Extended Analysis of Air Pollution and Cardiovascular Disease in the California Teachers Study Cohort

FINAL REPORT

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Abstract

Several studies have reported associations between long-term exposure to air pollution and mortality. A number of important questions remain, however, regarding the impact of how long-term exposure is measured, the existence of critical windows of exposure, the relative importance of various constituents of particulate matter, the relationship of chronic exposure to new cases (incidence) of disease, and the shape of the concentration-response function linking fine particulate matter with mortality. In an extension of previous work, we developed estimates of long-term air pollution exposure at the residences of over 100,000 female participants in the longitudinal California Teachers Study (CTS). We examined associations between several exposure metrics and the following outcomes: all-cause mortality, cause-specific mortality (principally diseases of the cardiovascular and respiratory systems), as well as new cases (incidence) of both fatal and non-fatal heart attacks and stroke. To derive the pollutant exposure metrics, we linked the CTS participants' addresses with monthly estimates of long-term exposure to particulate matter less than 2.5 microns in diameter (PM2.5), particulate matter less than 10 microns in diameter (PM10), ozone, carbon monoxide (CO), nitrogen dioxide (NO_2), nitrogen oxides (NOx), and sulfur dioxide (SO_2). The main analyses examined potential relationships of mortality and disease incidence with long-term residential exposures to PM10, ozone, CO, NO_2, NOx, and SO_2 from 1996 through 2005, and to PM2.5 beginning in 1999, when the latter pollutant began to be systematically measured statewide. Participants' addresses were linked as well with several cross-sectional measures of potential traffic-related exposures from the year 2000. We analyzed these relationships while adjusting for many individual-level and neighborhood variables, and undertook a variety of sensitivity analyses. We found elevated risks between long-term exposure to PM2.5 and mortality from ischemic heart disease as well as incidence of stroke, particularly among women who were post-menopausal at baseline. Long-term exposures to PM10, ozone and NOx were associated with elevated risks of ischemic heart disease mortality. PM10 exposure was also linked with incident stroke. The association of ozone with mortality was most likely due to its strong correlations with PM10 and PM2.5. Among never-smokers, NOx exposure was associated with elevated risks of cardiovascular and ischemic heart disease mortality. We did not find that women who had diabetes or who were overweight or obese were at increased risk of PM2.5-associated effects. Traffic density, a measure of the estimated number of vehicle miles traveled within 150 m of a participant's residence, was associated with all-cause, cardiopulmonary and cardiovascular mortality. In additional analyses of associations between long-term exposure to PM2.5 and mortality, we found that: (i) the exposure-response relationship was best described as linear; and (ii) significant effect estimates were evident by one year of exposure, with the magnitude of the association leveling off with increasing duration. This study provides additional evidence that long-term exposure to air pollution is associated with mortality from heart disease, and demonstrates as well that exposure to particulate matter is associated with the incidence of new cases of stroke.

Executive Summary

Background

Several studies in the United States and Europe have examined relationships between long-term exposure to air pollution and mortality, primarily from cardiovascular and respiratory diseases. All have found associations between at least one pollutant metric and one mortality category, but the results are not entirely consistent, possibly due in part to reliance on only one or a few years of exposure data, some of which were collected in the remote past or were imputed. Only two studies have examined incidence of new cardiovascular disease. This investigation examined whether long-term exposures to several air pollutants were associated with all-cause and several disease-specific categories of mortality, as well as with incidence of myocardial infarction and stroke, in a large cohort of California women, We also investigated the shape of the PM2.5-mortality exposure-response curve, and whether there were critical windows of exposure associated with elevated risks of mortality. In addition, we examined whether several traffic-related metrics were associated with the same mortality outcomes.

Methods

The California Teachers Study (CTS), a large prospective cohort of active and retired female public school teachers and administrators, provided the framework for this investigation. In previous work that we conducted with support from the Air Resources Board (ARB), outcome data were obtained through record linkage to statewide mortality and hospitalization files from cohort inception (1995) through 2002. This investigation extended the period of observation for our main analyses through 2005. The prior study involved mortality analyses of all-cause (non-traumatic) and cardiopulmonary (cardiovascular plus pulmonary) deaths, while this project examined several cause-specific mortality categories: cardiovascular, cerebrovascular, respiratory, and nonmalignant respiratory diseases, ischemic heart disease (IHD), and lung cancer. On entry into the study, the participants completed a baseline questionnaire, which included questions on demographics, personal characteristics, and medical history, including prior myocardial infarction (MI) and stroke. Therefore, incidence analysis was limited to these two conditions. As many first occurrences of MI and stroke prove fatal, we combined both hospitalization and mortality data for each of these events in the incidence analyses.

ARB staff developed and provided us with monthly averages for particulate matter with an aerodynamic diameter less than 2.5 μ (PM2.5), PM with an aerodynamic diameter less than 10 μ (PM10), ozone, nitrogen dioxide (NO_2), nitrogen oxides (NOx), carbon monoxide (CO), and sulfur dioxide (SO_2). ARB staff also developed pollutant surfaces of monthly average ambient concentrations using inverse distance weighted interpolation. These monthly averages and surfaces were developed for all relevant monitors operating in California from 1996 through 2005. PM2.5 data have been

routinely collected throughout the state since about March 1999, however, so the exposure assignments for fine particles began several years later than for the other pollutants.

All participants' addresses at baseline and through 2002 (for those who relocated) had been previously geocoded. For this project, we geocoded new addresses for participants who moved during the period 2003 – 2005. Exposure estimates for each subject's residence(s) were developed by spatial linkage of the geocoded locations to each monthly pollutant surface.

In our prior study (Lipsett et al. 2007), we generated several traffic metrics, including distance to the nearest highway, traffic density (i.e., vehicle miles traveled within 150 m of each residence), and vehicle density (from 2000 Census block data). For those CTS cohort members who relocated during the study period, we assigned all of the pollutant exposure metrics to each reported address.

The specific tasks for this project involved examination of:

1. Relationships of various pollutants with mortality due to all causes and to specific disease categories, including cardiovascular, cerebrovascular, respiratory, and nonmalignant respiratory diseases, IHD, and lung cancer.

2. Pollutant exposure effects in never-smokers with respect to: (i) all-cause, cardiopulmonary and IHD mortality, and (ii) incidence of MI and stroke.

3. Whether pollutant effects differ among potentially susceptible subgroups, which involved stratification on individual characteristics, including post-menopausal status, obesity and diabetes.

4. Effect estimates of PM2.5 and other pollutants using different exposure periods to identify whether there are critical time windows most strongly related to cardiopulmonary outcomes.

5. Associations of PM2.5 constituents (including elemental and organic carbon, sulfate, nitrate, iron, copper, potassium, and silicon) with mortality due to all causes, as well as cardiopulmonary and pulmonary diseases, and IHD.

6. The sensitivity of the PM2.5 results [in our prior report] to the use of pre-1999 estimated fine particle concentrations.

7. The shape of PM2.5/mortality exposure-response relationship.

8. Relationships between several traffic metrics and cardiopulmonary outcomes, modeling effects of extremes of traffic metric distributions.

The statistical analysis was conducted using Cox proportional hazard regression models, adjusting for smoking status, total pack-years (for current and former smokers), body mass index, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, fiber and calories, physical activity, menopausal status, hormone

therapy use, family history of MI and stroke, use of blood pressure medication, aspirin use, and several Census-derived contextual (neighborhood) variables (income, income inequality, education, population size, racial composition, unemployment). In the main analysis (Tasks 1, 2 and 3, above), we allowed for one year of measured exposure prior to initiation of outcome follow-up to help ensure that we would be examining effects of chronic exposure. For all pollutants other than PM2.5, exposure assessment began in June 1996 and outcome follow-up began in June 1997, while for PM2.5 the corresponding times were March 1999 and March 2000. The analysis involved estimation of hazard ratios (HRs, analogous to relative risks), which provide a quantitative expression of the association between the long-term pollutant exposure and the outcomes of interest. Per-subject exposure in the regression models was represented as a time-dependent function *x(m)*, where the exposure value at month *m* was calculated as the average of monthly pollutant levels between the beginning of the exposure assessment and month *m*, inclusive. For each death (or hospital admission for MI or stroke) occurring in month m, the calculated exposure average for each case was compared to the average pollution exposure up to the same month *m* for everyone else in the cohort who was still alive and had not been hospitalized for MI or stroke.

We examined potential impacts of long-term exposures of PM2.5 in never-smokers, post-menopausal women, and those who had diabetes at baseline or who were obese. Additional sensitivity analyses included use of a summer-only ozone exposure model, two-pollutant models, and stratification by whether the participant had relocated or not during the observation period (i.e., movers vs non-movers).

To ascertain whether there were critical time windows of PM2.5 exposure more strongly related to mortality outcomes (Task 4), we evaluated the effect of using different windows of exposure: six months, one year, two years, three years and four years.

The exposure assessment in the PM2.5 constituents analysis (Task 5) was more limited than in the main analysis because there were only eight monitors available that were collecting data on PM2.5 mass and selected constituents as part of the U.S. Environmental Protection Agency's Speciation Trends Network (U.S. EPA 2008). These monitors went online at different times; the data for this analysis were collected once all were operative - from June 1, 2002 through July 31, 2007. Eight monitors were insufficient to create statewide pollutant surfaces. Therefore, we assigned monthly exposure values to each participant based on measurements taken at the monitor nearest her geocoded residential address. For these analyses we restricted our sample to women living within 30 km of one of the monitors.

The Cox proportional hazards models we used represent a linear relationship between the pollutant values and the logarithm of the disease hazard. To assess whether this association might better fit a non-linear relationship, we checked the fit of log-linear, quadratic and fractional polynomial models for PM 2.5 and IHD (Task 7).

We evaluated associations between several traffic variables and mortality (all-cause, cardiopulmonary, cardiovascular, and IHD) and incidence (MI and stroke) outcomes among non-movers (Task 8). Traffic metrics included: (i) proximity to a highway (within 150 m and beyond 150 m); (ii) traffic density (estimated vehicle distance traveled on all roads within 150 m of a geocoded residence); and (iii) vehicle density (the aggregate number of vehicles registered to occupied housing units divided by the area of the block group in which the study participant resided). We estimated HRs

using Cox proportional hazards models with the same set of individual-level and contextual variables as in the other analyses.

After consultation with the ARB Project Manager, we discontinued work on Task 6, as it was clear that we would not be able to adjust the estimated pre-1999 PM2.5 levels sufficiently to use these values in our epidemiological analyses.

Results

Most of the women in this cohort were non-Hispanic white (87%); two-thirds were never-smokers, with five percent current smokers. Approximately half were peri- or postmenopausal at baseline.

Although most HR point estimates for PM2.5 were greater than unity, only that for ischemic heart disease (IHD) mortality was significantly elevated (HR = 1.20, 95% CI 1.02-1.41). The HR point estimates for PM10 were uniformly lower than those for PM2.5. The outcomes with the strongest associations with PM10 were IHD mortality (HR = 1.06, 95% CI = 0.99-1.14) and incident stroke ((HR = 1.06, 95% CI = 1.00-1.13).

Fewer events were included in the analyses of NO_2, NOx, SO_2, and CO because: (i) the representative spatial ranges designated for these pollutant monitors were much smaller than for the ozone, PM2.5 and PM10 monitors, which meant that fewer participants' residences were included, and (ii) there were substantially fewer monitors for these pollutants than for PM10 and ozone. IHD mortality was significantly associated with NOx (HR = 1.25, 95% CI = 1.00-1.55), and the risk of cardiovascular mortality was elevated with a weaker association (HR = 1.13, 95% CI = 0.98-1.31). In contrast, the association between ozone and IHD mortality was of borderline significance (HR = 1.06, 95% CI = 0.99-1.14), with no corresponding increase in the HR for cardiovascular disease *in toto*. However, when the ozone analysis was restricted to summers only, the HR for IHD mortality was significantly elevated (HR = 1.09, 95% CI = 1.01-1.19).

In a two-pollutant model including year-round ozone and PM2.5, the HR for IHD mortality in association with PM2.5 increased in magnitude and significance (HR = 1.27, 95% CI = 1.03-1.56), while that for ozone declined to a null result (HR = 0.99, 95% CI = 0.87-1.13). Results were similar using PM2.5 and summer ozone levels. The HR for IHD mortality in association with ozone likewise decreased to nonsignificance in a two-pollutant model with PM10.

In the PM2.5 analysis restricted to women who were post-menopausal at baseline, the results were similar to those for the cohort as a whole, except that the HR for stroke incidence increased and became statistically significant (HR = 1.19, 95% CI = 1.02-1.38). In the analyses restricted to never-smokers only, the HRs tended to increase or remain more or less unchanged in relation to those for the entire cohort. Among never-smokers, PM10 was associated with nonmalignant respiratory disease mortality (HR = 1.15, 95% C.I. 1.00-1.33), PM2.5 was more strongly associated with cardiovascular mortality (HR = 1.13, 95% C.I. 0.98-1.29, as well as with IHD mortality HR = 1.28, 95% C.I. 1.05-1.57), and summer-only ozone with IHD mortality (HR = 1.12, 95% C.I. 1.01-1.23). In addition, long-term exposures to NOx continued to be associated with IHD mortality (HR = 1.40, 95% C.I. 1.07-1.83), and both NOx and SO_2 were associated with all-cause and

cardiovascular mortality, but these latter results were based on relatively few events (758 and 343 for NOx, and 152 and 69 for SO_2, respectively).

We found no evidence that those who were overweight or obese (BMI $\geq$ 25.0 kg/m^2 at baseline) were at greater risk from PM2.5 exposure than those who were not. Similarly, subjects with diabetes were not at increased risk of any of pollutant-related outcomes examined compared with non-diabetics; however, these analyses in general also involved few events among women with diabetes.

In the incidence analyses restricted to hospitalizations for MI and stroke, there were no significant associations of any pollutants with incident MI. However, PM10 was associated with incident stroke: HR = 1.09 (95% CI = 1.01-1.17), per 10 $\mu g/m^3$ increment of long-term estimated average exposure.

In the analysis examining mortality HRs for various pollutants among movers versus non-movers, there were few differences and, consistent with the results for the cohort as a whole, almost none was significant. The exception among the mortality categories was IHD, for which there appeared to be a greater impact among movers for PM2.5, the reverse for PM10 and ozone, and no difference for NOx and NO_2.

In the critical windows analysis for the entire PM2.5 subcohort, the HR for IHD increased from 1.12 (95% CI = 0.96-1.31) using a six-month window to 1.41 (95% CI = 1.15-1.73) using a three-year window. The point estimates for the HRs from a four-year window were approximately the same for cardiopulmonary and IHD mortality as those using the three-year window. The results are noticeably different when the analysis was limited to the women who had had at least four years of exposure. Within this group, the HRs remained essentially unchanged with windows of increasing duration beyond one year, at which time the HR for IHD mortality was 1.52 (95% CI = 1.18-1.98).

For the PM2.5 constituents analysis, the pollutants (organic and elemental carbon, nitrate, sulfate, potassium, iron, silicon and zinc) were all strongly inter-correlated, with the majority of correlation coefficients greater than 0.7. Significant associations were observed for PM2.5 mass, sulfate and nitrate exposures in relation to cardiopulmonary mortality, with a more modest association for silicon. PM2.5 mass and all of its components were associated with mortality from IHD, while none was associated with respiratory mortality. For IHD, the largest effect estimates were observed for EC and sulfate, although estimates were fairly similar among all the constituents except silicon and organic carbon, which had somewhat lower HRs.

The results of our assessment of various non-linear models (log-linear, quadratic, and fractional polynomial) showed that, within this dataset, nonlinear models of the exposure-response relationship between long-term PM2.5 exposure and IHD mortality offered no obvious improvement over a linear one.

We found that the highest decile of traffic density was associated with all-cause, cardiopulmonary and cardiovascular mortality. For vehicle density, the 25th to 49th percentile category was associated with cardiovascular mortality, HR = 1.17 (95% CI = 1.01-1.37. The other traffic metrics showed no association with these outcomes.

Conclusions

In this ongoing cohort study of over 100,000 female participants in the California Teachers Study, we found significant associations between IHD mortality and PM2.5 and NOx, with slightly lesser associations with PM10 and ozone. In single-pollutant models, the HRs for PM2.5 and NOx were modestly greater among never-smokers, as were associations with cardiovascular disease mortality as a whole. Incident stroke (combining fatal and nonfatal events) was associated with PM2.5 among women who were post-menopausal at baseline. Analyses limited to non-fatal incident stroke (i.e., hospitalizations only) identified associations with both PM2.5 and PM10.

Our finding of an increased risk of PM2.5-associated IHD mortality is consistent with those in several other cohort studies, though the magnitude of effect is somewhat lower than in most published estimates. However, we found no association of PM2.5 with all-cause mortality, in contrast to several other long-term air pollution studies in the U.S. The differences between our estimates and those of other investigations may be related to differences in the underlying health status of the study populations, the numbers of cases, methods of estimating exposure, particle composition and relative toxicity, and measurement and control of potential confounders.

We did not detect any significant differential effect of chronic PM2.5 exposure on women who had a diagnosis of diabetes or who were overweight or obese. Our findings regarding the lack of effect modification by diabetes is consistent with two other studies of older women; however, those same investigations did identify an increased susceptibility to PM2.5-associated effects among women who were overweight or obese.

This study provides evidence that long-term exposure to PM2.5, PM10, NOx, and ozone were all associated with increased risks for IHD mortality. However, the apparent increased risk of IHD mortality associated with long-term ozone exposure was most likely due to its correlation with particulate matter, while that for NOx was based on relatively small numbers of observations, and may also have been due to correlation with PM. That both PM measures were associated with incident stroke provides support for the notion that these pollutant mixtures may play an etiologic role in the development of circulatory disease.

In the critical windows analysis for the entire PM2.5 subcohort, the magnitude of the HRs linking PM2.5 exposure and mortality from cardiopulmonary and ischemic heart diseases increased as the duration of the prior exposure period increased up to three years. In contrast, when we limited this analysis to women who had had at least four years of measured exposure, the HRs were significantly elevated for the same outcomes, but the magnitudes of the HRs did not change with periods of exposure longer than one year. Few studies have investigated such critical windows; others have found such a leveling off after 12 months of exposure. In any case, elevated risks of mortality are evident in all cohorts within a year of follow-up: the effects are much larger than those observed in after acute or subacute (one to several days) exposures.

While the results of the PM2.5 constituents analysis were generally consistent with those of the main analysis, there were some differences as well that were likely attributable to differences in assignment of exposure, duration of measured exposure prior to follow-up, length of follow-up, and the substantially smaller number of events. We observed associations between both PM2.5 mass and nitrate and cardiopulmonary

mortality, while all of the PM2.5 constituents were associated with IHD mortality. However, given the strong inter-correlations among the constituents, we cannot definitively assign independent effects to any.

None of the non-linear models of the relationship between PM2.5 and IHD mortality provided a better fit than the linear model: the resulting HRs were very similar using a range near the mean of the distribution of PM2.5.

Finally, consistent with results reported by other investigators, we found that high traffic density was associated with all-cause, cardiopulmonary, and cardiovascular mortality.

Introduction

Several cohort studies have linked long-term exposure to air pollution, notably fine particulate matter with aerodynamic diameter less than 2.5 micrometers (PM2.5), with both all-cause and cardiopulmonary mortality (Dockery et al. 1993; Laden et al. 2006; Pope et al. 1995, 2002, 2004; Abbey et al. 1999; Hoek et al. 2002, Enstrom 2005; Nafstad et al. 2004; Miller et al. 2007; Puett et al. 2009). All have found associations between at least one pollutant metric and one mortality category, but neither the quantitative nor the qualitative results are entirely consistent. In addition, concerns about the extent of exposure misclassification in these studies persist, since several relied on only one or a few years of PM2.5 exposure data, and some used data collected in the remote past and imputed data. Among the most widely cited studies, Pope et al. examined the mortality experience of several hundred thousand adults in up to 151 U.S. cities who participated in the American Cancer Society Cancer Prevention Study II (ACS CPS II) cohort (Pope et al. 1995, 2002, 2004), though fewer cities and participants were involved in the PM2.5 analyses. After controlling for individual risk factors such as smoking, occupational exposures, body mass index, and alcohol consumption, average fine particle measurements in these metropolitan areas were associated with small, but significant, increases in relative risks (RRs) per 10 $\mu g/m^3$ increase in PM2.5 for all-cause (1.06, 95 % CI = 1.02-1.11), cardiopulmonary (1.09, 95 % CI = 1.03-1.16), and lung cancer (1.14, 95 % CI = 1.04-1.23) mortality (Pope et al. 2002). These results were based on PM2.5 levels estimated in 51 cities for about 319,000 participants. The Harvard Six Cities (HSC) study included far fewer subjects (n=8,111 at baseline); however, those investigators found similar results for several Midwestern and Eastern cities (Dockery et al. 1993), which was confirmed in a recent follow-up analysis suggesting that decreases in PM2.5 were associated with decreased relative risks for all three mortality categories (Laden et al. 2006). For the follow-up period of 1974 – 1998, these investigators reported relative risks per 10 $\mu g/m^3$ increase in PM2.5 of 1.16 (95 % CI = 1.07-1.26) for all-cause, 1.28 (95 % CI = 1.28-1.44) for cardiovascular, and 1.27 (95 % CI = 0.96-0.69) for lung cancer mortality. The HSC and ACS CPS II studies used only one air pollution monitoring site per city or metropolitan area, though the areas of coverage for these monitors were significantly different. The HSC study deployed monitors specifically for the purpose of the study and had relatively small spatial catchment areas, while the ACS CPS II monitors covered very large areas, often larger than Metropolitan Statistical Areas.

