64,000 km^2.

Eligible subjects for the VEAPS trial ($n = 353$) were men and women ≥ 40 years of age with slightly increased LDL cholesterol (≥ 3.37 mmol/L) but with no clinical signs or symptoms of cardiovascular disease (CVD) (Hodis et al. 2002). Subjects with diabetes, diastolic blood pressure > 100 mm Hg, thyroid disease, serum creatinine > 0.065 mmol/L, life-threatening diseases, or high alcohol intake were excluded.

BVAIT ($n = 506$) had a similar design to that of VEAPS. Men and women > 40 years of age were prescreened to meet study criteria (fasting plasma homocysteine ≥ 8.5 μmol/L; postmenopausal for women; no evidence of diabetes, heart disease, stroke, or cancer). Subjects were excluded on the basis of any clinical signs or symptoms of CVD, diabetes or fasting serum glucose ≥ 140 mg/dL, triglyceride levels ≥ 150 mg/dL, serum creatinine > 1.6 mg/dL, high blood pressure, untreated thyroid disease, life-threatening disease with prognosis < 5 years, or high alcohol intake.

Thus, our study included "healthy" subjects with biomarkers (elevated LDL cholesterol or homocysteine) that suggested an increased risk of future CVDs ($n = 859$). Fifty-eight subjects were excluded in the exposure assignment process because they lived outside the area with $PM_{2.5}$ data. Three subjects had missing data in at least one of the covariates used in the models. Our total sample consisted of 798 participants.

Health measures, including CIMT. Our main outcome of interest is CIMT. In both trials, high-resolution B-mode ultrasound images of the right common carotid artery were obtained before the intervention (baseline) with a 7.5-MHz linear array transducer attached to an ATL Ultramark-4 Plus Ultrasound System (Ultramark, Bothell, WA). We used this baseline CIMT measurement as the outcome. Details of this highly reproducible method are published (Hodis et al. 2002; Selzer et al. 1994, 2001). Blood pressure, height, and weight were measured with standard procedures.

The baseline questionnaires included an assessment of all major CVD risk factors and covariates, including clinical events, diet, use of prescription medications, physical activity, current and past smoking and passive smoking, and vitamin supplements. Age, education, and other sociodemographic factors were available for each subject. Fasting blood samples were also drawn for lipid measurements. Data used in our analyses were collected with the same tools in both trials.

Exposure assignment. To assess exposure we chose a novel approach derived from a geographic information system (GIS) and geostatistics. This method allows for assignment of long-term mean ambient concentrations of $PM_{2.5}$ to the ZIP code area of each subject's residential address (Künzli and Tager 2000). The resulting surface of $PM_{2.5}$ covered the entire Los Angeles metropolitan area. The surface is derived from a geostatistical model and data from 23 state and local district monitoring stations (during 2000). These monitors are located across the Los Angeles region to characterize urban levels of pollution. To assign exposure, $PM_{2.5}$ data were interpolated using a combination of a universal kriging model

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with a quadratic drift and a multiquadric radial basis function model (Bailey and Gatrell 1995; Burrough and McDonnell 1998). We averaged the two surfaces based on 25-m grid cells. Examination of errors from the universal model showed that > 50% of the study area had assigned values within 15% of monitored concentrations, whereas 67% were within 20%. The larger errors were on the periphery of our study area, where the density of study participants was the lowest. We linked the ZIP code centroids of each subject with the exposure surface through a geocoding database [Environmental Systems Research Institute (ESRI) 2004]. Figure 1 illustrates the $PM_{2.5}$ surface with the geolocated ZIP codes. Individually assigned $PM_{2.5}$ data had a range from 5.2 to 26.9 µg/m³ (mean, 20.3), thus exceeding the range observed across 156 metropolitan areas used in the largest cohort study of air pollution and mortality (Pope et al. 2002). All models were implemented with ArcScript from ESRI (Redlands, CA).
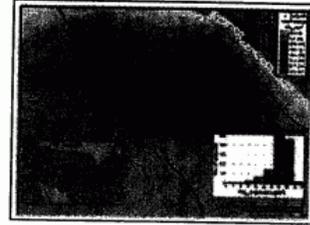

Figure 1. ZIP code locations of the study population geocoded on the $PM_{2.5}$ surface, modeled with 2000 $PM_{2.5}$ data, and distribution of individually assigned concentrations.