Most prior cohort studies of PM2.5 have examined mortality from cardiovascular causes, but only two have examined incident disease. Miller et al. (2007) identified significantly increased risks of incident (HR = 1.24, 95% CI = 1.09-1.41) and fatal cardiovascular events (HR = 1.76, 95% CI = 1.25-2.47) associated with a 10 $\mu g/m^3$ increase in one year of annual average PM2.5 exposures in the observational study of the Women's Health Initiative (WHI). Using data from the Nurses' Health Study, Puett et al. (8) recently found that long-term exposure to estimated PM2.5 was associated with death from coronary heart disease (CHD), but not with overall incident CHD.

The extent to which long-term exposure to particulate matter, ozone or any other air pollutant may be linked with cardiac, respiratory, or malignant disease is an issue of

enormous public health and regulatory significance. State and federal annual average ambient air quality standards for particulate matter are based primarily on the results of two large cohort studies (Dockery et al. 1993; Laden et al. 2006; Pope et al. 2002). However, there are inconsistencies among the published studies with respect to the magnitudes of effect associated with different pollution metrics, which may be related in part to exposure assessment and degree of misclassification, as noted above, as well as differences in characteristics of the cohorts, neighborhood effects, or to chance alone.

This report analyzes data from the California Teachers Study (CTS), an ongoing prospective cohort of over 100,000 female public school professionals in California. In an earlier analysis involving this cohort, we used concurrently monitored pollutant data from 1995 to 2002 to examine associations of long-term exposure to PM2.5, PM10 and several gaseous pollutants with risks of incident myocardial infarction (MI) and stroke, as well as with mortality from all causes and from several disease subcategories (Lipsett et al. 2007). In that report, we found significant associations of multiple pollutants with mortality and with incidence of MI and stroke. The current report extends the findings of our prior work, adding several years of pollutant and outcome data. The CTS cohort offered an opportunity to examine the relationships between specific air pollutants and chronic disease outcomes. The prevalence of active smoking among study participants at baseline was low (about five percent), allowing for careful examination of the impact of air pollution exposures. In addition, because of the similarity of the educational backgrounds and working environments for the cohort members, significant confounding or effect modification by these factors is unlikely. The size of the study also allowed for substantial statistical power. The vast majority of the cohort continues to reside in California, where large metropolitan areas contain an extensive air pollution monitoring network, providing opportunities for refined exposure assessment over extended periods of time. The participants' home addresses were geocoded, which also allowed for analyses of the impacts of exposure to local traffic emissions.

The specific tasks in this investigation included analyses of:

1. Relationships of various pollutants with mortality due to all causes and to specific disease categories, including cardiovascular, cerebrovascular, respiratory, and nonmalignant respiratory diseases, IHD and lung cancer.

2. Pollutant exposure effects in never-smokers with respect to: (i) all-cause, cardiopulmonary and IHD mortality, and (ii) incidence of MI and stroke.

3. Whether pollutant effects differ by potentially susceptible subgroups, which involved stratification on individual characteristics, including post-menopausal status, obesity and diabetes.

4. Effect estimates of PM2.5 and other pollutants using different exposure periods in order to identify whether there are critical time windows most strongly related to cardiopulmonary outcomes.

5. Associations of PM2.5 constituents (including elemental and organic carbon, sulfates, nitrates, iron, copper, potassium, and silicon) with the following mortality categories: all causes, cardiopulmonary and pulmonary diseases, and IHD.

6. The sensitivity of the PM2.5 results [in our prior report] to the use of pre-1999 estimated fine particle concentrations.

7. The shape of PM2.5/mortality exposure-response relationship using both Cox regression and flexible splines.

8. Relationships between several traffic metrics and cardiopulmonary outcomes, modeling effects of extremes of traffic metric distributions.

These tasks are addressed below as follows: Tasks 1, 2 and 3 are grouped together in the Materials and Methods, Results and Discussion sections (under the subheading "Main Analysis"), while Tasks 4 ("Critical Windows"), 5 ("PM2.5 Constituents Analysis"), 7 ("Exposure-response Relationship"), and 8 ("Traffic Analysis") are each addressed separately.

After conferring with the ARB Project Manager, we discontinued work on Task 6. PM2.5 was routinely measured throughout California beginning in 1999, limiting the duration of analysis using measured data in our prior investigation to the period 1999-2002. In the earlier report (Lipsett et al. 2007), we had conducted some analyses using a database containing several pre-1999 years of reconstructed (i.e., estimated) PM2.5 data. This database had been developed under a separate contract for ARB using predictive regressions with other pollutants that were correlated with PM2.5 at 40 sites throughout California (Blanchard and Tanenbaum 2005). The HRs for a variety of outcomes resulting from the use of these estimated PM2.5 data were uniformly higher than those using measured data from 1999 – 2002. However, the regression methods used in estimating the pre-1999 data would have dampened the normal variability in PM2.5 levels. We concluded: "The method of developing the historical PM2.5 database may have led to systematic underestimation of the variance of actual PM2.5 concentrations and therefore overestimation of the associated hazard ratios. Thus, without further quantitative investigation of the extent of the measurement error introduced during the creation of this database, we believe that the use of these estimated values of PM2.5 in epidemiological investigations should be limited and that any results based on the use of these data should be interpreted with caution." While we proposed several approaches to examine what might have contributed to the problems with the use of the reconstructed PM2.5 dataset (beyond HR inflation due to variance underestimation), on further reflection and discussion with other epidemiologists and biostatisticians, we were persuaded that these reconstructed pre-1999 data could not be corrected sufficiently to use in this study.

Materials and Methods

Study Population

The California Teachers' Study (CTS) is a prospective study of 133,479 current and former female public school employees who completed baseline questionnaires in response to two mailings to all 329,684 active and retired female enrollees in the State Teachers Retirement System (STRS). The STRS is a quasi-public agency that manages retirement investments for California educators (teachers and administrators) employed in public school systems, including all primary and secondary school teachers as well as faculty in the state junior college and university systems. STRS members are employed in approximately 1,160 public school districts, community college districts, county offices of education, and state reporting entities throughout California. All California public school employees must pay into and receive retirement benefits through STRS; membership continues as long as retirement contributions remain on deposit with the program. The STRS maintains current address information on members even after they retire or leave California.

The CTS cohort was established in 1995 using State of California cigarette tax revenues, initially for investigating a previously reported excess incidence of breast cancer in public school teachers and administrators. The study was developed by a consortium of investigators from the former California Department of Health Services (now the California Department of Public Health) and three active research institutions that manage regional registry operations as part of California's statewide cancer surveillance program (the Cancer Prevention Institute of California [formerly the Northern California Cancer Center], the University of California, Irvine and the University of Southern California (USC)). The design and on-going follow-up of the CTS cohort is a collaborative effort of the study's co-investigative group representing researchers with diverse and complementary areas of expertise. One of the co-investigators for this study, Dr. Peggy Reynolds, is a founding member of the CTS and remains an active member of its Steering Committee.

There have been four waves of questionnaires for the CTS: 1995 (baseline or Wave I), Wave II (1997), Wave III (2000), and Wave IV (2005). Self-reported chronic conditions were recorded in Wave I, and hospitalization information was also collected in Waves II and III. For this investigation only the responses to Waves I and III were utilized. In these analyses, survey data from these questionnaires were used to characterize factors that may be important confounders/effect modifiers of the air pollution/health outcome relationships. Data on numerous other potential risk factors for chronic disease were included in the CTS database, including (among others) age, race, exercise patterns, diet, active and passive smoking exposures, alcohol use, weight, height, menopausal status, marital status, individual and family medical histories, and use of medications and hormones. The baseline questionnaire also included questions on history of chronic disease, including specifically any history of a prior MI or stroke.

The CTS cohort is well characterized, diverse, and represents a range of socioeconomic levels, depending in part on spousal income. The mean age of the participants at enrollment was 54, with 90% between ages 30 and 80. The cohort is multiethnic but primarily white (86.7%) and born in the United States (93.6%). At baseline, 124,614 (93.3%) of the women lived in California. Approximately 78% of the cohort members were elementary or high school teachers for the majority of their careers and over 50% were employed in the school system more than 15 years. A full description of the CTS cohort is available elsewhere (Bernstein et al. 2002).

Record linkage is conducted annually to mortality files and to the statewide cancer registry (both administered by the California Department of Public Health), and to a statewide file of hospitalization data, administered by the Office of Statewide Health Planning and Development (OSHPD). Ongoing routine follow-up of the cohort includes updating name and residential information of CTS members for the purposes of future contacts as well as for outcome linkage. The primary method for address updates comes via the US Postal Service (USPS). Of the approximately 75,000 name and address changes recorded for the cohort through December 2005, 66% came via notification of changes of address made to the USPS. In preparation for each of the nonprofit mailings sent to CTS members, the address data files are processed electronically by a USPS-designated service agency. The second largest source of ongoing name and address updates is the cohort members themselves -- via changes of address recorded on questionnaire covers, postage paid postcards included in annual newsletter mailings, telephone calls to a 24-hour toll-free line, and e-mail notifications. An additional form of active follow-up involves periodic phoning of cohort members who have not responded to mailings. Projects completed by skilled medical interviewers, as well as high-volume outbound call centers, facilitate collection of additional address change and address verification information.

Supplementing these “active” follow-up methods, “passive” methods are also extensively utilized for the purpose of verification of state of residence or vital status. Since the main outcome measures for the initial cohort involve record linkage against statewide cancer registry and OSHPD databases, confirmation of residency in California is critical. Resources such as drivers license records, voter registration rolls, property tax files, and Social Security vital status records are used. All these resources added to the active follow-up contribute to a “cohort viability score,” which is a composite measure of the various forms of residency confirmation. This score shows that slightly more than 95% of the cohort had verifications in 2000 or later.

Use of data on human subjects in the main CTS cohort study was reviewed and initially approved by the California Committee for the Protection of Human Subjects, Health and Human Services Agency, in June 1995 and annually thereafter. The same committee approved use of the CTS data specifically for this investigation in August 2004 and has renewed the approval annually since then as well.

Outcome Assessment

There are several sources of information on health outcomes among the CTS cohort. Record linkages of the CTS cohort were conducted annually through 2005 to mortality and hospital discharge data by CTS co-investigators at USC. Mortality outcomes were ascertained through files administered by the California Department of Public Health as well as with the Social Security Administration death master file. These linkages were performed using probabilistic record linkage utilizing AUTOMATCH (Jaro, 1995). Secure internet-based retrieval software permits real-time viewing and printing of California death certificates. In the main analysis, ICD-9 codes were used to code deaths occurring through 1998 and ICD-10 codes were used for deaths during 1999 through 2005 (Table 1).

Table 1: ICD codes used for mortality and incidence outcomes

Mortality Outcome	**ICD-9 codes Deaths: 1997-1998**	**ICD-10 codes Deaths: 1999-2005***
All-cause	001-799	A00-R99
Cardiovascular	390-459	I00-I99
Respiratory	162, 460-519	C34, J00-J98
Non-malignant respiratory	460-519	J00-J98
Lung cancer	162	C34
Ischemic Heart Disease	410-414	I20-I25
Cerebrovascular	430-438	I60-I69
Incidence Outcome	**ICD-9 codes Hospitalizations: 1997-2005 Deaths: 1995-1998**	**ICD-10 codes Deaths: 1999-2005**
Myocardial infarction	410	I21
Stroke	431-434,436	I61-I64

* The PM2.5 constituents analysis included deaths through July 2007.

Incidence data were ascertained through linkage with hospital discharge data collected and maintained by OSHPD. This database contains information about admissions to all California hospitals except military facilities. The data include up to 25 diagnoses and up to 21 procedures per admission. OSHPD does not collect patient names, but since 1991 this database has included Social Security number, date of birth, sex, race, and ethnicity. Using these variables, probabilistic record linkages are performed annually under separate funding (NCI R01 CA77398). The record linkage used in this study was conducted through December 31, 2005, to determine the incidence of MI and stroke. Table 1 summarizes ICD codes used to categorize the incidence outcomes. Women were excluded from the incidence analyses if they reported a previous heart attack or stroke on the baseline questionnaire or had a hospitalization due to either of these events prior to

the initiation of follow-up. Initial episodes of MI or stroke are often fatal; therefore, to capture incidence of these events, we created a variable combining hospitalization and death for each of these outcomes. In the incidence analyses, unique subject identifiers allowed us to avoid double-counting a hospitalization that subsequently resulted in a fatality from MI or stroke.

Calculation of Follow-up

Person-days at risk were calculated as the number of days between June 1, 1997, for analyses of all pollutants except PM2.5 (for which risks were calculated from March 1, 2000) and the earliest of four dates: (i) the date of death (for mortality analyses); (ii) the date of hospitalization or death (for MI and stroke incidence analyses); (iii) December 31, 2005; or (iv) the date of first relocation to a non-California address for at least four months before any of (i)-(iii) occurred. If a woman moved out of state for less than four months, she remained in the risk set, but was not assigned pollutant values during her time away. In the incidence analyses for MI and stroke, we only counted until the first episode: time after a first hospitalization for either of these conditions was censored. Hospital admission that resulted in death was counted as a single event. Women who died from a cause other than the outcome of interest during the follow-up period were censored at the time of their deaths.

Geocoding Study Participants' Addresses

In our earlier work, we geocoded the participants' baseline addresses at cohort inception as well as all subsequent addresses for those individuals who had moved within California through December 2002. For the main analysis, we geocoded all new addresses for participants relocating within California from January 2003 through December 2005, along with a few pre-2003 addresses that had been corrected in the CTS database since our prior analysis. The following paragraphs summarize the process for geocoding all the addresses, including those from the prior study as well as the 2003-2005 update.

We received 199,872 address records for period 1995 through 2005 from the CTS data center at USC. Each record represents a name change, move, or residency confirmation supplied from various sources, including the baseline and follow-up study questionnaires, respondent telephone calls or correspondence, and linkages to DMV, postal, and other records. Prior to geocoding the address information, we reviewed the data and, in consultation with USC staff, eliminated duplicate records, as well as records that were likely to be address corrections or reformatting rather than true moves. Furthermore, we restricted the file to those CTS members who resided in California at the time of the baseline questionnaire. After removal of the duplicate addresses, name change records, and non-California addresses, 194,687 address records (for 124,614 individuals) remained to be geocoded. This total included 77,390 single addresses of members who

had never moved, with the balance representing multiple addresses of 47,224 movers, some of whom relocated more than once.

These address records were standardized to USPS format using ZP4 address correction software (Version 58, Semaphore Corporation, Pismo Beach, CA). Post Office (P.O.) Box addresses were flagged as non-geocodeable; the remaining addresses were batch geocoded against three different street datasets: Navigational Technologies (2005q2), Geographic Data Technology's Dynamap2000 (2005q1), and TeleAtlas (2004q1). More than 90% of the addresses were successfully geocoded via batch processing, with success defined as a match score of 100 on all three street datasets. To maintain consistency with traffic count data, we created the exposure database using the geocoding coordinates from Dynamap 2000. More than 95% of the remaining addresses were geocoded through manual review with sufficient precision for point scale analyses, using Dynamap 2000 as the default source of geocoding coordinates. Of the total numbers of address records, approximately 99% of those that were not P.O. boxes were geocoded, though among women who relocated during the study period, this figure was approximately 97%. Thus, a total of 162,925 residential addresses were available for estimating exposure to air pollutants.

Address geocoding was subsequently extended through July 2007 for the PM2.5 constituents analysis.

Air Pollution Exposure Estimates

Main Analysis

Monthly average PM10, ozone, NO_2, NOx, CO, and SO_2 from June 1996 through December 2005 were calculated from fixed-site monitors, requiring a minimum of 75% completeness in any given month for each monitor to be included in the database. For PM2.5, monthly averages were created from Federal Reference Method monitors that were available from 1999 through 2005. The monitors used in this investigation are part of California's State and Local Air Monitoring Network (http://www.arb.ca.gov/aqd/netrpt/netrpt.htm), which is intended for the most part to represent general population exposures. The PM2.5 averages also included data from the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, which measures pollutants that affect visibility in national parks and similar protected areas. Pollutant surfaces of monthly average ambient concentrations for ozone, PM10, PM2.5, NO_2, NO_X, SO_2, and CO were developed via inverse distance-weighted (IDW) interpolation, using ArcGIS v. 9.3 (ESRI, Redlands, CA). To maximize spatial coverage, all monitors available each month were used (Table 2). However, as some monitors were added to the network or were taken offline, the numbers of monitors used to estimate the pollutant surfaces varied.

Table 2: Monthly pollutant monitor counts: California Teachers Study cohort, June 1996 to December 2005

Pollutant	Minimum	Maximum	Mean
CO	78	92	84
NO_2	92	113	104
NOx	84	110	100
Ozone	149	182	168
PM2.5	56	82	77
PM10	135	167	150
SO_2	31	52	38

*PM2.5 monitor count is from 1999 to 2005

Most air pollution monitoring stations in California are assigned spatial scale designations (e.g., neighborhood, urban and regional), which define an approximate radial range for which monitors are intended to provide representative data: micro-scale, middle, neighborhood, urban and regional. In consultation with ARB staff, we decided to exclude from this analysis all monitors designated as micro- or middle scale, as these were considered to be representative of ambient concentrations only up to about 0.5 km. We also decided to limit the representative radial ranges for pollutants (i.e., neighborhood versus urban/regional). For instance, the representative ranges for neighborhood monitors were designated as 20 km for ozone and PM2.5, 10 km for PM10 and 3 km for CO, NOx, NO_2, and SO_2, while the ranges for urban/regional monitors were 50 km for ozone, 20 for PM2.5 and PM10, and 5 km for the other gases. We chose a fairly conservative distance of 20 km for PM2.5, a pollutant of special interest given its importance in previous studies, since a range of 30 km or greater could have been justified as well.

Women whose residences were within the designated representative range of a given pollutant monitor were included in the analysis, while those whose homes were outside the representative range of any monitor for that pollutant were excluded. Monthly exposure estimates were created via spatial linkage of the geocoded residential addresses to the IDW pollutant surfaces. More specifically, 250 m grids were superimposed unto the pollutant surfaces, and all residences within a given grid in a given month, were assigned the interpolated pollutant value for that grid for that month. At the time of each death or hospital admission, the average pollution exposure for each individual remaining in the cohort was recalculated, allowing comparison between the case's long-term average exposure until the date of the event with those of all others still in the risk set.

Table 3: Numbers of residences and person-months of exposure associated with particulate and gaseous pollutants in the California Teachers Study cohort

Pollutant	Spatial Scale (km)		Residences (in range)	Total Person-months of Exposure*
	Neighborhood	Urban/Regional		
Ozone (1-hr max)	20	50	146,072	11,071,600
PM2.5	20	20	100,302	5,794,752
PM10	10	20	83,336	6,642,333
NO_2 (1hr max)	3	5	14,441	1,338,116
NOx (1hr max)	3	5	18,482	1,671,513
CO (8-hr avg max)	3	5	13,278	1,232,881
SO_2 (24hr avg)	3	5	3,928	372,358

*All analyses except PM2.5: June 1996 – December 2005; PM2.5 analyses: March 1999 – December 2005.

We created buffers around the remaining monitors based on the latter's spatial scales. Subjects whose residences were not within the set of buffers were excluded from the analyses. Monitors with no measurement data during the period of interest (1996 through 2005) were also excluded. Table 3 lists the numbers of residences and person-months of exposure associated with the different scale designations for each pollutant.

PM2.5 Constituents Analysis

The exposure assessment in the PM2.5 constituents analysis was more limited than in the main analysis because relatively few PM2.5 monitors could provide relevant air quality data. PM2.5 mass and selected constituents were collected and analyzed by the U.S. Environmental Protection Agency (EPA) as part of the Speciation Trends Network (U.S. EPA 2008). The 24-hr averaged measurements were usually obtained on an every third- or sixth-day basis. Based on prior evidence of associations from time-series studies (Mar et al. 2006; Ostro et al. 2008) and from other epidemiological and toxicological studies, we examined long-term exposures to PM2.5 mass and the following eight constituents: elemental carbon (EC), organic carbon (OC), sulfate (SO_4), nitrate (NO_3), iron (Fe), potassium (K), silicon (Si), and zinc (Zn). Filters were analyzed by EPA staff for EC and OC using the total optical transmittance method; for SO_4, NO_3, and K using ion chromatography; and for trace elements using X-ray fluorescence. One PM2.5 monitor in each of the following eight counties collected data on PM2.5 and its constituents: Fresno, Kern, Los Angeles, Riverside, Santa Clara, San Diego, Sacramento, and Ventura. These monitors became operative at different times; the data for this

analysis were collected once all were operative - from June 1, 2002 through July 31, 2007.

Eight monitors were insufficient to create statewide pollutant surfaces. Therefore, we assigned each subject a monthly exposure value based on the monitor nearest her geocoded residential address. For these analyses we restricted our sample to women living within 30 km of one of the monitors. This distance is larger than that used in the main analysis. ARB experts with whom we consulted indicated that California's PM2.5 monitors could in many cases represent a range of up to 50 km. To be conservative we used 20 km in the main analysis, but increased the buffer size to 30 km to obtain a larger sample size for the PM constituents analysis.

Traffic Analysis

Traffic exposure metrics were developed for our earlier analyses, but since the same metrics were used in the current analysis, we are providing a summary of the methodology used. Several vehicle-related exposure metrics were assigned to each geocoded residence: (1) proximity to a major highway (i.e., within or beyond 150 m); and (2) traffic density (vehicle miles traveled within 150 m); and (3) 2000 Census Block Group vehicle density. All road-based metrics were calculated using TeleAtlas' Dynamap 2000 (2nd quarter, 2005 release) street database.

Distance to the nearest major highway (within 20 km) was calculated for each geocoded residence. Major highways were defined as those having a functional classification code of "A1" (primary road with limited access, e.g., an interstate or other freeway with on-ramps and off-ramps) or "A2" (primary road without limited access).

Traffic density was calculated by summing vehicle distance traveled on all measured roads within 150 m of a geocoded residence. Vehicle distance traveled for each road is the number of vehicles on the road multiplied by the length of the road (See Figure 1).

Vehicle density was calculated using the aggregate number of vehicles in occupied housing units (variable name H046001) divided by the land area of the block group within which the teacher resided.