Statistical analyses. We tested the univariate and multivariate associations between CIMT and ambient $PM_{2.5}$ using linear regression analyses. Extensive residual diagnostics indicated some heteroskedasticity, which was rectified with the natural log-transformed CIMT. We adjusted for factors that were statistically associated with both CIMT and ambient $PM_{2.5}$ (age, male sex, low education, and low income). Next, we expanded the models using covariates that were associated with either $PM_{2.5}$ or CIMT, including indicator variables for current second-hand smoke exposure and current and former personal smoking. We then added covariates that play a role in atherosclerosis such as blood pressure, LDL cholesterol, or proxy measures such as reporting treatment with antihypertensives or lipid-lowering medications at study entry. These factors may affect the pathophysiologic pathways linking air pollution exposure and atherosclerosis (Ross 1999); thus, such models may overadjust the coefficients. We chose this conservative approach to test the sensitivity of the effect estimates under a broad range of model assumptions.

There is increasing evidence that host factors such as age, sex, or underlying disease and risk profiles may modify the effects of air pollution (Pope et al. 2002; Zanobetti and Schwartz 2002). Furthermore, the finding of atherosclerosis in PM-exposed rabbits was based on a hyperlipidemic trait (Suwa et al. 2002). Therefore, we also stratified by sex, age (< 60 years, ≥ 60 years), smoking status, and lipid-lowering drug therapy.
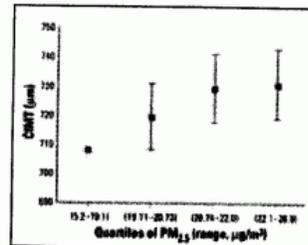
Results

Table 1 summarizes the main characteristics of the study population and among main subgroups. Table 2 presents the percent change in CIMT in association with a 10 µg/m³ contrast in ambient $PM_{2.5}$ concentrations for three cross-sectional regression models. The unadjusted model indicates a 5.9% [95% confidence interval (CI), 1-11%] increase in CIMT per 10 µg/m³ $PM_{2.5}$. For the observed contrast between lowest and highest exposure (20 µg/m³ $PM_{2.5}$), this corresponds to a 12.1% (2.0-23.1%) increase in CIMT. The only covariate with a substantial effect on the point estimate was age, which reduced the effect from 5.9 to 4.3% (0.4-9%) per 10 µg/m³ $PM_{2.5}$. This change agrees with the age-related effect modification. Otherwise, effect estimates across the models remained robust, in the range of 3.9-4.3% with *p*-values from 0.05 to 0.1. To corroborate the exposure-response relationship, we also categorized $PM_{2.5}$ levels into quartiles. Figure 2 shows the adjusted mean CIMT across these four groups of equal sample size at the mean levels of the covariates (age, sex, education, and income). The trend across the exposure groups was statistically significant (*p* = 0.041). The unadjusted means of CIMT among these quartiles of exposure were 734, 753, 758, and 774 µm, respectively.

The associations between CIMT and $PM_{2.5}$ were substantially stronger among 109 subjects reporting lipid-lowering medication at study entry, both in men and in women (Table 2, Figure 3). The crude effect reached 15.8% (2-31%) per 10 µg/m³ $PM_{2.5}$, with adjusted values ranging between 12 and 16%. Despite the small sample size, *p*-values of all models were mostly < 0.1 and often < 0.05.

Results also suggest significant age and sex interactions, with much larger effects in women and in the older age group (Figure 3). Effect estimates in

Table 1.

Table 2.

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women were statistically significant and typically in the range of 6-9% per 10 $\mu g/m^3$ $PM_{2.5}$. Associations were strongest among women $\geq$ 60 years of age (n = 186), leading to crude estimates of 19.2% (9-31%). Adjusted coefficients ranged from 14 to 19%, being statistically significant in all models and sensitivity analyses.

Among never smokers (n = 502), the effect estimate reached 6.6% (1.0-12.3%). The estimate was small and not significant in current (n = 30) and former smokers (n = 265).

Discussion

Our study presents the first evidence for an association between CIMT and long-term exposure to ambient air pollution. As recently reviewed in a statement of the American Heart Association (Brook et al. 2004) substantial epidemiologic and experimental evidence suggests a contribution of ambient air pollutants on cardiovascular mortality and morbidity. However, these studies focus on acute and subacute effects on cardiac autonomic function, inflammatory or thrombogenic markers, arrhythmia, myocardial infarction, cardiovascular hospital admission, and death. The only outcome considered in long-term air pollution studies has been mortality. The relative risks for acute effects on mortality have been substantially smaller than those observed for long-term associations (Pope et al. 2002; Samet et al. 2000). As shown previously, cohort studies are capable of capturing acute and chronic effects of air pollution on the course of diseases that ultimately lead to premature death (Künzli et al. 2001). In contrast, time-series and panel studies investigate only the associations of event occurrence with the most recent exposure (Künzli et al. 2001). Thus, if air pollution has both acute and cumulative long-term effects, one expects larger mortality coefficients in cohort studies. CIMT reflects long-term past exposure; thus, we provide the first evidence for chronic effects of air pollution on atherogenesis that may in part explain the above mentioned discrepancy between acute and long-term risk estimates (Pope et al. 2002; Samet et al. 2000).

Figure 2. Mean CIMT ± 1 SE among quartiles of the $PM_{2.5}$ distribution. The *y*-axis shows mean CIMT levels at the population average of the adjustment covariates (age, sex, education, and income). The first quartile is the reference group.
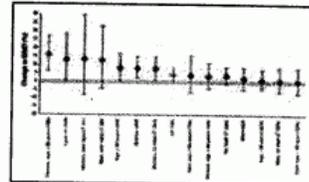

Figure 3. Percent difference and 95% CI in CIMT associated with a 10 $\mu g/m^3$ contrast in ambient $PM_{2.5}$ in all subjects and in subgroups. Lipid-LT, lipid-lowering therapy. All estimates are based on the cross-sectional linear model with log intima-media thickness as the dependent variable and home outdoor $PM_{2.5}$ as the independent variable, adjusted for sex, age, education, and income. Numbers in parentheses are numbers of subjects per group. Data are ordered by size of point estimate; the null effect line is indicated by a dash.

There are several major aspects to be considered in the interpretation of this new finding, mainly the strength in the exposure assignment, the limited evidence for bias, the differences in effects within subgroups, and plausibility.

Exposure assignment. The individual residence-based assignment of exposure represents a substantial improvement over most studies that have relied on central monitors or on binary road buffers combined with basic interpolation (Hoek et al. 2002; Pope et al. 2004). As a sensitivity analysis, we used weighted least-squares models with the weights specified as the inverse of the standard errors from the universal kriging model to down-weight estimates with larger error. In addition, we implemented models based solely on the universal kriging estimate. In both instances results were robust and similar to what we found with our main model.

Time-activity studies show that people spend most of their time in or around home, and our restriction of exposure assessment on residential address captures the most relevant part of exposure (Leech et al. 2002). $PM_{2.5}$ generally displays spatially homogeneous distributions across small areas such as neighborhoods and blocks, and as a result, the ambient conditions at the ZIP code centroid likely reflect the levels expected at home outdoors (Roosli et al. 2000). $PM_{2.5}$ of outdoor origin will also penetrate indoors, and correlations between long-term outdoor PM concentrations and indoor levels of PM from outdoor origin is high (Sarnat et al. 2000). Exposure to ambient air pollution while working and during commute are not included in our exposure term but are considered to be a relevant source of exposure (Riediker et al. 2003). Although most likely a random misclassification with biases toward the null, the errors may affect subgroups differently, thus explaining part of the observed interactions.

In Los Angeles, no clear trends have been observed in $PM_{2.5}$ concentrations over the past 5-10 years. The year 2000 surface characterizes the prevailing mean $PM_{2.5}$ concentrations across several years and can be considered a measure of long-term past exposure. This year also sits in the middle of the baseline recruitment period. Overall, the various limitations in our exposure assignment may add some random error, biasing results toward weaker associations (Thomas et al. 1993).