The Federal Highway Performance Monitoring System (HPMS) provides vehicle counts for roads. The original CalTrans street dataset that linked to HPMS data was digitized from 1:100,000 scale U.S.G.S. Digital Line Graph (DLG) maps, so the spatial precision is poor relative to current street files used for geocoding. In the original CalTrans street dataset, all streets were geographically represented by a single street centerline. The GDT street data represent divided roads (including most freeways) by two parallel centerlines, one for each direction of travel. Traffic count data is a measure of two-way traffic on a street, so when linked to the conflated GDT streets, divided roads will be double counted. Based on the functional classification coding in the Dynamap data, divided roads ("A" followed by "1"-"4" followed by "5"-"8") were selected and the vehicle counts on those segments were halved. Some (approximately 1/8th) of the identifiers used to link the CalTrans streets to the HPMS traffic data appear to be

different in the conflated GDT data, preventing linkage. For streets whose names were coded as a route identifier, a new ID field could be constructed by replacing the last six numbers from the Segment ID field with the first six numbers from the street name field. For all road-based measures, missing data were assigned a non-null minimum exposure value (50 km for proximity to major highways and the minimum calculated values for road and traffic densities).

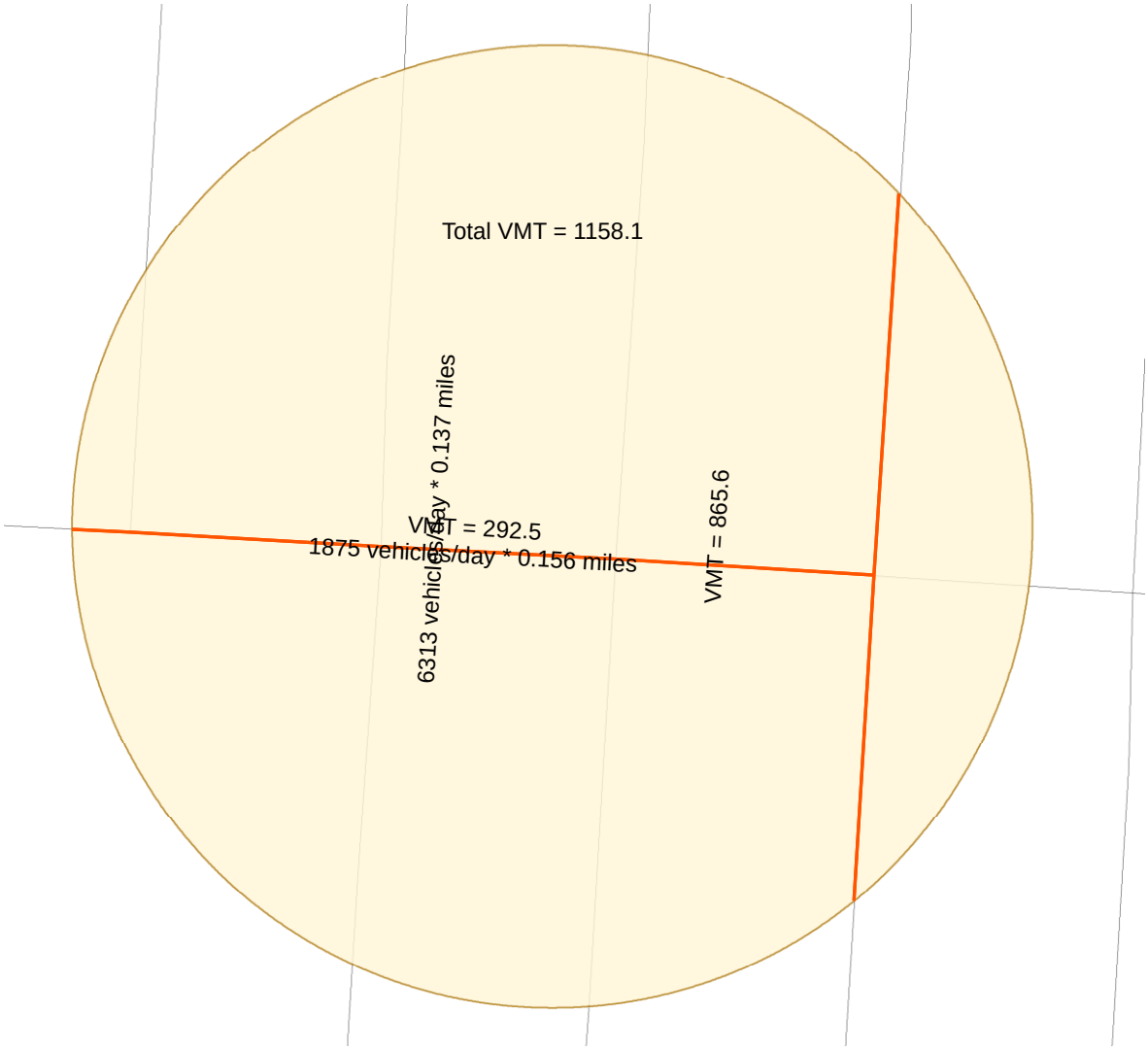


Figure 1: Example of traffic density estimation within a circular buffer zone

Covariates

Cardiovascular disease outcomes constituted the principal outcomes of interest in this analysis. Therefore, we selected most of the individual-level predictor variables for the regression analyses based on previous studies of cardiovascular disease, including

investigations that examined the influence of air pollutants on cardiovascular and cardiopulmonary mortality (Dockery et al. 1993; Pope et al. 2002; Jerrett et al. 2005).

Age was divided into two-year strata between ages 30 and 79 and three-year strata between ages 80 and 88, and one stratum for women aged 89 and older. Race/ethnicity was categorized into three strata as well: non-Hispanic white, all others (African-American, Hispanic, Asian, Pacific Islander, and Native American) and unknown/not provided. Age and race were adjusted for in the models by creating multiple strata for analysis; e.g., each age stratum included three race/ethnicity substrata. Marital status categories included married/living with partner, not married (i.e., divorced, separated, widowed, never married), and unknown/missing. We based smoking status on two questions from the baseline questionnaire. Women were asked if they had ever smoked 100 or more cigarettes during their lifetime and, if so, when they started and stopped smoking. Using this information we categorized respondents as never, former, or current smokers. We measured smoking pack-years (i.e., the number of packs smoked per day times number of years smoked) as one continuous value for former and current smokers. Second-hand smoke (SHS) exposures were categorized into three groups: those with exposure to household SHS, those without such exposure, and those with unknown exposure. Household SHS exposure was based on the women's report of ever having lived as an adult with a smoker.

We calculated body mass index (BMI or weight/height^2) for each participant based on her questionnaire responses regarding her weight and height. The women were grouped into BMI categories as follows: less than 20.0 kg/m^2, 20.0-24.9 kg/m^2, 25-29.9 kg/m^2, 30-39.9 kg/m^2, 40 kg/m^2 or more, and height or weight not provided. Physical activity, defined as the average number of hours per week of moderate or strenuous activity over a women's lifetime, was categorized as low (less than 1.99 hours per week), medium (1.99-4.93 hours per week), high (4.94 hours per week or more), and not provided. Alcohol consumption categories included non-drinkers, separate dummy variables for any beer, wine and alcohol consumption, and unknown/missing. We also created tertiles of daily caloric intake (less than 1300.17 kcal, 1300.17-1749.30 kcal, 1749.31 kcal or more, and unknown), fat (less than 41.64 g/day, 41.64-63.00 g/day, 63.01 g/day or more, and unknown) and fiber (less than 11.81 g/day, 11.81-17.04 g/day, 17.05 g/day or more, and unknown).

Menopausal status and menopausal hormone therapy (HT) use were combined into the following categories: pre-menopausal, peri/post-menopausal and no HT use, peri/post menopausal and past HT use, peri/post-menopausal and current use of estrogen, peri/post-menopausal and current use of estrogen plus progestin, and unknown menopausal status or HT use.

Family history of MI or stroke was defined as an occurrence of these events in either the respondent's mother or father. These were then summarized into dichotomous variables. High blood pressure medication and aspirin use were combined and summarized into categories including no medication, intermittent, regular, and unknown dosages.

Ecological variables at the block group level were derived from 2000 Census data in order to control for "contextual" neighborhood confounding (Jerrett et al. 2005). These contextual variables represent social, economic, and environmental settings at a group level that may be associated with disease outcomes at the individual level. Such

effects may interact with individual-level variables or may be independently associated with the outcomes. The contextual effects in this study were selected based on their identification in prior studies, particularly the ACS CPS II studies (Jerrett et al. 2005), and include ethnic/racial composition (black, white, and Hispanic), income, unemployment, population size, income inequality, and education.

Statistical Analysis

Main Analysis

Of the 124,614 women living in California at baseline, we excluded women who: (i) had no available pollutant data, (ii) had less than 12 months exposure data at the start of the outcome follow-up period, (iii) had consented to participate only in studies of breast cancer, (iv) were younger than age 30 at the beginning of follow-up, (v) had moved or died before the beginning of follow-up, or (vi) were missing information for continuous variables used in the regression models. The numbers excluded were different for the analyses of PM10 and the gases versus those involving PM2.5, for which follow-up began nearly three years later. The numbers of women in each exclusion category, and the resultant analytic cohort sizes for PM10 and the gases and for PM2.5, are presented in Table 4. We examined the covariate distributions for the full cohort versus those resulting from these exclusions and found them to be virtually identical, indicating that this process did not produce any obvious differential distribution of variables in the analytical cohorts that might have affected the regression results.

Analyses of incident MI and stroke were further restricted to those women who reported no history of such events on the baseline questionnaire and had no prior outcome-specific occurrence reported in the OSHPD database. As many first occurrences of MI and stroke prove fatal, we included both hospitalization and mortality data in the analyses of incidence of these outcomes. Unique subject identification codes allow for incidence analyses combining hospital admission and mortality data without "double-counting" any events that result in both hospitalization and death.

We used Cox proportional hazards models to estimate hazard rate ratios (HRs) and 95% confidence intervals (CI) for associations between each pollutant and the outcomes of interest. For each study subject, estimated pollution exposure data were available for most months, starting in June 1996 for PM10 and the gases and March 1999 for PM2.5. Our initial analytical approach was to create monthly individual exposure estimates via spatial linkage of the geocoded residential addresses to the IDW pollutant surfaces. Then, for each individual and each pollutant, the value for all person-months of exposure were summed and then divided by the total months of exposure, to create an average measure of overall long-term exposure until the time of an event or the end of the observation period. However, because of the marked declines in the ambient concentrations of most air pollutants in California during the study period (See Figures 2

and 3), women who survived without incident to December 2005 would have had lower average levels of exposure compared with those who died or were admitted to hospital with an MI or stroke earlier on. This would have resulted in associations of higher levels

Table 4: California Teachers Study cohort exclusions (in parentheses) for mortality analyses in relation to long-term exposures to PM10+gases and to PM2.5

	PM10+gases*	PM2.5
Exposure start date	June 1996	March 1999
Follow-up start date	June 1997	March 2000
Follow-up and exposure end date	Dec 2005	Dec 2005
CTS cohort at baseline	133,479	133,479
Not geocoded to a CA address at baseline	(8,865)	(8,865)
CTS cohort with CA address at baseline	124,614	124,614
No available pollutant data* at exposure start date	(12,028)	(31,484)
With pollutant data at exposure start date	112,586	93,130
Additional Exclusions:		
Less than 12 months of exposure data between exposure start date and initiation of follow-up	(2,057)	(13,282)
Breast cancer analyses only	(15)	(10)
Less than age 30 at follow-up start date	(3,421)	(740)
Moved or died before follow-up start date	(1,383)	(2,415)
Missing continuous covariates	(3,926)	(3,194)
Available N for final mortality analyses	101,784	73,489

* For analyses of PM10 and gases, we excluded women who had no ozone data available at the exposure start date because the monitoring network and spatial coverage for this pollutant are the most extensive in California. Women who had no ozone data were very unlikely to have data available for any other pollutant.

of exposure with mortality or hospitalization for MI or stroke, and lower levels with no events, which would result in a systematic inflation of the hazard ratios. The results of those analyses are described in Appendix A. To avoid this problem, we revised the approach to include an individualized exposure metric that would not be subject to the bias introduced by the temporal pollutant trend, as described below.

Per-subject exposure in the regression models was represented as a time-dependent function *x(m)*, where the exposure value at month *m* was calculated as the average of monthly pollutant levels between the beginning of the exposure assessment and month *m*, inclusive. For each death (or hospital admission for MI or stroke) occurring in month *m*, the calculated exposure average for each case was compared with the average pollution exposure up to the same month *m* for everyone else in the cohort who was still alive and who had not been hospitalized for MI or stroke.

Figure 2: Trends of average annual PM2.5 and PM10 exposure estimates for participants in the California Teacher Study cohort, 1996 - 2005

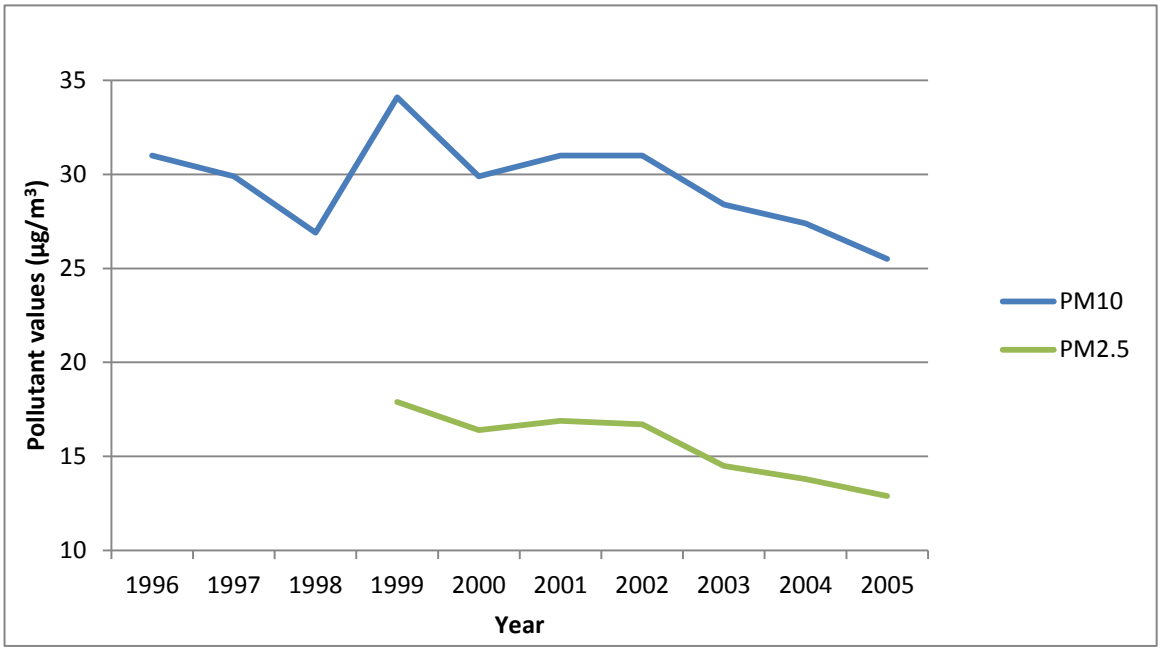
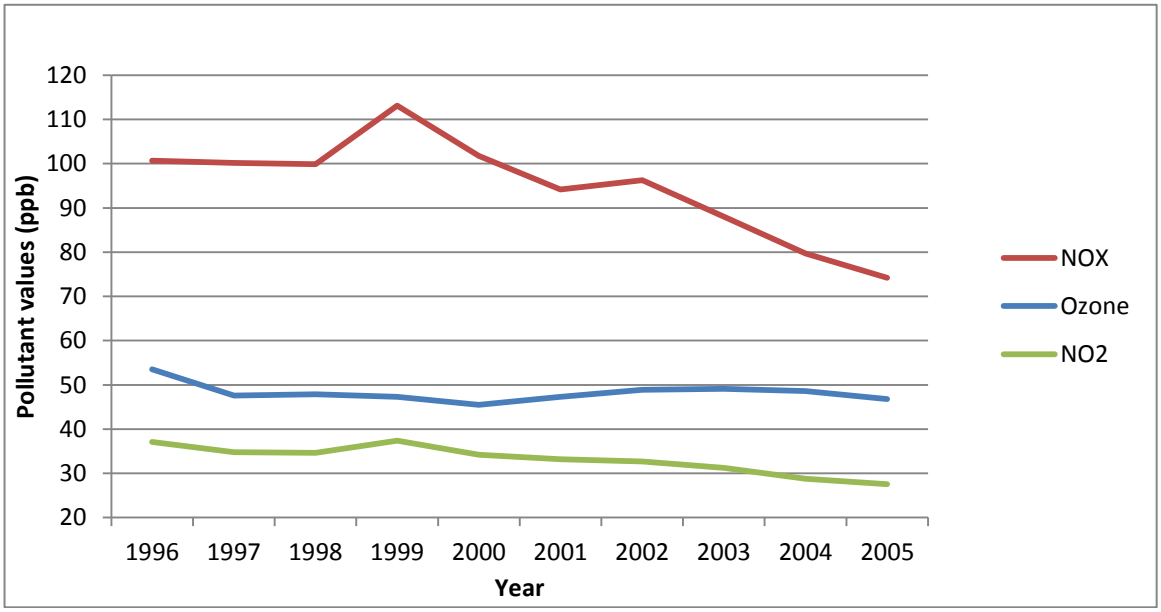


Figure 3: Trends of average annual gaseous pollutant exposure estimates for participants in the California Teacher Study cohort, 1996 - 2005



To ensure that all participants would have a minimum of one year of exposure to the pollutant of interest, we limited outcome follow-up to those who had had at least 12 months of exposure data. Thus, exposure measurements for ozone, NO_2, NOx, CO, SO_2 and PM10 were initiated in June 1996, while outcome follow-up began in June 1997; both continued until the end of the observation period (December 31, 2005). For PM2.5, the corresponding start dates for exposure and cohort follow-up were March 1999 and March 2000, respectively, through December 2005.

HRs and 95% CIs were scaled to the interquartile range (IQR), based on distributions for women for each pollutant. For purposes of comparison with other studies of particulate matter, we scaled HRs for PM2.5 and PM10 to increments of 10 $\mu g/m^3$.

Models were adjusted for age and race by creating strata as described in the covariate section, above, while other personal risk factors (marital status, smoking status, smoking pack-years, SHS exposure, BMI, physical activity, alcohol consumption, dietary caloric intake, fat and fiber consumption, family history of MI or stroke, high blood pressure medication, and aspirin use), female-specific risk factors (menopausal status and hormone therapy), and contextual variables (racial composition, income, unemployment, population size, income inequality, and education) were included as model variable terms.

Disease incidence and survival times may be more similar among study subjects who live in communities closer together and share a common demographic profile than among those who live in communities separated by greater distances, regardless of air pollution exposures. In this instance, the data may be subject to spatial autocorrelation. We attempted to deal with this issue in two ways. First, as described in the preceding paragraph, using the census tract as a unit of analysis, we included a number of contextual variables in all models. Second, we evaluated the use of a spatial random-effects model similar to that employed in an analysis of the ACS CPS II data (Pope et al. 2002). This model is a Cox Poisson regression model, extended to include random effects for the clustering of geographic units (Ma et al. 2003). Cohort members within a cluster are allowed to have correlated survival times, rather than treating each subject as independent.

We undertook several additional sensitivity analyses. We analyzed associations with ozone measured only in the third quarter (summer) rather than for the full year, since this pollutant has a distinctive seasonal pattern. We examined PM2.5 associations among potential susceptible subgroups by restricting the analysis to women who were post-menopausal at baseline. We also examined, through stratification, whether individuals who had diabetes or were overweight or obese at baseline were at greater risk. Additionally, we restricted analyses to never-smokers in order to eliminate the potential impact of a history of active smoking on associations between PM2.5 and cardiopulmonary outcomes. For outcomes with elevated HRs for more than one pollutant, we ran two-pollutant models. We examined incidence of non-fatal MI and stroke by restricting the analysis to events involving hospitalization only. Finally, we looked at whether there were differences in effect estimates between movers and non-movers.

Critical Windows

To ascertain whether there were critical time windows of PM2.5 exposure more strongly related to mortality outcomes, we evaluated the effect of using different windows of exposure: six months, one year, two years, three years and four years. In these analyses the pollutant exposure metric was restricted to the monthly PM2.5 values within the critical time period prior to each event or, for survivors, the end of follow-up. These analyses were done for the entire PM2.5 subcohort who survived at least six months after the initiation of outcome follow-up. However, the population at risk decreased with each event, so that we were not examining all of the potential critical windows in the same people. Therefore, we repeated the analysis with only those women who had experienced at least four years of exposure, excluding those who had died (or who had moved out of state) before this minimum period of exposure had elapsed. In other words, in these latter analyses, we could compare the mortality HRs for all the different windows of PM2.5 exposure within the same population. This necessitated initiating the outcome follow-up in March 2003, four years after the initiation of the exposure assessment in March 1999.

PM2.5 Constituents Analysis

The initial analytical approach for the PM2.5 constituents analysis was based on creating a single average exposure value for each participant, similar to the first approach used in the main analysis. However, the temporal decline in pollution during the observation period markedly affected the HRs for this analysis as well. For example, annual average PM2.5 levels decreased by about 25%, while those for OC and nitrates dropped by 30% and 33%, respectively. As a result, in the original study, cohort members who survived to the end of study period had exposure estimates that were significantly lower due to the marked decreases in ambient air pollutant concentrations. Thus, particularly for events occurring early in the observation period, the exposure estimate assigned to a participant who died at time *t* would tend to be greater than the average exposures of the participants who composed the remainder of the risk set, i.e., those who were still alive at time *t* and who subsequently experienced lower pollution levels.