We also assigned ambient ozone to ZIP code centroids. Inclusion of ozone in the models had no impact on the $PM_{2.5}$ coefficients or the SEs. Ozone and $PM_{2.5}$ were not correlated (r = -0.17), and the $PM_{2.5}$ estimates were not substantially

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different in low- and high-ozone regions. The estimates of association for ozone were positive but not statistically significant and much smaller than for $PM_{2.5}$. This finding must be put in context of the specific challenges in determining long-term exposure to ozone, which are substantially different than in the case of PM exposure. In contrast to $PM_{2.5}$ from outdoor origin, ambient ozone levels have lower correlations with personal exposure (Avol et al. 1998; Sarnat et al. 2000, 2002); therefore, the ability to detect effects of ozone will likely be reduced due to greater misclassification.

Biases. Our subjects were a nonrandom sample of "healthy" volunteers with above-average education, meeting strict inclusion criteria for the two clinical trials. Although we cannot exclude some systematic selection biases affecting the cross-sectional data, it is unlikely that subjects with preclinical signs of atherosclerosis would have been more likely to volunteer if they lived in more polluted areas. Although the selection of subjects limits the generalization to other populations, we do not expect this to lead to over- or underestimating the cross-sectional associations. The two trials recruited subjects independently; thus, the effects may be compared across trials to evaluate the potential influence of selecting volunteers. The populations differed with regard to age, smoking habits, baseline LDL and treatment, blood pressure, active and passive smoking, and other relevant factors; thus, the $PM_{2.5}$ coefficients were smaller and were not statistically significant in the VEAPS trial with its younger population. However, after taking these factors into account, the associations with ambient $PM_{2.5}$ were similar. For example, among elderly women of VEAPS ($n = 70$) and BVAIT ($n = 116$), the effect estimate was 18.1% (-0.1 to 36.3.%) and 13.6% (2.8-24.4.%), respectively. There is some evidence for larger effects in subjects with cardiovascular risk factors, indicated by prescriptions of lipid-lowering treatment. Our trials excluded subjects with clinically manifest CVDs. Moreover, if air pollution amplifies systemic inflammation among those prone to atherosclerosis, exclusion of subjects with high LDL may be a source of bias. One may expect effect estimates in a less selected, less healthy population to be larger than those reported.

The wealth of baseline data from these clinical trials offered the opportunity to control for a broad array of covariates. Apart from the effect of age adjustment, estimates were robust to numerous combinations of covariates, including income, education, active and passive tobacco smoke, cardiovascular prescriptions, vitamin intake, and physical activity. Uncontrolled or residual confounding appears to be an unlikely explanation for these results. Among women, adjustment for hormone replacement therapies did not affect the $PM_{2.5}$ estimates.

In previous studies, we found that spatial autocorrelation in the residuals could affect the size and significance of pollution coefficients (Jerrett et al. 2003a). We investigated spatial autocorrelation of the unstandardized residuals. We assessed autocorrelation with first-order, adjusted first-order, and second-order spatial weight matrices based on nearest neighbor contiguity, but we found no evidence of spatial autocorrelation. This supports the conclusion that the models supply efficient unbiased estimates (Jerrett et al. 2003b). As part of our sensitivity analyses, we also derived $PM_{2.5}$ surfaces using different interpolations and weighted least squares with weights equal to the inverse of the standard error of the exposure estimate. All approaches produced very similar results.

Evidence for effect modification. The data suggest substantial interactions with age, sex, smoking, and underlying cardiovascular risk factors. Given the reduced sample size among subgroups, the recruitment of volunteers, and the cross-sectional nature of the data, it is difficult to fully explore the causes of the observed modifications of associations and to establish susceptibility profiles. If the exposure misclassifications differed across subgroups, part of the interactions may be explained by differential exposure error. The sex and age difference could also be an artifact due to measurement error in the assigned exposure because time spent in commuting and location of work places may be different in men and women and in the young and elderly. Empirical studies on mobility suggest women have smaller activity spaces than men and younger groups, meaning they tend to spend more time in and around the home (Kwan and Lee 2004), and the same is probably true of the elderly compared with younger groups. Exposure measurement error may be reduced in those spending more time at home, leading to stronger effects (Thomas et al. 1993). Moreover, differences in statistical power may play a role as well; as shown at least for the 25-40-year age range, power to detect effects on CIMT is larger in women than in men (Stein et al. 2004).