To avoid this problem, we re-analyzed the dataset using time-varying exposures of pollution in which the exposure estimates for everyone remaining alive in the risk set were re-calculated at the time of each death, in order to compare their average exposures up to that time with that of the individual who had died. In this way, similar periods of pollution exposure were compared for both decedents and survivors, without subsequent pollution trends influencing the survivors' exposure estimates. In this revised approach, we used a similar set of individual and contextual covariates in a Cox proportional hazards model, including members of the cohort residing within 30 km of a monitor. Pollutants entered separately into the model included PM2.5 mass, EC, OC, sulfate, nitrate, iron, potassium, silicon and zinc.

Rationales for the selection of specific PM2.5 components include:

- Elemental carbon: this is considered to some extent to be a surrogate measure of diesel exhaust pollution (see below), but is also found in emissions from other sources of combustion, such as wood smoke.

- Organic carbon: OC is derived from both direct emissions of particles and, through chemical reactions in the atmosphere, as a secondary product of fuel combustion. Key sources include gasoline and diesel engine exhaust, residential wood combustion, agricultural and prescribed burning, and stationary combustion sources. Diesel fine particulate emissions consist of both OC and EC fractions along with trace amounts of inorganic compounds. The OC fraction of diesel exhaust contains heavy hydrocarbons such as lubricating oils and polycyclic aromatic hydrocarbons (PAHs) with low volatility. The EC fraction is a mixture of graphite-like particles and is basically soot. There is no physical property to clearly distinguish between the OC and EC fractions so most measurements of OC/EC from particulate samples are defined by the method of analysis. Several time-series studies of short-term exposures to OC link this pollutant with cardiovascular mortality, and ER visits for cardiovascular disease.

- Sulfate: Sulfates have been identified in other studies as important predictors of cardiopulmonary mortality. However, besides motor fuels, for which the sulfur content is low in California, and emissions from ships involved in goods movement, there are few sources of sulfur emissions in California. Therefore, sulfates make up a much smaller proportion of PM2.5 in California than in the East coast and Midwest (Bell et al. 2007).

- Nitrates: although the toxicology data on nitrates are mixed, there are several epidemiological studies that link short-term exposure to nitrate particles to cardiovascular mortality in Santa Clara County, as well as in six California counties, and the Netherlands.

- Silicon is a crustal element and constitutes a large component of soil and resuspended road dust particles. It may be enriched with and serve as a surrogate for many toxic components in road dust, such as brake and tire debris, and semivolatile compounds. Silicon may also represent a general marker for proximity to traffic. In addition, there are a few epidemiological and toxicology studies that have demonstrated the potential for cardiovascular effects from direct exposure to silicon: (i) ST-segment depression, a marker for myocardial ischemia, in dogs; (ii) heart rate variability in boilermaker construction workers; and (iii) cardiovascular mortality in a time-series study in Phoenix.

- Potassium is a marker of biomass combustion and residential wood burning, both important localized sources of PM2.5 in California.

- Zinc is a marker for combustion sources and is generated in high concentrations in a number of industrial processes. It is one of several metals that may play a role in the biological activity of combustion particles.

- Iron is thought to play an important role in particle-induced oxidative stress, one of the generally accepted mechanisms of particle-associated toxicity. It may be a component of soil-associated particles, or of combustion processes.

Exposure-Response Relationship

The Cox proportional hazards models in our analyses represent a linear relationship between pollutant values and the logarithm of the disease hazard. To assess whether this association might better fit a non-linear relationship, we checked the fit of other models for PM 2.5 and ischemic heart disease. Flexible spline or lowess curves were not possible using the SAS Cox regression routine (PHREG). Therefore, we tested a series of other models, including log-linear, quadratic and fractional polynomial, the latter two of which accommodate a range of non-linear forms (Greenland 1995).

Traffic Analysis

Associations between several traffic variables and mortality (all-cause, cardiopulmonary, cardiovascular, and IHD) and incidence (MI and stroke) outcomes were evaluated among non-movers. Traffic metrics included: (i) proximity to a highway (within 150 m and beyond 150 m); (ii) traffic density (<50th percentile, 50th-74th, 75th-89th, ≥90th percentile); and (iii) vehicle density (<25th percentile, 25th-49th, 50th-74th, 75^{th}-89^{th}, ≥90th percentile). We estimated HRs for each category within these variables using Cox proportional hazards models with the same set of individual-level and contextual variables as in the other analyses, and also tested for linear trend across exposure categories, treating the latter as an ordinal variable.

We used SAS software for the Cox proportional hazards models in most of these analyses (SAS Institute, Inc., Cary, NC 2000). The random effects modeling was conducted with the program Cox-Poisson (v. 9.06), invoked through the R programming language (R Development Core Team, 2006).

Results

Main Analysis

Table 5 presents descriptive statistics for the members of the study population whose addresses were geocodeable, and includes separate data for movers and non-movers. At baseline, these participants were predominantly non-Hispanic white (87%), about two-thirds of whom were never-smokers, while five percent were current smokers. A majority of the population reported having a normal or low weight (as reflected in the BMI variable). With few exceptions, movers and non-movers tended to be quite similar. The exceptions include the following: (1) movers tended to be younger, with 28% under age 40 and 29% age 60 and above, while the corresponding percentages for non-movers were 10% and 35%; (2) as a consequence, movers were more likely to be premenopausal (46% versus 34% for non-movers); (3) movers were slightly less likely to be married or living with a partner; (4) movers reported engaging in slightly more physical activity; and (5) movers were less likely to report having had a family history of MI or stroke.

Table 6 displays the county of residence for the cohort at baseline. As would be expected, the residential distribution of the study participants reflects that of California's population as a whole, with the majority of the cohort living in the populous counties of Southern California. Table 7 summarizes the exposure data used in the study. For example, aggregating over all of the individual estimates, the long-term mean of 24-hour average values of PM2.5 was 15.6 $\mu g/m^3$ with an interquartile range (IQR) of 8.0 $\mu g/m^3$ and an overall range of 3.1 to 28.4 $\mu g/m^3$. The mean one-hour maximum ozone concentration was 48.1 ppb, with an IQR of 11.0 ppb. Descriptive statistics are also provided for PM10, NO_2, NOx, SO_2, and CO.

Table 5: Percentage distributions of covariates at baseline among members of the CTS cohort whose addresses were geocoded (n=124,614)

	Total Cohort	Non-movers	Movers
	N=124,614	N=77,390	N=47,224
	%	%	%
Age (years)			
20-29	4	1	9
30-39	13	9	19
40–49	26	28	23
50–59	24	27	20
60–69	17	20	12
70–79	11	11	11
≥ 80	5	4	6
Race/ethnicity			
Non-Hispanic White	87	86	86
Other	11	12	11
Unknown	2	2	2
Smoking			
Never Smokers	67	66	67
Current smoker	5	5	5
Former smoker	28	29	28
Total smoking pack-years among current and former smokers (mean)	15.3	15.4	15.1
BMI (kg/m^2)			
< 20.0 (underweight)	10	10	11
20.0 – 24.9 (normal weight)	48	47	49
25 – 29.9 (overweight)	24	25	22
30 – 39 (obese)	12	12	11
≥ 40 (extremely obese)	1	2	2
Unknown	4	4	5
Marital status			
Married/Living with partner	44	46	41
Divorced/Widowed/Separated/Never Married	21	20	22
Unknown	35	34	37
Alcohol consumption			
No alcohol consumption	33	32	32
Beer (yes)	24	23	26
Wine (yes)	57	57	54
Liquor (yes)	30	30	30
Unknown	6	5	6

Table 5: Percentage distributions of covariates at baseline among members of the CTS cohort whose addresses were geocoded (n=124,614) (continued)

	Total Cohort	Non-movers	Movers
SHS adult home exposure			
No SHS exposure	45	44	47
SHS exposure	49	50	48
Unknown	6	6	5
Dietary fat (g/day)			
< 41.64	30	30	29
41.64-63.00	31	31	30
≥ 63.01	30	30	30
Unknown	9	9	11
Dietary fiber g/day)			
< 11.81	30	30	30
11.81-17.04	31	31	30
≥ 17.05	30	30	30
Unknown	9	9	10
Dietary calories (kcal/day)			
< 1300.17	30	30	29
1300.17-1749.30	31	31	30
≥ 1749.31	30	29	31
Unknown	9	9	10
Physical activity (hours/week)			
< 1.99 (low)	32	34	30
1.99-4.93 (medium)	34	34	33
≥ 4.94 (high)	33	31	36
Unknown	1	1	1
Menopausal status/ hormone therapy use			
Premenopausal	38	34	46
Peri/post-menopausal and no HT use	13	14	11
Peri/post-menopausal and past HT use	8	9	8
Peri/post-menopausal and current use of estrogen	13	14	11
Peri/post-menopausal and current use of estrogen plus progestin	14	15	11
Unknown menopausal status or HT use	14	14	13
Parental history of MI			
No	67	65	70
Yes	33	35	30
Parental history of stroke			
No	79	78	81
Yes	21	22	19

Table 5: Percentage distributions of covariates at baseline among members of the CTS cohort whose addresses were geocoded (n=124,614) (continued)

	Total Cohort	Non-movers	Movers
Hypertension medication use			
No regular use	80	79	82
1-3 days/week (intermittent)	1	1	1
4-7 days/week (regular)	15	16	14
Unknown	4	4	4
Aspirin use			
No regular use	76	75	77
1-3 days/week (intermittent)	10	11	10
4-7 days/week (regular)	11	11	10
Unknown	3	3	3

Tables 8 and 9 summarize inter-pollutant correlations for the periods March 1999 - December 2005 (including PM2.5) and June 1996 - December 2005 (for all pollutants except PM2.5), respectively. These represented the correlations among the estimated exposures for the participants, not the concentrations measured at fixed-site monitors. For example, PM2.5 was highly correlated with PM10 and NO_2 ($r = 0.91$ and 0.81, respectively), moderately correlated with ozone ($r = 0.54$) and least correlated with SO_2 ($r = 0.02$).

Table 10 displays estimated hazard ratios for cardiovascular mortality for non-pollutant variables included in the final multivariate models (i.e., for the participants who had PM2.5 data available), both for the entire study population, and disaggregated by residential mobility. The HRs for known risk factors for cardiovascular mortality are generally in the expected directions, e.g., current smoking, BMI (obesity), marital status, alcohol consumption, decreased physical activity, menopausal status, and use of blood pressure medication. Of the dietary factors, the highest dietary fat stratum was clearly associated with an elevated HR, but the confidence intervals of all others included unity. Interestingly, family history of stroke or MI was not associated with cardiovascular mortality in this analysis, nor was SHS exposure. Several variables were more strongly associated with cardiovascular mortality among the non-movers than movers (e.g., current smoking), and vice versa (single marital status, extreme obesity (BMI $\geq$ 40).

Table 6: California Teachers Study participants' counties of residence at baseline (1995)

COUNTY	COUNT	COUNTY	COUNT
ALAMEDA	5292	ORANGE	11528
ALPINE	7	PLACER	1309
AMADOR	187	PLUMAS	165
BUTTE	1197	RIVERSIDE	5064
CALAVERAS	232	SACRAMENTO	4682
COLUSA	82	SAN BENITO	185
CONTRA COSTA	4480	SAN BERNARDINO	5886
DEL NORTE	80	SAN DIEGO	10876
EL DORADO	868	SAN FRANCISCO	1729
FRESNO	3573	SAN JOAQUIN	2030
GLENN	115	SAN LUIS OBISPO	1491
HUMBOLDT	821	SAN MATEO	2595
IMPERIAL	462	SANTA BARBARA	1728
INYO	109	SANTA CLARA	6289
KERN	2511	SANTA CRUZ	1576
KINGS	409	SHASTA	781
LAKE	229	SIERRA	16
LASSEN	127	SISKIYOU	279
LOS ANGELES	26163	SOLANO	1363
MADERA	472	SONOMA	2327
MARIN	1362	STANISLAUS	1971
MARIPOSA	110	SUTTER	370
MENDOCINO	582	TEHAMA	204
MERCED	831	TRINITY	49
MODOC	42	TULARE	1535
MONO	51	TUOLUMNE	318
MONTEREY	1547	VENTURA	3260
NAPA	763	YOLO	802
NEVADA	650	YUBA	163

Table 7: Descriptive statistics for air pollutants used to estimate long-term exposures among participants in the California Teachers Study

Pollutant	Units	Averaging time	Mean (SD)	Inter-quartile range	Min-Max Range
Ozone	ppb	1-hr max	48.11 (8.72)	11.02	25.39 - 82.63
Summer Ozone*	ppb	1-hr max	61.16 (16.58)	22.96	24.05 - 116.01
PM2.5**	$\mu g/m^3$	24-hr avg	15.64 (4.48)	8.02	3.11 - 28.35
PM10	$\mu g/m^3$	24-hr avg	29.21 (9.73)	15.05	9.19 - 82.64
NO_2	ppb	1-hr max	33.59 (9.63)	10.29	5.24 - 67.19
NO_X	ppb	1-hr max	95.60 (34.5)	48.31	7.31 - 221.4
SO_2	ppb	24-hr avg	1.72 (0.62)	0.43	0.21 - 3.65
CO	ppm	8-hr avg	1.05 (0.36)	0.49	0.28 - 3.34

* Summer ozone includes July, August and September values from 1996 through 2005
** PM2.5 data were limited to March 1999 - December 2005

Table 8: Spearman correlation coefficients (r) for estimated pollutant exposures among CTS participants for the period March 1999 – December 2005

	Ozone	PM2.5	PM10	NOx	NO_2	CO	SO_2
Ozone	1.00	0.54	0.74	-0.08	0.51	0.08	-0.17
PM2.5		1.00	0.91	0.52	0.81	0.53	0.02
PM10			1.00	0.24	0.80	0.37	0.54
NOx				1.00	0.79	0.81	0.49
NO_2					1.00	0.72	0.67
CO						1.00	0.80
SO_2							1.00

Table 9: Spearman correlation coefficients (r) for estimated pollutant exposures among CTS participants for the period June 1996 – December 2005 (all pollutants except PM2.5)

	Ozone	PM10	NOx	NO_2	CO	SO_2
Ozone	1.00	0.73	-0.12	0.52	0.08	-0.30
PM10		1.00	0.23	0.81	0.31	0.13
NOx			1.00	0.78	0.76	0.40
NO_2				1.00	0.71	0.43
CO					1.00	0.63
SO_2						1.00

Table 10: Hazard ratios for nonpollutant covariates in relation to cardiovascular mortality for CTS participants with PM2.5 data available *

	Total cohort	Non-movers	Movers
	N=73,489; # events=1,630	N=47,657; # events=820	N=25,832; # events=810
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Smoking status			
Never smokers	1.00		
Current smoker	1.57 (1.21, 2.04)	1.70 (1.22, 2.37)	1.45 (0.95, 2.21)
Former smoker	1.00 (0.86, 1.15)	1.06 (0.87, 1.30)	0.93 (0.76, 1.15)
Total smoking pack-years among current and former smokers	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)
BMI (kg/m^2)			
< 20.0	1.09 (0.92, 1.30)	1.10 (0.85, 1.42)	1.03 (0.81, 1.33)
20.0-24.9	1.00	1.00	1.00
25 – 29.9	0.91 (0.80, 1.03)	0.96 (0.80, 1.15)	0.86 (0.71, 1.04)
30 – 39	1.13 (0.95, 1.34)	1.25 (0.99, 1.59)	1.03 (0.79, 1.33)
≥ 40	2.60 (1.73, 3.92)	2.36 (1.36, 4.08)	2.90 (1.56, 5.42)
Unknown	1.04 (0.90, 1.22)	1.15 (0.92, 1.44)	0.94 (0.76, 1.16)
Marital status			
Married/Living with partner	1.00	1.00	1.00
Divorced/Widowed/Separated/Never Married	1.23 (1.05, 1.45)	1.01 (0.82, 1.26)	1.50 (1.16, 1.93)
Unknown	2.50 (2.14, 2.91)	2.23 (1.83, 2.73)	2.84 (2.22, 3.64)
Alcohol consumption			
No alcohol consumption	1.00	1.00	1.00
Beer (yes)	0.97 (0.82, 1.14)	0.97 (0.77, 1.21)	1.03 (0.80, 1.32)
Wine (yes)	0.83 (0.74, 0.93)	0.77 (0.65, 0.91)	0.88 (0.75, 1.04)
Liquor (yes)	0.86 (0.75, 0.97)	0.88 (0.73, 1.05)	0.85 (0.70, 1.03)
Unknown	0.90 (0.72, 1.13)	0.88 (0.61, 1.25)	0.98 (0.72, 1.32)
SHS exposure at home			
No SHS exposure	1.00	1.00	1.00
SHS exposure	0.98 (0.87, 1.10)	0.91 (0.77, 1.07)	1.07 (0.91, 1.26)
Unknown	0.96 (0.75, 1.23)	0.96 (0.68, 1.34)	1.06 (0.73, 1.53)
Dietary fat (g/day)			
< 41.64	1.00	1.00	1.00
41.64-63.00	1.08 (0.94, 1.25)	1.17 (0.96, 1.42)	1.02 (0.82, 1.26)
≥ 63.01	1.31 (1.07, 1.61)	1.34 (1.01, 1.78)	1.30 (0.97, 1.75)
Unknown	1.08 (0.86, 1.36)	1.09 (0.78, 1.52)	1.03 (0.76, 1.40)
Dietary fiber (g/day)			
< 11.81	1.09 (0.92, 1.28)	1.24 (0.98, 1.56)	0.97 (0.76, 1.23)
11.81-17.04	1.03 (0.89, 1.19)	1.07 (0.87, 1.32)	0.99 (0.80, 1.22)
≥ 17.05	1.00	1.00	1.00
Unknown	1.08 (0.86, 1.36)	1.09 (0.78, 1.52)	1.03 (0.76, 1.40)

Table 10: Hazard ratios for nonpollutant covariates in relation to cardiovascular mortality for CTS participants with PM2.5 data available (continued)

Dietary calories (kcal/day)			
< 1300.17	1.00	1.00	1.00
1300.17 – 1749.30	0.92 (0.78, 1.08)	0.91 (0.73, 1.14)	0.95 (0.75, 1.20)
≥ 1749.31	0.90 (0.71, 1.15)	0.89 (0.63, 1.24)	0.95 (0.67, 1.35)
Unknown	1.08 (0.86, 1.36)	1.09 (0.78, 1.52)	1.03 (0.76, 1.40)
Physical activity (hours/week)			
≥ 4.94	1.00	1.00	1.00
1.99-4.93	1.09 (0.94, 1.26)	1.22 (1.01, 1.46)	1.07 (0.88, 1.29)
< 1.99	1.16 (1.01, 1.32)	1.09 (0.88, 1.34)	1.04 (0.85, 1.29)
Unknown	1.52 (1.10, 2.09)	1.40 (0.84, 2.33)	1.55 (1.01, 2.37)
Menopausal status and hormone therapy use:			
Premenopausal	1.00	1.00	1.00
Peri/post-menopausal and no HT use	2.21 (0.99, 4.96)	1.75 (0.67, 4.55)	3.57 (0.83, 15.31)
Peri/post-menopausal and past HT use	1.73 (0.77, 3.89)	1.38 (0.52, 3.61)	2.74 (0.64, 11.82)
Peri/post-menopausal and current use of estrogen	1.82 (0.81, 4.10)	1.47 (0.56, 3.85)	2.81 (0.66, 12.09)
Peri/post-menopausal and current use of estrogen plus progestin	1.51 (0.67, 3.42)	1.20 (0.46, 3.15)	2.37 (0.55, 10.25)
Unknown menopausal status or HT use	2.02 (0.90, 4.52)	1.73 (0.66, 4.52)	2.91 (0.68, 12.47)
Family history of MI			
No	1.00	1.00	1.00
Yes	0.97 (0.87, 1.08)	1.06 (0.92, 1.23)	0.88 (0.76, 1.03)
Stroke Family history of stroke			
No	1.00	1.00	1.00
Yes	1.01 (0.90, 1.13)	1.08 (0.92, 1.26)	0.93 (0.79, 1.10)
Blood pressure medication:			
No regular use	1.00	1.00	1.00
Intermittent	1.36 (0.89, 2.06)	1.27 (0.67, 2.40)	1.33 (0.76, 2.33)
Regular	1.62 (1.45, 1.80)	1.76 (1.51, 2.05)	1.45 (1.24, 1.69)
Unknown	1.49 (1.23, 1.80)	1.49 (1.13, 1.97)	1.50 (1.14, 1.96)
Aspirin use			
No regular use	1.00	1.00	1.00
Intermittent	0.95 (0.77, 1.17)	1.06 (0.81, 1.40)	0.84 (0.60, 1.18)
Regular	1.28 (1.14, 1.44)	1.28 (1.08, 1.52)	1.27 (1.07, 1.50)
Unknown	1.00 (0.80, 1.27)	1.07 (0.75, 1.51)	0.89 (0.64, 1.22)

* Models adjusted for all variables listed, in addition to age and race (see text in Methods Section).

Table 11: Hazard ratios for mortality and for incident MI and stroke, per 10 μg/m^3 increment of PM2.5 (2000-2005) and PM10 (1996-2005) for the California Teachers Study cohort

	PM2.5			PM10		
Outcome	# events	N	HR (95% CI)	# events	N	HR (95% CI)
All-cause mortality	4,147	73,489	1.01 (0.95, 1.09)	4,694	61,181	1.00 (0.97, 1.04)
Cardiovascular mortality	1,630	73,489	1.07 (0.95, 1.19)	1,863	61,181	1.03 (0.98, 1.08)
Respiratory mortality	638	73,489	1.10 (0.92, 1.32)	728	61,181	1.02 (0.94, 1.11)
NM-Respiratory mortality	404	73,489	1.21 (0.97, 1.52)	453	61,181	1.08 (0.98, 1.19)
Lung cancer mortality	234	73,489	0.95 (0.70, 1.28)	275	61,181	0.93 (0.81, 1.07)
IHD mortality	773	73,489	1.20 (1.02, 1.41)	843	61,181	1.06 (0.99, 1.14)
Cerebrovascular mortality	382	73,489	1.16 (0.92, 1.46)	486	61,181	0.99 (0.89, 1.09)
MI incidence	722	72,403	0.98 (0.83, 1.16)	837	60,307	0.98 (0.91, 1.06)
Stroke incidence	969	72,230	1.14 (0.99, 1.32)	1,179	60,204	1.06 (1.00, 1.13)

Models adjusted for age, race, smoking status, total pack-years, BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period for PM2.5: March 1999-December 2005; cohort follow-up period: March 2000-December 2005. Exposure period for PM10: June 1996-December 2005; cohort follow-up period: June 1997-December 2005. MI = myocardial infarction; NM = nonmalignant; IHD = ischemic heart disease; HR = hazard ratio; CI = confidence interval.