The finding that those reporting prescriptions of lipid-lowering medications at baseline showed stronger associations of CIMT with $PM_{2.5}$ merits further investigation. This result agrees with the observed effects of PM on atherosclerosis in experiments conducted in hyperlipidemic rabbits (Goto et al. 2004; Suwa et al. 2002). The systemic inflammatory and atherogenic reaction in these rabbits was related to the amount of PM contained in the alveolar macrophages. In our study, being under lipid-lowering therapy is an indicator for risk profiles prone to atherogenesis. Those subjects were mostly men (64%) and, on average, older, more often active or passive smokers, and almost twice as likely to report antihypertensive treatment. The systemic response to ambient PM may amplify and expand the oxidation of LDL cholesterol among these susceptible subjects, consequently contributing to injury in the artery wall (Goto et al. 2004; Ross 1999). Investigations of short-term effects of ambient air pollution on mortality also suggest that underlying risk profiles such as diabetes may amplify susceptibility to ambient PM (Zanobetti and Schwartz 2002), and similar findings have been shown with smoking and diabetes mellitus in association with CIMT (Karim et al. 2005). To clarify the relevance of lipid status, it would be interesting to investigate our hypothesis among cohorts with familial hypercholesteremia (Wiegman et al. 2004; Wittekoek et al. 1999).

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As shown in Figure 3, the size of the point estimate was larger among the older subjects. Future research needs to clarify whether air pollution contributes to atherosclerosis only after a certain age or early on. Effects of air pollution on lung development have been observed during adolescence and may be a result of both pulmonary and chronic systemic inflammatory effects (Gauderman et al. 2002); thus, it is conceivable that atherogenic responses may occur early in life. The age dependence of the effects may also be codetermined by genetic factors (Humphries and Morgan 2004; Ross 1999).

We also observed larger effects in women. If other cardiovascular risk factors such as occupational exposures dominate atherosclerosis in men, we would expect a smaller effect signal and less precision in the estimates among men. We also hypothesize that interactions may reflect biologic causes. If premenopausal women are protected against atherosclerosis by endogenous hormones, loss of hormonal protection would lead to increased vulnerability after menopause (Kannel et al. 1976). This could explain part of the interaction by both age and sex.

Active and passive smoking did not confound results in either the total sample or among subgroups. Adjustment for active tobacco smoke led to a slight increase in the effect estimate; thus, residual confounding is unlikely to overestimate the effects. However, $PM_{2.5}$ associations were clearly stronger in never smokers compared with smokers (data not shown). This gradient was also observed in all subgroups with significant $PM_{2.5}$ associations (Figure 3). Oxidative and inflammatory effects of smoking may dominate to such an extent that the additional exposure to ambient air pollutants may not further enhance effects along the same pathways. The difference in the effects of $PM_{2.5}$ in smokers and nonsmokers needs further investigation. The American Cancer Society cohort study does not reveal a clear pattern of a smoking interaction for the association of ambient air pollution and cardiovascular death (Krewski et al. 2004; Pope et al. 2004). In the Study on Air Pollution and Lung Diseases in Adults (SAPALDIA), associations between air pollution and level of pulmonary function did not differ by smoking status (Ackermann-Liebrich et al. 1997).

Some U.S. studies indicate effect modification of air pollution by socioeconomic status (SES) with much stronger effects among the less educated (Pope et al. 2002). The cause of this interaction pattern is not well understood. SES status was rather homogeneous in these mostly well-educated volunteers, providing little power to investigate interactions of pollution with SES. If lower SES also positively modifies effects of air pollution on atherosclerosis, our population would provide an underestimate of the health effects in the general population (O'Neill et al. 2003). Further research on samples representative of the population will be needed to assess whether the high SES in the clinical trials biases the effects toward the null.

Future research should focus on identifying factors that determine susceptibility to $PM_{2.5}$. We are initiating studies on subjects with inflammatory metabolic syndromes prone to accelerated atherosclerosis such as postmenopausal women, diabetics, or obese or physically inactive people. To corroborate the cross-sectional findings, follow-up studies are ultimately needed to investigate the association of concurrent levels of air pollution exposure with the progression of CIMT.