Table 11 summarizes the results for all-cause and cause-specific mortality, as well as incidence of MI and stroke, in relation to PM2.5 and PM10. These results are presented in terms of the increase in the HR per 10 μg/m^3 increase for long-term estimated exposures. Although most HR point estimates for PM2.5 were greater than unity, only that for IHD mortality was significantly elevated (HR = 1.20, 95% CI 1.02-1.41). The HR point estimates for PM10 were uniformly lower than those for PM2.5. The outcomes with the strongest associations with PM10 were IHD mortality (HR = 1.06, 95% CI 0.99-1.14) and incident stroke (HR = 1.06, 95% CI 1.00-1.13). The HRs for stroke for both particulate metrics were suggestive of an increase in risk, but neither was statistically significant at $p < 0.05$.

Table 12 summarizes the regression results for the gaseous pollutants, scaled to the interquartile range (IQR) of exposure for 1996-2005. Fewer outcome events were included in the analyses of NO_2, NOx, SO_2, and CO because: (i) the representative spatial ranges designated

for these pollutant monitors were much smaller than for the ozone, PM2.5 and PM10 monitors, which meant that fewer participants' residences were included; and (ii) there were substantially fewer monitors for these pollutants than for PM10 and ozone. None of the outcomes except cardiovascular diseases showed a relationship with any of the gaseous pollutants. IHD mortality was associated with NOx (HR = 1.25, 95% CI = 1.00-1.55), and the risk of cardiovascular mortality was elevated with a weaker association (HR = 1.13, 95% CI = 0.98-1.31). In contrast, the association between ozone and IHD mortality was of borderline significance (HR = 1.06, 95% CI = 0.99-1.14), with no corresponding increase in the HR for cardiovascular disease *in toto*. However, when the ozone analysis was restricted to summers only, the HR for IHD mortality was significantly elevated (HR = 1.09, 95% CI = 1.01-1.19) (Table 13).

Tables 14 – 19 present the results of several sensitivity analyses. In the PM2.5 analysis restricted to women who were post-menopausal at baseline (Table 14), the results were similar to those for the cohort as a whole, except that the HR for stroke incidence increased and became statistically significant (HR = 1.19, 95% CI = 1.02, 1.38, based on 907 events, compared with 1.14, 95% CI = 0.99, 1.32, based on 969 events for the full cohort). This analysis was based on menopausal status reported at baseline, which would have resulted in misclassifying some women as premenopausal when the PM2.5 follow-up began in March 2000. We did not have follow-up questionnaire data on menopausal status, but in order to see whether such misclassification might have produced biased results, we ran an additional analysis in which the women were stratified into those < 50 years of age and those who were $\geq$ 50 years old in March 2000. Few of the latter group would have been premenopausal. There were too few events in the women < 50 to provide stable HR estimates; however, the results for women $\geq$ 50 were essentially unchanged for all outcomes listed in Table 14.

Table 15 presents the results of analyses restricted to never-smokers only. Here the HRs tended to increase or remain more or less unchanged in relation to those for the entire cohort, though for a number of the outcomes the width of the confidence intervals increased, reflecting the smaller numbers of events. Among the findings of interest among never-smokers, PM10 was associated with nonmalignant respiratory disease mortality (HR = 1.15, 95% C.I. 1.00-1.33), PM2.5 was more strongly associated with cardiovascular mortality (HR = 1.13, 95% C.I. 0.98-1.29, as well as with IHD mortality HR = 1.28, 95% C.I. 1.05-1.57), and summer-only ozone with IHD mortality (HR = 1.12, 95% C.I. 1.01-1.23). In addition, long-term exposures to NOx continued to be associated with IHD mortality (HR = 1.40, 95% C.I. 1.07-1.83), and both NOx and SO_2 were associated with all-cause and cardiovascular mortality, but these latter results were based on relatively few events (758 and 343 for NOx, and 152 and 69 for SO_2, respectively).

Women who were overweight or obese did not appear to be at greater risk of PM2.5-associated events than women who were not (Table 16). Comparing women who were overweight, obese or extremely obese with those who were not, none of the HRs for the former category (i.e., BMI $\geq$ 25) was significantly elevated, and most of the point estimates were lower than those with BMI < 25. Similar results were noted when PM10 or NOx was used as the pollutant variable (data not shown).

Somewhat different results were observed for women who reported having diabetes at baseline (Table 17). There were relatively few events in this subpopulation, so none of the PM2.5-related HRs was significant. Still, the HR for MI incidence among diabetic women was 1.31 (95% CI 0.83 – 2.06), based on 115 events, while that for women who were non-diabetic was 0.95 (95% CI 0.79 – 1.14), based on 607 events, suggesting the possibility of differential pollutant susceptibility. Although the HR point estimates for MI incidence among women with

diabetes were greater than those for women without diabetes when PM10 (1.11 vs. 0.99, respectively) or NOx (1.19 vs. 0.99, respectively) was used as the pollutant variable, the differences were not so pronounced as that for PM2.5.

The results of two-pollutant models for IHD mortality using either PM2.5 or PM10 with ozone and NOx are presented in Table 18. In the PM2.5/ozone model, the HR for PM2.5 increased slightly (from 1.20 to 1.27), while that for ozone decreased and became nonsignificant (from 1.06 to 0.99). This was based on about half the number of deaths compared with the model with ozone alone (732 vs 1,358). (Examining ozone only [without PM2.5 in the model] for just these 732 events gave the following result: HR=1.08, 95% CI = 0.97-1.20.) Similarly, in the PM10/ozone model, the HR for PM10 remained about the same, while that for ozone declined (from 1.06 to 0.97). This was based on 843 deaths. (Re-running this analysis on just these 843 events without PM10 in the model gave this result for ozone: HR=1.06, 95% CI = 0.94-1.19.) Using 3rd-quarter-only ozone levels in two-pollutant models with PM2.5 and PM10 increased the ozone HRs somewhat, but they were still not significant. In models with either particulate metric and NOx, none of the HRs was significant, though the number of events was quite small, due to the restricted buffer zone that we used around the NOx monitors, which markedly limited the numbers of participants whose residences were within the monitors' representative ranges.

Table 19 presents the results of analyses examining non-fatal (i.e., hospitalization-only) incident MI and stroke. Only PM10 showed a relationship with incident stroke (HR = 1.09, 95% CI = 1.01-1.17). No pollutant exposure was associated with incident MI.

In the analysis examining mortality hazard ratios for various pollutants among movers versus non-movers, there were few differences and, in keeping with the results for the cohort as a whole, almost none was significant. The exception among the mortality categories was IHD. Table 20 displays the results for the IHD HRs among movers and non-movers. The results are somewhat mixed, with a greater impact among movers for PM2.5, the reverse for PM10 and ozone, and essentially no difference for NOx and NO_2.

As noted in the Methods section, to examine possible residual spatial autocorrelation that might remain after adjusting for individual-level and contextual census tract covariates, we used a Cox-Poisson program that allowed random effects for spatial adjacencies, under development by Dr. Edward Hughes. In analyses of the ACS CPS II data, the Cox-Poisson model used pollutant averages across cities as spatial units. We were able to use the program successfully when the exposure metric for each woman consisted of a single long-term average. In our current approach, however, the use of zip codes as spatial units, as well as monthly per-subject exposure assignments, resulted in much greater computational demands. Analyzing the resultant file as time-dependent exposures with spatial random effects exceeded the computational capacity of all available computers save a 64-bit Windows machine with six Gigabytes of RAM. Even on that computer we needed to pare back the number of variables in the models. Moreover, we were unable to duplicate the analysis run with the SAS PHREG routine because the Cox Poisson program lacked PHREG's "multipass" function, which is needed to select specific cumulative pollutant values for each successive risk set. Therefore, we could not finalize the spatial autocorrelation analysis, and report here only the SAS results. The Cox-Poisson random effects model that we used represents the state of the art in this field, but additional work and expense beyond the scope of this project are needed to refine its utility for the CTS dataset.

Table 12: Hazard ratios for mortality and for incident MI and stroke for the California Teachers Study cohort, based on estimated long-term exposures at participants' residences, scaled to pollutant interquartile ranges (1996-2005)

Pollutant	Outcome	# events	N	IQR	HR* (95% CI)
Ozone	All-cause mortality	7,381	101,784	11.02	0.97 (0.94, 1.00)
	Cardiovascular mortality	2,919	101,784	11.02	1.00 (0.95, 1.05)
	Respiratory mortality	1,135	101,784	11.02	1.02 (0.94, 1.11)
	NM-Respiratory mortality	702	101,784	11.02	1.07 (0.97, 1.19)
	Lung cancer mortality	433	101,784	11.02	0.96 (0.84, 1.09)
	IHD mortality	1,358	101,784	11.02	1.06 (0.99, 1.14)
	Cerebrovascular mortality	728	101,784	11.02	0.97 (0.88, 1.07)
	MI incidence	1,317	100,340	11.02	1.03 (0.95, 1.11)
	Stroke incidence	1,875	100,223	11.00	1.02 (0.95, 1.08)
NOx	All-cause mortality	1,208	15,397	49.31	1.04 (0.95, 1.15)
	Cardiovascular mortality	499	15,397	49.31	1.13 (0.98, 1.31)
	Respiratory mortality	198	15,397	49.31	0.88 (0.70, 1.12)
	NM-Respiratory mortality	128	15,397	49.31	0.86 (0.64, 1.17)
	Lung cancer mortality	70	15,397	49.31	0.92 (0.60, 1.40)
	IHD mortality	238	15,397	49.31	1.25 (1.00, 1.55)
	Cerebrovascular mortality	118	15,397	49.31	1.03 (0.77, 1.39)
	MI incidence	188	15,149	48.82	1.02 (0.80, 1.29)
	Stroke incidence	310	15,117	49.69	1.06 (0.88, 1.28)

Table 12: Hazard ratios for mortality and for incident MI and stroke for the California Teachers Study cohort, based on estimated long-term exposures at participants' residences, scaled to pollutant interquartile ranges (1996-2005) (continued)

Pollutant	Outcome	# events	N	IQR	HR* (95% CI)
NO_2	All-cause mortality	1,010	12,366	10.29	0.97 (0.91, 1.04)
	Cardiovascular mortality	408	12,366	10.29	0.98 (0.88, 1.09)
	Respiratory mortality	174	12,366	10.29	0.95 (0.81, 1.13)
	NM-Respiratory mortality	107	12,366	10.29	0.93 (0.75, 1.15)
	Lung cancer mortality	67	12,366	10.29	1.00 (0.75, 1.33)
	IHD mortality	193	12,366	10.29	1.07 (0.92, 1.25)
	Cerebrovascular mortality	104	12,366	10.29	0.86 (0.70, 1.06)
	MI incidence	161	12,172	10.27	1.05 (0.90, 1.24)
	Stroke incidence	254	12,136	10.35	1.02 (0.90, 1.16)
CO	All-cause mortality	997	11,412	0.49	0.93 (0.84, 1.02)
	Cardiovascular mortality	409	11,412	0.49	0.95 (0.81, 1.11)
	Respiratory mortality	155	11,412	0.49	0.83 (0.65, 1.07)
	NM-Respiratory mortality	103	11,412	0.49	0.83 (0.60, 1.14)
	Lung cancer mortality	52	11,412	0.49	0.89 (0.57, 1.39)
	IHD mortality	198	11,412	0.49	0.90 (0.72, 1.13)
	Cerebrovascular mortality	92	11,412	0.49	0.78 (0.55 1.11)
	MI incidence	163	11,234	0.49	0.90 (0.71, 1.14)
	Stroke incidence	247	11,215	0.49	0.93 (0.77, 1.13)

Table 12: Hazard ratios for mortality and for incident MI and stroke for the California Teachers Study cohort, based on estimated long-term exposures at participants' residences, scaled to pollutant interquartile ranges (1996-2005) (continued)

Pollutant	Outcome	# events	N	IQR	HR* (95% CI)
SO_2	All-cause mortality	257	3,428	0.43	1.11 (1.00, 1.23)
	Cardiovascular mortality	107	3,428	0.43	1.07 (0.91, 1.25)
	Respiratory mortality	29	3,428	0.43	1.03 (0.70, 1.52)
	NM-Respiratory mortality	16	3,428	0.43	-
	Lung cancer mortality	13	3,428	0.43	-
	IHD mortality	49	3,428	0.43	1.03 (0.80, 1.32)
	Cerebrovascular mortality	23	3,428	0.43	1.22 (0.79, 1.87)
	MI incidence	43	3,375	0.43	1.06 (0.80, 1.42)
	Stroke incidence	56	3,356	0.43	1.17 (0.93, 1.47)

* Models adjusted for age, race, smoking status, total pack-years BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period: June 1996-December 2005; cohort follow-up period: June 1997-December 2005. MI = myocardial infarction; NM = nonmalignant; IHD = ischemic heart disease; IQR = interquartile range; HR = hazard ratio; CI = confidence interval. Units for all pollutants are in ppb except CO, for which units are in ppm.

Table 13: Hazard ratios* for mortality and for incident MI and stroke in the California Teachers Study cohort, based on summer ozone interquartile ranges (1996 – 2005)

Outcome	# events	N	IQR	HR* (95% CI)
All-cause mortality	7,381	101,784	22.96	0.97 (0.94, 1.01)
Cardiovascular mortality	2,919	101,784	22.96	1.02 (0.96, 1.07)
Respiratory mortality	1,135	101,784	22.96	1.03 (0.94, 1.12)
NM-Respiratory mortality	702	101,784	22.96	1.09 (0.97, 1.21)
Lung cancer mortality	433	101,784	22.96	0.95 (0.82, 1.10)
IHD mortality	1,358	101,784	22.96	1.09 (1.01, 1.19)
Cerebrovascular mortality	728	101,784	22.96	0.99 (0.88, 1.10)
MI incidence	1,317	100,340	22.95	1.04 (0.96, 1.12)
Stroke incidence	1,875	100,223	22.94	1.02 (0.95, 1.09)

* Models adjusted for age, race, smoking status, total pack-years BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period: June 1996-December 2005; cohort follow-up period: June1997-December 2005. MI = myocardial infarction; NM = nonmalignant; IHD = ischemic heart disease; IQR = interquartile range in ppb; HR = hazard ratio; CI = confidence interval

Table 14: Hazard ratios for mortality and for incident MI and stroke, per 10 μg/m^3 increment of estimated long-term average PM2.5 for the California Teachers Study cohort (restricted to women who were post-menopausal at baseline)

Outcome	# events	N	HR (95% CI)
All-cause mortality	3,886	36,976	1.00 (0.93, 1.08)
Cardiovascular mortality	1,598	36,976	1.06 (0.95, 1.19)
Respiratory mortality	614	36,976	1.10 (0.91, 1.32)
NM-Respiratory mortality	398	36,976	1.17 (0.93, 1.47)
Lung Cancer mortality	216	36,976	0.97 (0.71, 1.33)
IHD mortality	760	36,976	1.21 (1.02, 1.42)
Cerebrovascular mortality	376	36,976	1.13 (0.90, 1.43)
MI incidence	655	35,989	0.98 (0.82, 1.17)
Stroke incidence	907	35,927	1.19 (1.02, 1.38)

* Models adjusted for smoking status, total pack-years BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period: March 1999-December 2005; cohort follow-up period: March 2000-December 2005. MI = myocardial infarction; NM = nonmalignant; IHD = ischemic heart disease; HR = hazard ratio; CI = confidence interval

Table 15: Hazard ratios for mortality and for incident MI and stroke in relation to long-term pollutant exposures among the California Teachers Study cohort (restricted to women who were never-smokers at baseline)

Pollutant	Outcome	# events	N	PM scale (10 μg/m^3)/Gas IQR (ppb)	HR (95% CI)
PM10	All-cause mortality	2,821	41,209	10.00	1.00 (0.96, 1.04)
	Cardiovascular mortality	1,256	41,209	10.00	1.02 (0.95, 1.08)
	Respiratory mortality	265	41,209	10.00	1.11 (0.97, 1.26)
	NM-Respiratory mortality	203	41,209	10.00	1.15 (1.00, 1.33)
	Lung cancer mortality	62	41,209	10.00	1.00 (0.75, 1.31)
	IHD mortality	564	41,209	10.00	1.06 (0.97, 1.16)
	Cerebrovascular mortality	332	41,209	10.00	0.93 (0.82, 1.05)
	MI incidence	534	40,694	10.00	1.03 (0.94, 1.13)
	Stroke incidence	734	40,601	10.00	1.05 (0.97, 1.14)
PM2.5	All-cause mortality	2,513	50,229	10.00	1.03 (0.94, 1.13)
	Cardiovascular mortality	1,074	50,229	10.00	1.13 (0.98, 1.29)
	Respiratory mortality	241	50,229	10.00	1.30 (0.97, 1.74)
	NM-Respiratory mortality	191	50,229	10.00	1.26 (0.91, 1.76)
	Lung cancer mortality	50	50,229	10.00	1.62 (0.83, 3.16)
	IHD mortality	513	50,229	10.00	1.28 (1.05, 1.57)
	Cerebrovascular mortality	255	50,229	10.00	1.24 (0.93, 1.64)
	MI incidence	460	49,585	10.00	1.03 (0.83, 1.27)
	Stroke incidence	592	49,453	10.00	1.17 (0.97, 1.41)

Table 15: Hazard ratios for mortality and for incident MI and stroke in relation to long-term pollutant exposures among the California Teachers Study cohort (restricted to women who were never-smokers at baseline) (continued)

Pollutant	Outcome	# events	N	IQR	HR (95% CI)
Ozone (year-round)	All-cause mortality	4,426	68,611	10.65	0.97 (0.93, 1.00)
	Cardiovascular mortality	1,921	68,611	10.65	1.00 (0.95, 1.06)
	Respiratory mortality	435	68,611	10.65	1.07 (0.95, 1.21)
	NM-Respiratory mortality	332	68,611	10.65	1.10 (0.95, 1.27)
	Lung cancer mortality	103	68,611	10.65	0.98 (0.76, 1.27)
	IHD mortality	892	68,611	10.65	1.08 (0.99, 1.18)
	Cerebrovascular mortality	493	68,611	10.65	0.92 (0.82, 1.04)
	MI incidence	818	67,775	10.65	1.03 (0.94, 1.13)
	Stroke incidence	1,138	67,628	10.63	1.03 (0.95, 1.11)
Ozone (summer only)	All-cause mortality	4,426	68,611	22.54	0.97 (0.93, 1.01)
	Cardiovascular mortality	1,921	68,611	22.54	1.02 (0.95, 1.09)
	Respiratory mortality	435	68,611	22.54	1.07 (0.93, 1.23)
	NM-Respiratory mortality	332	68,611	22.54	1.10 (0.94, 1.29)
	Lung cancer mortality	103	68,611	22.54	0.98 (0.74, 1.30)
	IHD mortality	892	68,611	22.54	1.12 (1.01, 1.23)
	Cerebrovascular mortality	493	68,611	22.54	0.92 (0.81, 1.05)
	MI incidence	818	67,775	22.53	1.02 (0.93, 1.13)
	Stroke incidence	1,138	67,628	22.52	1.03 (0.95, 1.13)

Table 15: Hazard ratios for mortality and for incident MI and stroke in relation to long-term pollutant exposures among the California Teachers Study cohort (restricted to women who were never-smokers at baseline) (continued)

Pollutant	Outcome	# events	N	IQR	HR (95% CI)
NOx	All-cause mortality	758	10,549	49.19	1.10 (0.98, 1.24)
	Cardiovascular mortality	343	10,549	49.19	1.23 (1.03, 1.47)
	Respiratory mortality	86	10,549	49.19	0.82 (0.57, 1.20)
	NM-Respiratory mortality	64	10,549	49.19	0.89 (0.57, 1.41)
	Lung cancer mortality	22	10,549	49.19	0.89 (0.41, 1.92)
	IHD mortality	156	10,549	49.19	1.40 (1.07, 1.83)
	Cerebrovascular mortality	86	10,549	49.19	1.17 (0.83, 1.63)
	MI incidence	125	10,393	48.84	1.10 (0.82, 1.47)
	Stroke incidence	195	10,364	49.20	1.04 (0.83, 1.31)
NO_2	All-cause mortality	609	8,224	10.51	0.99 (0.91, 1.08)
	Cardiovascular mortality	265	8,224	10.51	0.96 (0.85, 1.10)
	Respiratory mortality	68	8,224	10.51	1.01 (0.78, 1.33)
	NM-Respiratory mortality	48	8,224	10.51	1.15 (0.82, 1.61)
	Lung cancer mortality	20	8,224	10.51	0.96 (0.54, 1.71)
	IHD mortality	118	8,224	10.51	1.11 (0.91, 1.35)
	Cerebrovascular mortality	72	8,224	10.51	0.75 (0.59, 0.97)
	MI incidence	100	8,106	10.57	1.21 (0.98, 1.49)
	Stroke incidence	160	8,077	10.59	0.93 (0.78, 1.10)

Table 15: Hazard ratios for mortality and for incident MI and stroke in relation to long-term pollutant exposures among the California Teachers Study cohort (restricted to women who were never-smokers at baseline) (continued)

Pollutant	Outcome	# events	N	IQR	HR (95% CI)
CO*	All-cause mortality	616	7,584	0.50	0.93 (0.82, 1.05)
	Cardiovascular mortality	279	7,584	0.50	0.98 (0.81, 1.19)
	Respiratory mortality	61	7,584	0.50	0.81 (0.54, 1.22)
	NM-Respiratory mortality	46	7,584	0.50	1.03 (0.64, 1.65)
	Lung Cancer mortality	15	7,584	0.50	0.37 (0.13, 1.06)
	IHD mortality	133	7,584	0.50	1.04 (0.79, 1.37)
	Cerebrovascular mortality	61	7,584	0.50	0.74 (0.48, 1.15)
	MI incidence	97	7,478	0.50	1.04 (0.77, 1.41)
	Stroke incidence	153	7,455	0.50	0.86 (0.67, 1.09)
SO_2	All-cause mortality	152	2,170	0.46	1.18 (1.02, 1.36)
	Cardiovascular mortality	69	2,170	0.46	1.27 (1.01, 1.60)
	Respiratory mortality	7	2,170	0.46	--
	NM-Respiratory mortality	5	2,170	0.46	--
	Lung cancer mortality	2	2,170	0.46	-
	IHD mortality	31	2,170	0.46	1.33 (0.83, 2.14)
	Cerebrovascular mortality	17	2,170	0.46	1.27 (0.59, 2.72)
	MI incidence	28	2,140	0.46	0.87 (0.54, 1.42)
	Stroke incidence	35	2,125	0.47	1.23 (0.86, 1.76)

Models adjusted for smoking status, total pack-years BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period: June 1996-December 2005; cohort follow-up period: June 1997-December 2005. MI = myocardial infarction; NM = nonmalignant; IHD = ischemic heart disease; IQR = interquartile range; HR = hazard ratio; CI = confidence interval.
* Unlike the other gases, units for CO are in ppm, not ppb.

Table 16: Hazard ratios for mortality and for incident MI and stroke, per 10 µg/m^3 increment of long-term average PM2.5, for the California Teachers Study cohort, stratified by body mass index (BMI)

Outcome	BMI categories	# events	N	HR* (95% CI)
All-cause mortality	Underwt+Normal	2,073	42,651	1.06 (0.96, 1.17)
	Overwt+obese+extr obese	1,526	27,748	0.96 (0.86, 1.08)
CP mortality	Underwt+Normal	1,165	42,651	1.10 (0.96, 1.25)
	Overwt+obese+extr obese	772	27,748	0.98 (0.83, 1.15)
CV mortality	Underwt+Normal	812	42,651	1.02 (0.87, 1.20)
	Overwt+obese+extr obese	569	27,748	1.03 (0.85, 1.24)
Respiratory mortality	Underwt+Normal	353	42,651	1.29 (1.01, 1.64)
	Overwt+obese+extr obese	203	27,748	0.85 (0.62, 1.17)
NM_Respiratory mortality	Underwt+Normal	225	42,651	1.41 (1.04, 1.92)
	Overwt+obese+extr obese	122	27,748	0.88 (0.59, 1.32)
Lung Cancer mortality	Underwt+Normal	128	42,651	1.08 (0.72, 1.62)
	Overwt+obese+extr obese	81	27,748	0.81 (0.48, 1.35)
IHD mortality	Underwt+Normal	397	42,651	1.19 (0.94, 1.49)
	Overwt+obese+extr obese	258	27,748	1.11 (0.84, 1.47)
Cerebrovascular mortality	Underwt+Normal	177	42,651	1.06 (0.75, 1.50)
	Overwt+obese+extr obese	124	27,748	1.32 (0.88, 1.98)
MI incidence	Underwt+Normal	306	42,155	0.85 (0.65, 1.10)
	Overwt+obese+extr obese	330	27,267	1.02 (0.79, 1.30)
Stroke incidence	Underwt+Normal	435	42,047	1.22 (0.98, 1.51)
	Overwt+obese+extr obese	411	27,210	0.91 (0.73, 1.14)

* HRs per 10µg/m^3 increment of PM2.5. Exposure Mar 1999 – Dec 2005; Cohort follow-up Mar 2000 – Dec 2005. Models adjusted for all personal risk factors and contextual variables.

BMI categories:

Underweight (16.0-19.9 kg/m^2)
Normal (20.0-24.9 kg/m^2)
Overweight (25.0-29.9 kg/m^2)
Obese (30.0-39.9 kg/m^2)
Extremely obese (40.0-54.6 kg/m^2)

Table 17: Hazard ratios for mortality and for incident MI and stroke in relation to long-term PM2.5 exposures among participants in the California Teachers Study cohort, stratified by presence or absence of diabetes

Outcome	Diabetes	# events	N	HR* (95% CI)
All-cause mortality	No	3,760	70,855	1.03 (0.95, 1.10)
	Yes	387	2,634	1.05 (0.82, 1.44)
CP mortality	No	2,051	70,855	1.08 (0.98, 1.19)
	Yes	217	2,634	1.16 (0.85, 1.60)
CV mortality	No	1,459	70,855	1.07 (0.95, 1.20)
	Yes	171	2,634	1.19 (0.83, 1.71)
Respiratory mortality	No	592	70,855	1.10 (0.92, 1.33)
	Yes	46	2,634	1.02 (0.48, 2.16)
NM Respiratory mortality	No	367	70,855	1.23 (0.97, 1.56)
	Yes	37	2,634	1.24 (0.52, 2.98)
Lung Cancer mortality	No	225	70,855	0.95 (0.70, 1.29)
	Yes	9	2,634	--
IHD mortality	No	688	70,855	1.19 (1.00, 1.42)
	Yes	85	2,634	1.18 (0.71, 1.97)
Cerebrovascular mortality	No	342	70,855	1.17 (0.91, 1.49)
	Yes	40	2,634	1.42 (0.60, 3.34)
MI incidence	No	607	69,950	0.95 (0.79, 1.14)
	Yes	115	2,453	1.31 (0.83, 2.06)
Stroke incidence	No	862	69,780	1.18 (1.01, 1.38)
	Yes	107	2,450	0.93 (0.58, 1.48)

* HRs per 10μg/m^3 increment of PM2.5. Exposure Mar 1999 – Dec 2005; Cohort follow-up Mar 2000 – Dec 2005. Models adjusted for all personal risk factors and contextual variables.

Table 18: Hazard ratios for ischemic heart disease (IHD) mortality in relation to long-term average pollution for the California Teachers Study, using two-pollutant models

Pollutant	# events	N	PM scale (10 $\mu g/m^3$)/Gas IQR (ppb)	HR* (95% CI)
PM2.5	732	68,496	10.00	1.27 (1.03, 1.56)
Ozone (full year)	732	68,496	11.15	0.99 (0.87, 1.13)
PM2.5	732	68,494	10.00	1.21 (0.97, 1.52)
Ozone (3^{rd} quarter)	732	68,494	23.46	1.04 (0.89, 1.21)
PM2.5	136	10,363	10.00	0.98 (0.56, 1.70)
NOx	136	10,363	51.74	1.30 (0.88, 1.93)
PM10	843	61,181	10.00	1.07 (0.96, 1.20)
Ozone (full year)	843	61,181	14.58	0.97 (0.81, 1.17)
PM10	843	61,181	10.00	1.04 (0.93, 1.18)
Ozone (3^{rd} quarter)	843	61,181	27.29	1.03 (0.86, 1.24)
PM10	164	11,130	10.00	1.03 (0.84, 1.25)
NOx	164	11,130	26.42	1.12 (0.89, 1.40)

* All models adjusted for all personal risk factors and contextual variables. For models using PM2.5, the exposure period was from March 1999 – Dec 2005, and the cohort follow-up was from March 2000 – Dec 2005. For models with PM10, the exposure period was from June 1996 – Dec 2005 and the cohort follow-up was from June 1997 – Dec 2005.

Table 19: Hazard ratios for incident MI and stroke based on hospitalizations only among participants in the California Teachers Study cohort

Pollutant	Outcome	# events	N	PM scale (10 $\mu g/m^3$)/Gas IQR	HR (95% CI)
PM2.5	MI incidence	531	72,403	10.00	0.97 (0.80, 1.18)
	Stroke incidence	731	72,230	10.00	1.10 (0.93, 1.31)
Ozone (ppb)	MI incidence	933	100,340	11.02	1.04 (0.95, 1.13)
	Stroke incidence	1,396	100,223	11.00	1.03 (0.96, 1.10)
PM10	MI incidence	583	60,307	10.00	0.99 (0.90, 1.08)
	Stroke incidence	863	60,204	10.00	1.09 (1.01, 1.17)
NOx (ppb)	MI incidence	127	15,149	48.82	0.99 (0.75, 1.32)
	Stroke incidence	235	15,117	49.69	1.13 (0.91, 1.39)
NO_2 (ppb)	MI incidence	108	12,172	10.27	1.03 (0.85, 1.26)
	Stroke incidence	183	12,136	10.35	1.12 (0.96, 1.31)
CO (ppm)	MI incidence	115	11,234	0.49	1.01 (0.77, 1.34)
	Stroke incidence	186	11,215	0.49	1.00 (0.81, 1.24)
SO_2 (ppb)	MI incidence	29	3,375	0.43	1.22 (0.84, 1.79)
	Stroke incidence	39	3,356	0.43	1.10 (0.82, 1.48)

* Models adjusted for age, race, smoking status, total pack-years BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). PM2.5 exposure period: March 1999-December 2005; PM2.5 cohort follow-up period: March 2000-December 2005. PM10 and gaseous pollutant exposure period: June 1996-December 2005; PM10 and gaseous pollutant cohort follow-up period: June1997-December 2005.

Table 20: Hazard ratios for various pollutants in relation to ischemic heart disease mortality for movers and non-movers in the California Teachers Study cohort

	Non-movers			Movers		
Pollutant	# events	N	HR (95% CI)	# events	N	HR (95% CI)
PM2.5	378	47,657	1.14 (0.90, 1.44)	395	25,832	1.29 (1.03, 1.62)
PM10	428	39,109	1.11 (1.00, 1.23)	415	22,072	1.00 (0.89, 1.11)
Ozone	689	65,140	1.10 (1.00, 1.23)	669	36,644	0.99 (0.89, 1.09)
NOx	120	9,928	1.31 (0.97, 1.84)	118	5,469	1.25 (0.91, 1.72)
NO_2	90	8,041	1.17 (0.93, 1.47)	103	4,325	1.02 (0.81, 1.29)

* Models adjusted for age, race, smoking status, total pack-years BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). PM2.5 exposure period: March 1999-December 2005; PM2.5 cohort follow-up period: March 2000-December 2005. PM10 and gaseous pollutant exposure period: June 1996-December 2005; PM10 and gaseous pollutant cohort follow-up period: June1997-December 2005. PM2.5 and PM10 results scaled to increment of 10 $\mu g/m^3$; ozone, NOx, and NO_2 scaled to interquartile ranges for movers and non-movers.

Critical Windows

Tables 21 and 22 provide results from the critical windows analysis, in which we examined the effects of using different periods of PM2.5 exposure prior to a participant's death to estimate the HR for a 10 $\mu g/m^3$ increment of PM2.5 and specific mortality categories. Table 21 presents the results for the entire subcohort, which decreased in size with each death, while Table 22 presents the results only for those women who had had at least four years of exposure.

For the entire PM2.5 subcohort, using a six-month prior exposure window, none of the HRs is significantly elevated, though that for IHD is nearly so. The HRs for CP mortality increase from 1.05 (95% CI = 0.96, 1.14) using a six-month window to 1.16 (95% CI = 1.03, 1.30), using the preceding three-year exposure. A similar pattern can be seen for the HRs for IHD, which increase from 1.12 (95% CI = 0.96-1.31) using the six-month window to 1.41 (95% CI = 1.15-1.73) using the three-year window. The point estimates for the HRs from the four-year window are approximately the same for CP and IHD mortality as those using the three-year window, though the four-year estimates are somewhat less precise because they are based on fewer events.

The results are strikingly different among the women who had had at least four years of

exposure (Table 22). Within this group, the HRs remain essentially unchanged with windows of increasing duration beyond one year, at which time the HR for CP mortality was 1.21 (95% CI = 1.03-1.40), while that for IHD mortality was 1.49 (95% CI = 1.14-1.95). In this analysis, the same events are being examined with different windows of exposure preceding them, while the results presented in Table 21 include events to which not all of the relevant windows could be applied. Because outcome follow-up for the Table 22 analysis began in March 2003, the size of the study population and the numbers of events in this table are less than those in the four-year window in Table 21, for which outcome follow-up began in March 2000.

Table 21: Hazard ratios for all-cause, cardiopulmonary (CP), and ischemic heart disease (IHD) mortality in relation to an increase of 10 μg/m^3 of long-term average PM2.5 restricted to specific periods of exposure preceding an event (entire PM2.5 subcohort).

Prior six-month exposure

Outcome	# events	N	HR (95% CI)	p value
All-cause mortality	4,051	73,489	1.01 (0.95, 1.08)	0.6948
CP mortality	2,213	73,489	1.05 (0.96, 1.14)	0.3319
IHD mortality	752	73,489	1.12 (0.96, 1.31)	0.1440

Prior 1-year exposure

Outcome	# events	N	HR (95% CI)	p value
All-cause mortality	4,076	73,489	1.00 (0.93, 1.08)	0.9849
CP mortality	2,227	73,489	1.07 (0.97, 1.18)	0.1608
IHD mortality	758	73,489	1.18 (1.00, 1.39)	0.0510

Prior 2-year exposure

Outcome	# events	N	HR (95% CI)	p value
All-cause mortality	3,489	72,402	1.03 (0.95, 1.11)	0.4992
CP mortality	1,898	72,402	1.11 (1.00, 1.23)	0.0515
IHD mortality	642	72,402	1.30 (1.09, 1.56)	0.0043

Prior 3-year exposure

Outcome	# events	N	HR (95% CI)	p value
All-cause mortality	2,837	71,229	1.05 (0.97, 1.15)	0.2333
CP mortality	1,542	71,229	1.16 (1.03, 1.30)	0.0134
IHD mortality	505	71,229	1.41 (1.15, 1.73)	0.0009

Prior 4-year exposure

Outcome	# events	N	HR (95% CI)	p value
All-cause mortality	2,183	70,175	1.07 (0.97, 1.18)	0.1643
CP mortality	1,179	70,175	1.17 (1.02, 1.34)	0.0223
IHD mortality	386	70,175	1.39 (1.10, 1.76)	0.0060

Models adjusted for all personal risk factors and contextual variables.

Table 22: Hazard ratios for all-cause, cardiopulmonary (CP), and ischemic heart disease (IHD) mortality in relation to an increase of 10 µg/m^3 of long-term average PM2.5, restricted to specific periods of exposure preceding an event (among women with at least four years of measured PM2.5 exposure, n=68,258)

Prior 1-year exposure

Outcome	# events	HR (95% CI)	p value
All-cause mortality	2,130	1.09 (0.97, 1.22)	0.1479
CP mortality	1,154	1.21 (1.03, 1.40)	0.0170
IHD mortality	377	1.49 (1.14, 1.95)	0.0033

Prior 2-year exposure

Outcome	# events	HR (95% CI)	p value
All-cause mortality	2,130	1.08 (0.97, 1.20)	0.1544
CP mortality	1,154	1.18 (1.02, 1.36)	0.0248
IHD mortality	377	1.48 (1.14, 1.90)	0.0028

Prior 3-year exposure

Outcome	# events	HR (95% CI)	p value
All-cause mortality	2,130	1.08 (0.98, 1.20)	0.1235
CP mortality	1,154	1.18 (1.02, 1.35)	0.0233
IHD mortality	377	1.46 (1.15, 1.87)	0.0023

Prior 4-year exposure

Outcome	# events	HR (95% CI)	p value
All-cause mortality	2,130	1.08 (0.98, 1.19)	0.1319
CP mortality	1,154	1.17 (1.02, 1.34)	0.0278
IHD mortality	377	1.44 (1.13, 1.83)	0.0031

Models adjusted for all personal risk factors and contextual variables.

PM2.5 Constituents Analysis

Table 23 presents descriptive statistics for the study population in this subanalysis, which included women whose residential addresses during the study period were within 30 km of one of eight fixed-site monitors measuring PM2.5 mass and its constituents. Because some of the monitors were less than 30 km from county lines, this group includes participants from several counties adjacent to those in which the monitors were located. More than one-third of the participants in the PM2.5 constituents analysis lived in Los Angeles County, compared with about 12% of the remainder of the cohort. Table 24 presents the descriptive statistics for the average concentrations of PM2.5 and its constituents during the exposure measurement period for this analysis (June 1, 2002- July 2007). Correlations among the pollutants are presented in Table 25. These pollutants were all strongly inter-correlated, with the majority greater than 0.7.

Table 26 provides results for the Cox regressions for PM2.5 mass and its constituents in relation to several mortality categories, with the HRs scaled to the interquartile pollutant ranges. No associations were observed between all-cause mortality with PM2.5 or its components. Significant associations were observed for PM2.5 mass, sulfate, and nitrate exposures in relation to cardiopulmonary mortality, with a more modest association for silicon. PM2.5 mass and all of its components were associated with mortality from IHD, while none was associated with respiratory mortality. For IHD, the largest effect estimates were observed for EC and sulfate, although estimates were fairly similar among the components, except for silicon and OC, which had somewhat lower estimates. The strongest association with IHD mortality, based on t-statistics, was observed for nitrate, although several other components exhibited strong associations.

When scaled from the IQR to a 10 $\mu g/m^3$ increment of long-term exposure to PM2.5, the HRs in this analysis were somewhat greater than in the main analysis. Specifically, the HR for PM2.5-associated IHD mortality was 1.31 (95% CI = 1.14-1.50), which is considerably higher than the main result 1.20 (95% CI = 1.02, 1.41). Potential reasons for this discrepancy are presented in the Discussion section.

Table 23: Baseline characteristics of the CTS participants whose residences were within 30 km of fixed-site PM2.5 speciation monitors compared with characteristics of the rest of the CTS cohort, August 2002 – July 2007

	Participants within 30 km buffers (n=43,220)	Total cohort excluding those in species 30km buffer analyses (n = 81,394)
Individual Characteristics		
Average age at intake (years) (sd)	53.4 (13.0)	53.5 (15.4)
Race (% white)	83.3	88.2
BMI (mean, kg/m^2)	25.1	24.8
Average dietary fat intake (g/day)	55.7	56.5
Never smoker (%)	68.3	65.0
Former smoker (%)	26.9	29.8
Current smoker (%)	4.8	5.2
Married (%)	45.2	43.7
Menopausal status		
Pre-menopausal (%)	38.3	38.8
Peri/Post menopausal and no hormone therapy use (%)	13.0	13.0
Peri/Post menopausal and current/past hormone therapy use (%)	35.2	34.4
Unknown menopausal status/hormone therapy use (%)	13.4	13.8
Family history of heart disease (%)	47.1	44.6
Mean daily dietary calories (kcal)	1,577	1,601
Average pack-years among former and current smokers	14.6	15.7
Adult SHS exposure (%)	49.1	48.8
Non-drinker (%)	34.2	31.0
Participant locations (proportion within each county)		
Alameda County	1.7	5.5
Fresno County	5.9	1.2
Kern County	3.3	1.1
Los Angeles County	36.5	12.4
Riverside County	4.4	3.6
Sacramento County	8.5	1.2
San Bernardino County	7.0	2.7
San Diego County	13.6	5.7
Santa Clara County	10.3	2.2
Ventura County	3.0	2.3
Other	5.8	62.1

Table 24: Descriptive statistics of individual-level pollutant exposures among participants whose residences were within 30 km of fixed-site PM2.5 monitors in the California Teachers Study cohort, June 1, 2002 – July 31, 2007

Pollutant	Mean	IQR	Min/Max
$PM_{2.5}$	17.5	6.1	6.8/38.7
Elemental carbon	1.1	0.65	0.20/2.4
Organic carbon	5.9	0.84	2.1/10.1
Sulfate	2.5	2.2	0.62/7.4
Nitrate	4.9	3.2	0.7/16.2
Iron	0.14	0.13	0.04/0.36
Potassium	0.11	0.07	0.02/0.35
Silicon	0.13	0.03	0.03/0.49
Zinc	0.01	0.01	0.00/0.04

All pollutants measured as 24-hour averages, in $\mu g/m^3$. IQR = interquartile range

Table 25: Correlations among PM2.5 mass and constituents based on individual-level exposure assessment for CTS participants residing within 30 km of fixed-site PM2.5 monitors

	PM2.5	EC	OC	SO_4	NO_3	Fe	K	Si	Zn
PM2.5	1.00	0.82	0.64	0.72	0.90	0.76	0.66	0.80	0.91
EC		1.00	0.67	0.73	0.74	0.96	0.80	0.58	0.90
OC			1.00	0.29	0.48	0.55	0.87	0.71	0.60
SO_4				1.00	0.79	0.79	0.47	0.44	0.67
NO_3					1.00	0.76	0.48	0.79	0.85
Fe						1.00	0.70	0.53	0.87
K							1.00	0.61	0.65
Si								1.00	0.70
Zn									1.00

Table 26: Association between mortality outcomes and $PM_{2.5}$ and its constituents using a 30 km buffer (n = 43,220)

Pollutant	IQR ($\mu g/m^3$)	All-cause (n = 2,519)		Cardiopulmonary (n = 1,357)		Ischemic Heart Disease (n = 460)		Respiratory (n = 355)	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
PM2.5	6.1	1.03 (0.98, 1.10)	0.26	1.11 (1.03, 1.21)	0.01	1.31 (1.14, 1.50)	0.0001	1.02 (0.87, 1.19)	0.84
EC	0.65	1.02 (0.93, 1.12)	0.65	1.07 (0.94, 1.22)	0.28	1.46 (1.17, 1.83)	0.0009	0.88 (0.68, 1.15)	0.35
OC	0.84	1.00 (0.95, 1.04)	0.91	1.04 (0.98, 1.11)	0.19	1.13 (1.01, 1.25)	0.0311	0.95 (0.84, 1.06)	0.35
Sulfates	2.2	1.06 (0.97, 1.16)	0.18	1.14 (1.01, 1.29)	0.03	1.48 (1.20, 1.82)	0.0003	1.04 (0.82, 1.31)	0.77
Nitrates	3.2	1.03 (0.98, 1.09)	0.27	1.11 (1.03, 1.19)	0.01	1.27 (1.12, 1.43)	0.0002	1.04 (0.90, 1.20)	0.58
Iron	0.13	1.01 (0.93, 1.11)	0.77	1.05 (0.93, 1.19)	0.40	1.39 (1.13, 1.72)	0.0023	0.88 (0.69, 1.13)	0.32
Potassium	0.07	1.01 (0.94, 1.08)	0.85	1.06 (0.97, 1.17)	0.22	1.27 (1.07, 1.49)	0.0049	0.90 (0.74, 1.09)	0.27
Silicon	0.03	1.02 (0.99, 1.06)	0.22	1.05 (1.00, 1.10)	0.04	1.11 (1.02, 1.20)	0.0121	0.98 (0.89, 1.08)	0.71
Zinc	0.01	1.03 (0.96, 1.11)	0.45	1.09 (0.98, 1.20)	0.10	1.33 (1.12, 1.58)	0.0011	0.97 (0.79, 1.18)	0.74

Hazard ratios, 95% confidence intervals (CIs) and p-values scaled to the interquartile range of each pollutant. All models are adjusted for smoking status, total pack-years, body mass index, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone replacement therapy use, family history of myocardial infarction or stroke, blood pressure medication and aspirin use; and neighborhood contextual variables (income, income inequality, education, population size, racial composition, unemployment).