Plausibility. From a biologic perspective, our results support the hypothesis that long-term exposure to ambient PM contributes to systemic inflammatory pathways, which are a relevant aspect of atherogenesis (Ross 1999). The findings indicate a biologically plausible link between the observed acute effects of ambient air pollution on systemic inflammation (Glantz 2002) and the long-term consequences of sustained vascular inflammation leading to increased atherosclerosis and, ultimately, cardiovascular death (Hoek et al. 2002; Pope et al. 2004). Among susceptible people, this may lead to artery wall lesions similar to those observed in the rabbit model (Fujii et al. 2002; Suwa et al. 2002). In these hyperlipidemic rabbits, 4-week PM exposure was associated with the progression of atherosclerotic lesions, coupled with an enhanced release of bone marrow monocytes. These precursors of macrophages play an important role in the atherogenic inflammatory responses (Goto et al. 2004; Ross 1999; Suwa et al. 2002). Given the central role of oxidized LDL in the initiation and progression of atherogenesis, suggestions that the plasma of automotive workers with high exposure to traffic exhaust is more susceptible to oxidation is also of interest (Sharman et al. 2002).

As a quantitative plausibility check, we compared the size of the $PM_{2.5}$ effects with effects of other risk factors on CIMT. Using smoking and environmental tobacco smoke (ETS) as a model for air pollution exposure, the size of our estimates appear plausible (Diez-Roux et al. 1995; Howard et al. 1994). Associations of ETS and current levels of air pollution with various respiratory outcomes are similar and support the notion of common underlying pathways (Künzli 2002). Smoking and ETS associate with stiffer and thicker artery walls, reflecting the systemic effect of these exposures (Howard et al. 1994; Mack et al. 2003). Exposure to ETS was associated with 2-3% thicker intima-media, which approximate the effects observed for a 10 μg/m^3 change in $PM_{2.5}$ (Diez-Roux et al. 1995; Howard et al. 1994). Using never smokers without ETS exposure as the referent group in our data, never smokers with ETS at home had 0.9% (-2.7 to 4.5%) thicker artery walls; former smokers' CIMT was increased on average by 3.4% (0.7-6.3%), and the 30 current smokers had 5% (-1.5 to 11.6%) thicker CIMT. The trend across these four categories of tobacco exposure was statistically significant. As shown in Table 1, smokers were underrepresented in these volunteers of well-educated participants.

The observed percent change in CIMT corresponds to an increase in the thickness of approximately 20-40 μm per 10

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$\mu g/m^3$ contrast in $PM_{2.5}$. This difference in CIMT translates into some 3-6% increase in the long-term risk for myocardial infarction (O'Leary et al. 1999). Pope et al. (2004) reported that long-term exposure to $PM_{2.5}$ was associated with an 18% (14-23%) increase in ischemic heart disease. Effect sizes reported here concur with these findings, indicating that a fraction of the total effect of ambient PM on cardiovascular mortality may be mediated through sustained long-term effects of air pollution on atherosclerosis (Künzli et al. 2001). This is in line with the proposed model (Künzli et al. 2001) in which some of the effects observed in cohort studies must reflect long-term contributions of air pollution to the underlying disease progression, whereas in other cases, air pollution contributes only to triggering of cardiovascular events or death (Bell et al. 2004; Künzli et al. 2001; Peters and Pope 2002).

From a biologic and policy perspective, we emphasize that $PM_{2.5}$ probably serves as a surrogate for the mixture of urban air pollution and constituents of PM. It is premature to conclude that $PM_{2.5}$ and its constituents are the atherogenic culprit per se. Atherosclerosis results from complex processes that may include a combination of various urban pollutants, host factors, and pathways that ultimately lead to the findings of a CIMT-$PM_{2.5}$ association.

In conclusion, we have presented the first epidemiologic evidence supporting the idea of a chronic vascular response to respiratory and systemic effects of PM exposure. Given the leading role of heart disease as a cause of death in most westernized countries and the growing contribution in developing countries, these findings may be of high public health relevance. Further investigations need to focus on susceptible groups and follow-up of cohorts to investigate the effect of air pollution on the progression of CIMT.

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