Exposure-response Analysis

The results of our assessment of various non-linear models (log-linear, quadratic, and fractional polynomial) are shown in Table 27. On the original, non-log scale of mortality rate, models 1 and 3 describe an exponential rise with pollutant concentration (i.e., an accelerating rate over the range of PM2.5 studied), with model 3 a much more steeply rising curve. Model 2 describes an increasing, but leveling off relationship with PM2.5, since the regression coefficient is less than 1. Model 4 describes a more flexible, but ultimately exponentially increasing curve. The linear and the alternative models fit the data almost equally well, producing similar IHD hazard ratios for a 10 $\mu g/m^3$ increase in long-term average PM2.5 (i.e., 20 $\mu g/m^3$ vs 10 $\mu g/m^3$), and nearly identical measures of fit (-2 log likelihood). The Akaike Information Criterion (AIC) statistic in the last column of Table 27 combines model fit with a penalty for adding unnecessary terms, so that models with lower AIC values are preferred (McCullagh and Nelder 1989). The AIC statistics across all these models are similar, but give a slight preference for the most parsimonious linear model 1. Thus, within this dataset, nonlinear models of the exposure-response relationship between long-term PM2.5 exposure and IHD mortality offer no obvious improvement over a linear one.

Table 27: PM2.5 and IHD mortality – Exposure-response models of varying parametric forms (n=73,489; # events = 773)

Model	Exposure coding	Regression coefficient	Hazard ratio	-2LL of model	DF	AIC
Linear	PM2.5	0.01782	1.20	9349.684	48	9445.684
Log-linear	log(PM2.5)	0.26345	1.20	9350.171	48	9446.171
Quadratic	PM2.5 +	-0.00906	1.16	9349.485	49	9447.485
	$(PM2.5)^2$	0.000804				
Fractional polynomial	$(PM2.5)^{1/2}$ +	-2.42566	1.19	9349.157	50	9449.157
	PM2.5 +	0.45897				
	$(PM2.5)^2$	-0.00414				

IHD – Ischemic heart disease; -2LLR = -2 log likelihood (a measure of model fit); DF = degrees of freedom; AIC = Akaike Information Criterion (another measure of model fit).

Traffic Analysis

Table 28 summarizes the descriptive data and definitions of various traffic metrics used in the analysis. Table 29 summarizes the results for traffic and vehicle metrics, examining mortality from all causes, as well as cardiopulmonary (CP), cardiovascular (CV) and ischemic heart diseases. Proximity to the nearest highway (i.e., residence within versus beyond 150 meters) was not associated with any of these outcomes, though there were very few events in each category among women residing within 150 meters. Traffic density was associated with all-cause mortality for all three categories above the 49th percentile, with HRs of 1.08 (95% CI = 1.00-1.17)(50th-74th percentile), 1.09 (95% CI = 1.00-1.20)(75th-89th percentile), and 1.18 (95% CI = 1.07-1.31)($\geq$ 90th percentile), respectively. The test for trend in the relationship between traffic density and all-cause mortality was highly significant. The highest traffic density category was also significantly associated with CP and CV mortality. For vehicle density, the 25th to 49th percentile category was associated with cardiovascular mortality, HR = 1.17 (95% CI = 1.01-1.37). None of the other vehicle density categories was significantly associated with any outcomes.

Table 28: Descriptive statistics for traffic and vehicle measures among non-movers, California Teachers Study Cohort, n=65,140

Traffic metric	N	Range
Proximity to highway		
Within 150 m	2,234	<150
Beyond 150 m	62,906	≥150
Traffic density		
≥90th percentile	6,514	≥3,575.3
75th-89th percentile	9,771	1,409.7 - 3,575.2
50th-74th percentile	16,285	170.0 - 1,409.6
<50th percentile	32,570	<170.0
Vehicle density		
≥90th percentile	6,511	≥7,087.3
75th-89th percentile	9,777	5,268.5 - 7,087.2
50th-74th percentile	16,290	3,499.8 - 5,268.4
25th-49th percentile	16,281	1,712.0 - 3,499.7
<25th percentile	16,281	<1,712.0

* Traffic variable definitions:
Distance to highway= Proximity of residence to a "major" highway, in meters. (Limited to within 20 km.)
Traffic density = Vehicle Miles Traveled within 150 meters of a residence using conflated TeleAtlas 2005q2 centerlines linked to HPMS 2000. Missing values set to minimum non-zero value (0.10442).
Vehicle Density = 2000 Census Block group count of aggregate number of vehicles available from occupied housing units.

Table 29: Hazard ratios for traffic metrics in relation to mortality (all-cause, cardiopulmonary, cardiovascular and ischemic heart disease) and incidence of MI and stroke among non-movers (n=65,140) in the CTS cohort (June 1997 through Dec 2005)

Traffic metric	All cause mortality (# events=4,026)		CP mortality (# events=2,100)		CV mortality (# events=1,491)	
	# events	HR (95% CI)	# events	HR (95% CI)	# events	HR (95% CI)
Proximity to highway						
Within 150 m	282	1.01 (0.87, 1.18)	87	0.86 (0.70, 1.07)	65	0.89 (0.69, 1.15)
Beyond 150 m	3,844	1.00 (ref)	2,013	1.00 (ref)	1,426	1.00 (ref)
Traffic density						
≥90th percentile	561	1.18 (1.07, 1.31)	307	1.15 (1.00, 1.32)	229	1.18 (1.00, 1.38)
75th-89th percentile	724	1.09 (1.00, 1.20)	387	1.07 (0.95, 1.21)	264	1.01 (0.87, 1.18)
50th-74th percentile	1,054	1.08 (1.00, 1.17)	559	1.09 (0.98, 1.21)	390	1.05 (0.92, 1.19)
<50th percentile	1,687	1.00 (ref)	847	1.00 (ref)	608	1.00 (ref)
Test for trend		p=<0.0006		p=0.0464		p=0.1091
Vehicle density						
≥90th percentile	430	1.01 (0.89, 1.15)	224	1.00 (0.84, 1.20)	150	1.04 (0.83, 1.29)
75th-89th percentile	637	1.03 (0.93, 1.15)	356	1.11 (0.96, 1.29)	246	1.14 (0.96, 1.36)
50th-74th percentile	968	0.97 (0.88, 1.06)	498	0.99 (0.86, 1.13)	359	1.04 (0.89, 1.22)
25th-49th percentile	1,084	1.04 (0.95, 1.14)	583	1.09 (0.96, 1.24)	426	1.17 (1.01, 1.37)
<25th percentile	907	1.00 (ref)	439	1.00 (ref)	310	1.00 (ref)
Test for trend		p=0.9703		p=0.8669		p=0.7878

Table 29: Hazard ratios for traffic metrics in relation to mortality (all-cause, cardiopulmonary, cardiovascular and ischemic heart disease) and incidence of MI and stroke among non-movers (n=65,140) in the CTS cohort (June 1997 through Dec 2005) (continued)

Traffic metric	IHD mortality (# events=689)		MI incidence (n=64,227; # events=776)		Stroke incidence (n=64,205; # events=1,083)	
	# events	HR (95% CI)	# events	HR (95% CI)	# events	HR (95% CI)
Proximity to highway						
Within 150 m	28	0.83 (0.56,1.21)	28	0.84 (0.57, 1.23)	43	0.94 (0.69, 1.27)
Beyond 150 m	661	1.00 (ref)	748	1.00 (ref)	1,040	1.00 (ref)
Traffic density						
≥90th percentile	110	1.17 (0.92, 1.48)	101	1.04 (0.82, 1.31)	135	1.06 (0.87, 1.29)
75th-89th percentile	126	1.02 (0.82, 1.26)	134	1.00 (0.81, 1.22)	190	1.08 (0.91, 1.29)
50th-74th percentile	171	0.98 (0.81, 1.19)	203	1.01 (0.85, 1.21)	304	1.15 (0.99, 1.33)
<50th percentile	282	1.00 (ref)	338	1.00 (ref)	454	1.00 (ref)
Test for trend		p=0.2788		p=0.8342		p=0.3894
Vehicle density						
≥90th percentile	60	0.73 (0.52, 1.01)	85	0.87 (0.65, 1.16)	118	1.09 (0.85, 1.39)
75th-89th percentile	109	0.92 (0.70, 1.19)	127	0.89 (0.70, 1.13)	179	1.12 (0.91, 1.38)
50th-74th percentile	178	0.97 (0.78, 1.22)	186	0.82 (0.66, 1.01)	288	1.10 (0.92, 1.32)
25th-49th percentile	187	0.99 (0.79, 1.23)	188	0.84 (0.68, 1.03)	264	0.96 (0.81, 1.15)
<25th percentile	155	1.00 (ref)	190	1.00 (ref)	234	1.00 (ref)
Test for trend		p=0.0957		p=0.3696		p=0.1573

Discussion

In an ongoing cohort study of over 100,000 female participants in the California Teachers Study, we developed estimates of long-term air pollution exposure at the subjects' residences and examined associations of these exposure estimates with several mortality categories and with incidence of MI and stroke. We conducted a number of analyses involving subsets of the population, including never-smokers, women who were post-menopausal at baseline, those who were overweight or obese, or who had a diagnosis of diabetes. Other analyses included: (i) an examination of the impact of using different exposure periods, (ii) whether specific constituents of PM2.5 were more strongly associated with mortality outcomes than PM2.5 mass; and (iii) the shape of the PM2.5/mortality exposure-response relationship. Finally, we examined the potential impacts of several traffic metrics on mortality and incidence of MI and stroke.

Main Analysis

We found significant associations between IHD mortality and PM2.5 and NOx, with slightly lesser associations with PM10 and ozone. The associations with PM2.5 and NOx were modestly greater among never-smokers, as were associations with cardiovascular disease mortality as a whole. Incident stroke (combining fatal and nonfatal events) was associated with PM10 and PM2.5, with a stronger association for PM2.5 among women who were post-menopausal at baseline Analyses of non-fatal incident stroke (i.e., hospitalizations only) found an association with PM10.

This investigation represents one of the largest prospective air pollution studies undertaken to date (Pope et al. 2004; Miller et al. 2007; Puett et al. 2009; Beelen et al. 2008). Unlike most prior studies, we developed individualized estimates of long-term exposure to PM2.5 and other pollutants at the participants' residences, including those who relocated during the study period. The low prevalence of active smoking in this cohort (5% at baseline) allowed for a potentially more clear-cut examination of the impact of air pollution exposures than in other investigations with substantial proportions of active smokers (e.g., ACS-CPS II, 22% active smokers; HSC study, 33 – 40% active smokers, depending on the city). Nationally, the age-adjusted prevalence of active smoking among women in the U.S. was 21% in 2000 (Centers for Disease Control 2002). In California, the age-adjusted smoking prevalence among women was 13.6 ($\pm$ 2.3%) in 1995 and 14.4% ($\pm$ 1.6%) in 2000, indicating that even in California, the CTS participants were substantially less likely to be smokers than women in the general population (Centers for Disease Control 1996; 2001). Despite the low prevalence of active smoking, we found that among smokers, there was approximately a 57% increase in risk of dying from cardiovascular disease, relative to never-smokers, during the follow-up period (Table 10).

Moreover, unlike most other cohorts, CTS participants share a relative uniformity of occupational status, precluding the need for statistical adjustment for toxic industrial exposures based on potentially problematic job exposure matrices. Thus, the CTS study

design and population characteristics included an individualized exposure assessment and diminished the potential for confounding and effect modification by non-pollutant variables.

We had originally assigned a single long-term average exposure per pollutant to each participant. However, because of the marked pollution declines over the study period (Figures 2 and 3), this approach resulted in assigning lower average exposures to survivors than to women who died or were hospitalized earlier in the study, which produced inflated HRs (Appendix A). (This phenomenon is also likely to have affected the results of our prior report (Lipsett et al. 2007). Therefore, we used a time-varying Cox model in which all participants' average exposures were recalculated each time a death or hospitalization for MI or stroke occurred. This allowed for comparison of the average exposure(s) for each case with the average exposure(s) of all others in the risk set at the time of the event.

With few exceptions (e.g., Puett et al. 2009), most other prospective air pollution studies have used different exposure assignment protocols. For example, some used exposures at the beginning and/or the end of the study period (Pope et al. 2002, 2004). Other studies included only a single year of exposure (Jerrett et al. 2005; Miller et al. 2007) or examined the impact of different exposure windows (from one to five years preceding each death) (Schwartz et al. 2008). Some studies included dozens of cities throughout the United States, so that pollutant changes over time were more heterogeneous (Pope et al 2002, 2004; Eftim et al. 2008). Puett et al. (2009) used a time-varying Cox model to calculate HRs for several particulate metrics; however, they limited the exposure averaging time to the 12 months preceding each event. Thus, few previous studies involved cities experiencing a fairly consistent change in exposures over a relatively long period.

As noted in the Results section, the hazard ratios for most of the cardiovascular risk factors in the regression models were generally in the expected directions, which provides a check on the internal validity of the data and modeling used in this analysis. Two notable exceptions were adult SHS exposure and parental history of disease (Table 10). The SHS variable from the baseline CTS survey available for this analysis was based on the only question that addressed such exposures, specifically: "As an adult, have the persons with whom you have lived smoked?" Therefore, it could not capture current SHS exposure. Even in univariate analyses, this variable was not associated with overall cardiovascular mortality. However, using several questions in the 1997 survey, the main California Teachers Study team developed a semi-quantitative cumulative adult SHS exposure variable. When we replaced the baseline SHS variable with this cumulative SHS variable (which was available for fewer participants), we found that the PM2.5 HR remained virtually unchanged for IHD (decreasing from 1.20 to 1.17), and cardiovascular mortality 1.07 (95% CI = 0.95-1.19) to 1.06 (95% CI = 0.92-1.23), still remaining nonsignificant. Moreover, it is unlikely that SHS exposure (i.e., at baseline) would be correlated with ongoing air pollution exposures. Thus, we do not think that the lack of a variable better capturing SHS exposure is likely to have confounded our pollution HR estimates. Some other studies (e.g., the HSC study (Dockery et al. 1993; Laden et al. 2006) have not adjusted for SHS exposure.

Our finding of an increased risk of PM2.5-associated IHD mortality is consistent with some, but somewhat lower than several other, published estimates. Our estimate of

the association between a 10 $\mu g/m^3$ increase in long-term PM2.5 exposure and increased risk of fatal IHD (HR = 1.20, 95% CI = 1.02 - 1.41) was of similar magnitude to that reported by Jerrett et al. (2005) in an analysis of the ACS CPS-II data for 22,905 Los Angeles residents involving interpolation and attribution of pollutant data to ZIP codes encompassing the participants' residential addresses (HR = 1.32, 95% CI=1.05-1.66). In the analysis of the national ACS CPS-II cohort from 1983-1998, average PM2.5 (measured from 1979-1983 and 1999-2000) was also associated with IHD mortality (HR = 1.18, 95% CI = 1.14-1.23) (Pope et al. 2004). In a follow-up to the HSC, Laden et al. (2006) reported a HR of 1.28 (95% CI = 1.13-1.44) for cardiovascular disease. These estimates are all lower than in other recent studies of PM and mortality from CHD in women. For instance, in the observational study of the WHI, the risk of death from CHD associated with a 10 $\mu g/m^3$ increase in estimated PM2.5 was more than doubled (HR = 2.21, 95% CI = 1.17-4.16, based on 80 cases) (Miller et al. 2007). Using modeled PM2.5 data to estimate 10-year exposures to participants in the Nurses' Health Study, Puett et al. (2009) reported a similarly elevated risk of death from CHD (HR = 2.02, 95% CI = 1.07-1.54, based on 379 cases), though this estimate was markedly attenuated when the investigators used annual average data from fixed-site monitors (HR = 1.47, 95% CI = 0.73-2.99). The differences between our estimates and those of these other investigations may be related to differences in the underlying health status of the study populations, the numbers of cases (there were 773 IHD cases in our study), methods of estimating exposure, particle composition and relative toxicity, and measurement and control of potential confounders.

In contrast, we found no association of PM2.5 with all-cause mortality, while several other long-term air pollution studies have found such associations (e.g., Puett et al. 2009; Jerrett et al. 2005; Laden et al. 2006). The associations with all-cause mortality that we found for NOx and SO_2 among never-smokers were based on relatively few events. Although our finding of no association of all-cause mortality with PM2.5 is different from those of several other U.S. cohorts, it is to some extent consistent with two recent studies, one from Canada (Gan et al. 2010) and the other from Holland (Beelen et al. 2008). Gan et al. (2010) estimated residential concentrations of several traffic-related pollutants (Black Smoke [BS], nitric oxide (NO), NO_2, and PM2.5) over a five-year period using land use regression in Vancouver, and found no association between estimated PM2.5 and CHD hospitalization or mortality during the following four-year period in several hundred thousand adults. Beelen et al. (2008) followed participants in the Netherlands Cohort Study on Diet and Cancer (n = 120,852) from 1987 through 1996, and reported no significant increases in all-cause or cardiovascular mortality associated with measured PM2.5. However, they reported slightly increased risks for these outcomes in relation to traffic intensity on the nearest road (see "Traffic Analysis," below). Because our analysis of NOx was limited to residences within either 3 or 5 km buffers, the elevated HRs that we observed for this pollutant may represent effects of local traffic emissions as well as transported products of combustion. Our results are also highly consistent with an analysis of the ACS cohort in the New York City region, which also found no effects for all-cause mortality, but elevated risks from PM2.5 exposure for IHD mortality that are of the same magnitude as those detected here (Krewski et al. 2009).

Lung cancer mortality was another outcome for which we found no association with any pollutant metric. This result is consistent with some other cohort studies (Beelen et al. 2008), but not others (Pope et al. 2002; Vineis et al. 2004). The only (nonsignificant) elevated lung cancer HR was for PM2.5 exposure among never-smokers (HR=1.62, 95% CI = 0.83-3.16), but this was based on only 50 cases. Overall there were relatively few cases in this population, reflecting perhaps the low prevalence of active smoking at baseline. In addition, the follow-up period in this study was short relative to the typical length of time necessary between the initiation of exposure to lung carcinogens and the clinical manifestation of disease (i.e., the latency period). In other words, since the latency for lung cancer expression can be measured in decades, it is likely that many, if not all, of the cases in our study were primarily due to exposures that predated our exposure follow-up period.

A couple of other California-specific studies of air pollutant exposure and mortality have produced mixed results (Enstrom 2005; Abbey et al. 1999; Chen et al. 2005). Enstrom (2005) found essentially no relationship between fine PM and all-cause mortality among nearly 36,000 elderly California participants in the ACS Cancer Prevention Study I (ACS CPS I) over the period 1973-2002. In that study, each individual was assigned countywide PM2.5 levels measured only during the period 1979-1983, so exposure misclassification may have affected the results. In addition, the ACS CPS I cohort was much older at intake and may have had different indoor/outdoor exposure-related behaviors relative to other cohorts in air pollution studies. Interestingly, for the initial follow-up period (1973-82), which included several years of fine particle measurements, Enstrom reported RRs for all-cause mortality among the whole cohort of 1.04 (95%CI = 1.01-1.07) per 10 $\mu g/m^3$ increase in PM2.5, and of 1.06 (95% CI = 1.01-1.12) for the younger members of the cohort (ages 43-64 in 1973). Also, the relative risk for the 20,210 women was slightly elevated and statistically significant (RR = 1.027, 95% CI = 1.005-1.050).

In the AHSMOG study (N = 6,338 Seventh Day Adventists throughout California), Abbey and colleagues (1999) attempted to reduce exposure measurement error by interpolating pollutant monitoring station data to the ZIP code centroids for the participants' home and work addresses. Those investigators found associations of long-term-exposure to particulate matter and ozone with deaths related to diseases of the lung, but, unlike the HSC and ACS CPS II studies, not with those involving the cardiovascular system. More recently, however, Chen et al. (2005) analyzed fatal (CHD) events in a subset (n=3,239) of the AHSMOG cohort who had been followed for 22 years. These investigators reported associations of PM10, PM2.5, and coarse particles (i.e., PM10-PM2.5) with fatal CHD in women, but not in men. In a multivariate model, the RR for fatal CHD per 10 $\mu g/m^3$ increase in PM2.5 was 1.42 (95% CI = 1.11-1.81) among the AHSMOG women.

Unlike studies focusing on impacts of acute PM2.5 exposures on potentially susceptible populations (e.g., O'Neill et al. 2005; Schneider et al. 2010), we did not detect any significant differential effect of chronic exposure on women who had a diagnosis of diabetes. This is consistent with the findings of both Puett et al. (2009) and Miller et al. (2007), though in both our study and these other two studies, there were relatively few cardiovascular events in women with diabetes. In contrast with both of

those investigations, however, we did not observe any greater susceptibility to PM2.5-associated effects among women who were overweight or obese.

In the analysis that was limited to never-smokers only, we found generally similar or elevated HRs in comparison to the whole cohort analysis in which smoking status and history were adjusted for in the regression models. None of the previously significant associations in the main analysis became nonsignificant when restricted to never-smokers, and in several instances were more strongly associated with the pollutants of interest (e.g., PM2.5 and NOx with IHD). Though based on fewer events, these findings are not likely to be affected by residual confounding due to a history of active smoking and therefore provide some support for inferring a causal relationship between the pollutants and the outcomes of interest.

Using summer ozone levels, we found a significant positive association with IHD mortality, but not overall cardiovascular or respiratory mortality. When the metric for estimating long-term exposure was year-round ozone, we also found a positive association with IHD mortality, which increased slightly when the analysis was restricted to never-smokers. Combining seasons can dilute the signal from the summer, when ozone concentrations are greatly elevated and people spend more time outdoors. Ozone penetrates indoors much less readily than PM2.5; therefore, outdoor exposures may be more important for ozone than for PM2.5. In two-pollutant models, there was no association of IHD mortality with ozone, whereas the HRs for PM2.5 and PM10 remained elevated, suggesting that the results for ozone were probably due to its positive correlation with particulate matter. When we re-ran these models without either particulate metric, including only the smaller numbers of events from the two-pollutant models, the ozone-associated HRs remained elevated, supporting the proposition that the effects observed were most likely due to confounding by PM. In several prior cohort studies, when ozone has been included in the models of long-term exposure, no associations with cardiopulmonary mortality have been observed (Dockery et al. 1993; Pope et al. 2002). However, Jerrett et al. (2009) reported slightly elevated significant positive associations of ozone with cardiovascular mortality in their analysis of the ACS CPS-II data, which diminished to null results in two-pollutant models with PM2.5. Unlike Jerrett et al., we found no association of overall respiratory mortality with long-term ozone exposure. On the other hand, when those investigators stratified on geographic area, they found no association of ozone with respiratory mortality in Southern California (Jerrett et al. 2009). However, both measures of ozone in our study suggested associations with nonmalignant respiratory mortality, which were of comparable magnitude to the ozone-associated relative risk for nonmalignant respiratory mortality among women in the Adventist Health Study (Abbey et al. 1999).

Due to the restrictions we placed on spatial interpolations for CO, NO_2, NOx, and SO_2 to reduce the potential for exposure misclassification, there were far fewer participants and events in all models involving these pollutants than in those for ozone, PM2.5, and PM10. Moreover, these gases are subject to considerable intra-urban variability, depending largely on local traffic patterns. For instance, NO_2 levels may sometimes vary significantly over a distance of a few hundred meters (Singer et al. 2004). Nonetheless, traffic emissions in particular can result in high local concentrations of the reactive free radicals NO and NO_2, the main constituents of measured NOx, as well as ultrafine particles and PM2.5. Ambient NOx levels have also been reported to be

correlated with concentrations of diesel particulate matter (CARB 2008). As noted in the discussion of the traffic analysis below, we found increasing mean long-term NOx exposures associated with increasing traffic density near the residences of the non-movers. This not only serves to provide a check on the internal validity of the traffic density categories, but also to support the NOx regression results. Still, although several of the NOx results were statistically significant, they should be interpreted with caution, as they were based on far fewer observations than the analyses for PM2.5 and PM10. Finally, as is true with all air pollution epidemiology studies, differential measurement error among the pollutants may have affected both the magnitude and the precision of the effect estimates.

We did not have data on residential addresses prior to cohort inception. Therefore, it is possible that there might have been some confounding by earlier exposures to the extent that they were correlated with our estimated exposure estimates during the follow-up period. We believe that such potential confounding is not likely to have had any significant impact on our analysis. This conclusion is based on the results of the critical windows analysis (Tables 21 and 22), which indicate an attenuation of PM2.5 risk estimates with longer exposure periods. This in turn suggests that confounding from remote exposures would be minimal.

Our comparisons of effect estimates between movers and non-movers showed no significant differences except with respect to IHD (Table 20). Interestingly, the HR for PM2.5 was higher among movers than non-movers, which was not true for PM10, ozone, NOx and NO_2. For the latter two, the numbers of events were quite small, and the HRs were essentially indistinguishable for movers and non-movers. There is no obvious explanation for the differences between PM2.5 versus PM10 and ozone. This discrepancy may be due in part to differences in the durations of follow-up for PM2.5 and the other pollutants, the subgroups of the population and numbers at risk, or other factors. One potentially relevant observation is that the numbers of IHD events for movers and non-movers were of comparable magnitude, indicating that the crude IHD mortality rates for movers were greater than those for the non-movers. This was true even though, as a whole, the movers were younger and more likely to be pre-menopausal at cohort inception.

Only two prospective investigations of long-term exposure to PM2.5 have reported associations with incident MI and stroke (Miller et al. 2007; Puett et al. 2009). Miller et al. (2007) followed nearly 66,000 participants in the WHI observational study without a history of cardiovascular disease for a median of six years, using as the exposure metric a one-year average of PM2.5 values measured at the monitor closest to their residence at baseline. They reported HRs of 1.06 (95% CI = 0.85-1.34) for incident MI and 1.28 (95% CI = 1.02-1.61) for stroke per 10 $\mu g/m^3$ increase in PM2.5. Our results are somewhat similar in that we identified an association with incident stroke (HR = 1.14, 95% CI = 0.99-1.32), particularly among women who were post-menopausal at baseline (HR = 1.19, 95% CI = 1.02-1.38), but no association with incident MI. In our sensitivity analysis that included only hospital admissions, incident stroke was positively associated with PM10.

Puett et al. (2009) modeled monthly PM2.5 levels at the residences of 66,250 women living in the northeast and Midwest of the United States in the Nurses' Health Study from 1992-2002. They found significantly elevated HRs for all-cause mortality in

relation to moving average estimated PM levels ranging from 3 to 48 months, with the estimates being of comparable magnitude for periods of 12 months or longer. In contrast, the risk of incident CHD (including nonfatal MI) was not significantly elevated overall (incident CHD HR = 1.11, 95% CI = 0.79-1.55; nonfatal MI HR = 0.73, 95% CI = 0.48-1.12). Our findings are similar to those of Puett et al. with respect to the lack of association with incident MI and CHD. Although PM10 and PM2.5 were highly correlated in our dataset, the PM2.5 HR point estimates for IHD mortality and stroke were greater. This may be due in part to the likelihood of greater exposure misclassification for PM10 than for PM2.5, as the former exhibits greater spatial heterogeneity.

Our analyses of MI and stroke were limited to women who did not report a history of either of these events on the baseline questionnaire. While some of these participants may have experienced a silent event, it is unlikely that such misclassification of disease would be differentially distributed by pollutant exposure. Also, these outcomes were measured here only as hospitalizations or deaths, which could have resulted in incomplete ascertainment. Nevertheless, there is no reason to think that silent or unrecorded events would have biased the results in a differential manner.

Acute events such as stroke may be attributable to both short-term as well as long-term pollutant exposures (Wellenius et al. 2005; Barnett et al. 2006; Linn et al. 2000; Franklin et al. 2007). However, it is unlikely that the effects reported here were due only to short-term exposures, as the magnitudes of increased risks identified in this investigation (19% for stroke among post-menopausal women) far exceed those reported in time-series investigations (e.g., 1.03% for stroke mortality (Franklin et al. 2007)). Without daily data for this entire time period we could not disaggregate short-term from long-term pollutant impacts. However, experimental evidence and other epidemiological studies of subclinical disease support the proposition that these long-term exposures were associated with incident disease in the CTS cohort.

In a rodent model of atherosclerotic disease, chronic exposure to low levels of PM2.5 (6-month study average = 15 $\mu g/m^3$) was associated with enhanced progression of disease, increased vasomotor tone, and vascular inflammation (Sun et al. 2005). In humans, progression of atherosclerotic disease can be observed subclinically as increases in carotid arterial intima medial thickness, which has been reported cross-sectionally in association with estimated residential annual mean concentrations of PM2.5 (Künzli et al. 2005) and, more recently, in pooled data from five clinical studies conducted in the Los Angeles basin (Künzli et al. 2010). Though the impact of PM2.5 in the rodent model reported by Sun and colleagues (2005) may not be comparable to atherogenesis in humans, the studies by Künzli et al. (both conducted in the Los Angeles area) suggest the existence of commonalities. While such subclinical outcomes could not be examined in the CTS, these mechanisms underscore the biological plausibility of our finding that long-term exposure to particulate matter was associated with incident stroke (Brook et al. 2004; 2010).

This study provides evidence that long-term exposure to PM2.5, PM10, NOx, and ozone were all associated with increased risks for IHD mortality. The apparent increased risk of IHD mortality associated with long-term ozone exposure was most likely due to its correlation with particulate matter, while that for NOx was based on relatively small numbers of observations, and may also have been due to correlation with PM. That both

measures of PM were associated with incident stroke provides support for the notion that these pollutant mixtures may play an etiologic role in the development of circulatory disease.

Critical Windows

For the three outcomes that we examined using PM2.5 exposure periods of increasing duration prior to an event, the HR point estimates for all-cause, CP, and IHD mortality increased from six months (when none was significant) to three years, leveling off at that point. The HR for IHD mortality became significant with one-year of prior exposure (HR = 1.18, 95% CI = 1.00-1.39), doubling when the prior exposure period was lengthened to three years (HR = 1.41, 95% CI = 1.15-1.73). A similar pattern was observed for CP mortality. When, however, this analysis was limited only to the women who had had at least four years of measured PM2.5 exposure, we found that extending the one year window of exposure to two, three or four years made little difference in the HRs (Table 22). Because this latter analysis was limited to those who had survived longer, fewer events were included in the shorter windows than in the analysis of the whole PM25 subcohort (Table 21).

Few studies have examined the issue of critical windows, the results of which are not entirely consistent. For example, in the Nurses' Health Study, Puett et al. (2009) looked at modeled PM2.5 exposure periods of 1, 3, 12, 24, 36, and 48 months prior to several outcomes. They found that the HRs at one year and longer were of comparable magnitude and were all greater than those at one or three months for all-cause mortality, a first CHD event, and a fatal CHD event. Our results in Table 22 are consistent with their finding that there was no additional increase in the HR with an exposure window longer than one year. As in our analysis in Table 21, they also found an attenuation in the HRs for several of the outcomes after more than three years of prior exposure. This suggests that more recent exposures may represent a "critical window" in the exacerbation of cardiovascular disease. In the reanalysis of the HSC cohort, Schwartz et al. (2008) also found that more immediate exposures (i.e., in the year of death or the previous year) were most strongly related to all-cause mortality. In contrast, using a subsample of the ACS CPS II data, Krewski et al. (2009) found little difference between exposures one to five years prior versus six to 10 years prior using PM2.5 estimated from PM10 data. One thing that emerges from all of these analyses, however, is that elevated risks of mortality are evident in these cohorts within a year of follow-up and that the effects are much larger than those demonstrated from acute (several days') exposures.

PM2.5 Constituents Analysis

While the results of the PM2.5 constituents analysis were generally consistent with those of the main analysis, there were some differences as well. As in the main analysis, there were no associations between PM2.5 or any of its constituents with either

all-cause mortality or respiratory mortality. In contrast, PM2.5 mass and all of its constituents were clearly associated with IHD mortality, but the strength of the associations were greater than in the main analysis, particularly for EC and sulfate, while the HRs for silicon and OC were at the low end.

There are several potential reasons why the overall PM2.5 mass HR for IHD was greater in this analysis (1.31, 95% CI = 1.14-1.50) compared with the main one (1.20, 95% CI = 1.02-1.41). First, the former estimate was based on more than 40% fewer events (460 vs. 773), and could be subject to greater stochastic variability. Second, the method of assigning exposure differed. In the main analysis, the women's residences were linked with statewide IDW-generated PM2.5 surfaces, while in the constituents analysis the exposure assignments were based directly on pollutant measurements taken at one of eight fixed-site monitors. (Over one-third of the women in the constituents analysis resided in Los Angeles, and their exposures were linked with the PM2.5 speciation monitor in that county.) Third, in the main analysis the follow-up took place from March 2000 through December 2005, whereas in the constituents analysis, the follow-up started in August 2002 and continued through July 2007. When we restricted outcome follow-up in the main analysis to the period August 2002-December 2005 and to the women who were subjects in the PM2.5 constituents analysis, the HR (again scaled to 10 $\mu g/m^3$) was 1.43 (95% CI = 1.03-1.99), based on 260 events. This point estimate was modestly greater (but also less precise) than that obtained when the follow-up in the constituents analysis was curtailed in December 2005, i.e., HR = 1.26 (95% CI = 1.08-1.47), based on 350 events. Thus, when the analysis was limited to the same cohort of women followed for the same duration, the results of the two approaches were comparable.

Exposure-response Analysis

In our examination of the shape of the exposure-response function, we compared the linear model used in our main analyses with log-linear, quadratic, and fractional polynomial models. The outcome of interest was IHD, as this was the only mortality outcome consistently associated with estimated ambient pollution levels. We found that none of the non-linear models provided a better fit than the linear model, and that the resulting HRs were very similar. Previous studies on the shape of the function have demonstrated mixed results. For example, in the analysis of the HSC cohort, Schwartz et al. (2008) found that a linear function provided the best fit to the data for all-cause mortality. In contrast, using the ACS-CPS II cohort, Krewski et al. (2009) found that log(PM2.5) generated a slightly better fit than a linear term for most of the health endpoints investigated. However, the HRs from the two models were quite similar when evaluated near the mean of the PM2.5 distribution.

Traffic Analysis

In our previous report (Lipsett et al. 2007), none of the traffic metrics was associated with any outcome. We speculated that "it is possible that our approach of evaluating these metrics over their interquartile ranges may be partly responsible for the lack of association," in part because responses to traffic-associated pollution are likely to be nonlinear. In this investigation, we found that the highest decile of traffic density was associated with all-cause, CP and CV mortality. For vehicle density, the 25^{th} to 49^{th} percentile category was associated with cardiovascular mortality, HR = 1.17 (95% CI = 1.01-1.37). The other traffic metrics showed no association with these outcomes.

Other studies have reported effects among those who resided in close proximity to major roads (Hoek et al. 2002; Finkelstein et al. 2004; Beelen et al. 2008; Gan et al. 2010). For instance, Beelen et al. (2008 reported a slightly increased risk of cardiopulmonary mortality (1.06, 95% CI = 1.00-1.12) in relation to traffic intensity on the nearest road, scaled to an increment of 10,000 motor vehicles/24 hours. Those investigators also found a statistically significant relative risk linking long-term exposure per 10 $\mu g/m^3$ increase in black smoke (BS – a traffic-associated pollutant) with mortality due to "natural [all] causes" (RR = 1.05, 95% CI = 1.00=1.11), and a near-significant association with respiratory mortality (RR = 1.22, 95% CI = 0.99=1.50). Gan et al. (2010) found that long-term (five-year) residential estimates of black carbon (primarily a traffic-related pollutant) in Vancouver was associated with a similar increase in CHD mortality (RR = 1.06, 95% CI = 1.03-1.09, scaled to the interquartile range of a five-year average of black carbon, estimated using land-use regression). In that study, other traffic-related pollutants, including PM2.5, NO, and NO_2, were not related to mortality, but these were estimated to have been at very low concentrations.

As our NOx findings tend to corroborate the results of the traffic density analysis, we calculated the mean long-term NOx exposure levels for non-movers in the traffic categories (n = 9,928) and found the following:

Traffic density category	**n**	**NOx - Mean (SD) (ppb)**
$\geq 90^{th}$	1,204	109.07 (32.60)
$75^{th} – 89^{th}$	1,876	102.02 (33.56)
$50^{th} – 74^{th}$	2,600	93.28 (36.35)
$<50^{th}$	4,248	89.96 (31.63)

While these numbers are based on far fewer participants than those used in the traffic analyses (because we restricted the estimation of NOx levels to individuals whose residential addresses were within either three or five km of a fixed-site monitor), they provide support for the internal validity of the traffic density categories and for the regression results.

Summary and Conclusions

In an extension of previous work, we developed monthly and long-term estimates of air pollution at the residences of over 100,000 female participants in the longitudinal California Teachers Study (CTS). We examined associations between these long-term exposures and several measures of mortality as well as new cases (incidence) of heart attacks and stroke. To derive the pollutant exposure metrics, we linked the CTS participants' addresses with monthly estimates of PM2.5, PM10, ozone, CO, NO_2, NOx and SO_2. The main analyses examined potential relationships of mortality and disease incidence with long-term residential exposures to PM10, ozone, CO, NO_2, NOx, and SO_2 from 1996 through 2005, and to PM2.5 beginning in 1999. Participants' addresses were linked as well with several cross-sectional measures of potential traffic-related exposures from the year 2000, including: (i) proximity to a highway (within 150 m or beyond 150 m); (ii) traffic density, a measure of the estimated number of vehicle miles traveled within 150 m of a participant's residence; and (iii) vehicle density, or the number of registered vehicles in occupied housing units divided by the area of the participant's Census block. Using Cox proportional hazards regression models, we analyzed these relationships while adjusting for many individual-level and neighborhood variables, and undertook a variety of sensitivity analyses. We also examined critical windows of exposure for the PM2.5/IHD mortality relationship, explored the relative impact of PM2.5 constituents on mortality, and compared the fit of linear and several nonlinear models to PM2.5/mortality relationships.

1. In main analysis, the principal outcomes included the following:

a. Long-term exposure to PM2.5 was associated with IHD mortality and incidence of stroke, particularly among post-menopausal women.

b. Long-term exposure to PM10 was associated with elevated risks of IHD mortality and with incident stroke.

c. Ozone exposure was associated with IHD mortality, particularly in regressions using a third-quarter (summer) metric, but this association was most likely due to its correlations with PM2.5 and PM10.

d. NOx exposure was associated with an elevated risk of IHD mortality and more weakly associated with cardiovascular mortality. These associations were strengthened in an analysis restricted to never-smokers, among whom the risk of all-cause mortality was also elevated. Nonetheless, because these results were based on far fewer observations than for PM and ozone, they should be interpreted with caution. However, as NOx largely represents vehicular emissions, these results tend to corroborate our findings in the traffic analysis.

e. SO_2 exposure was associated with all-cause and cardiovascular mortality only in the analysis of never-smokers. These associations were based on very small numbers

of deaths, and therefore cannot inspire much confidence on our part. However, these results are consistent with findings in some other U.S. cohort studies.

f. We did not find that women who had diabetes at baseline or who were overweight or obese were at increased risk of PM2.5-associated mortality or disease incidence.

g. In general, we found little difference in effect estimates between movers and non-movers except in the case of IHD mortality. The HR for PM2.5 was greater among movers, while those for PM10 and ozone were greater for non-movers, and those for NOx and NO_2 essentially indistinguishable.

2. In the critical windows analysis for the entire PM2.5 subcohort, we found that the magnitude of the HRs linking PM2.5 exposure and mortality from cardiopulmonary and ischemic heart diseases increased as the duration of the prior exposure period increased from six months to three years. The HRs at four years were indistinguishable from those at three. In contrast, when we limited this analysis to women who had had at least four years of measured exposure, the HRs were significantly elevated for the same outcomes, and the magnitudes of the HRs did not change with windows of exposure longer than one year.

3. The PM2.5 constituents were all strongly inter-correlated. Significant associations were observed for PM2.5 mass, sulfate, and nitrate exposures in relation to cardiopulmonary mortality, with a more modest association for silicon. PM2.5 mass and all of its components were associated with mortality from IHD, with the largest effect estimates observed for EC and sulfate, although estimates were fairly similar among the components, except for silicon and OC. The PM2.5 mass HRs in this analysis were somewhat greater than those for PM2.5 in the main analysis, which could have been due a number of factors related to exposure assignment.

4. Traffic density, a measure of the estimated number of vehicle miles traveled within 150 m of a participant's residence, was associated with all-cause, cardiopulmonary, and cardiovascular mortality.

5. In our examination of the shape of the PM2.5/IHD mortality exposure-response function, we found no improvement of fit to the data when we used log-linear, quadratic, and fractional polynomial models compared with a simple linear model.

6. This investigation has both strengths and limitations.

a. Strengths of this analysis include the:

(i) large size of this cohort. This is the one of the largest air pollution cohort studies undertaken.

(ii) low prevalence of active smoking among the study participants.

(iii) large proportion of women at risk of developing cardiovascular disease by virtue of their age and post-menopausal status.

(iv) relative uniformity of occupational status, averting the need to control statistically for potentially toxic exposures that would be common in industrial environments.

(v) temporal and spatial resolution of pollutant exposures at the participants' residences, including both movers and non-movers.

(vi) ability to examine incidence of MI and stroke, not just fatal events, via linkage with comprehensive hospitalization as well as mortality data in California.

b. Limitations of this study include:

(i) restriction of the study population to one gender.

(ii) unknown error introduced into the development of pollutant surfaces by the use of all available monitors for each pollutant for the IDW interpolation. While maximizing the spatial coverage in relation to the subjects' addresses, this approach resulted in a dataset based on variable numbers of monitors over time and space, as they were deployed or taken out of operation

(iii) use of cross-sectional traffic data from 2000 to estimate exposures throughout the follow-up period.

(v) the paucity of observations for the analysis of NO_2, NOx, SO_2, and CO due in part to the small radial distances we imposed on spatial interpolation. This decision was made to reduce exposure misclassification for these pollutants, which are subject to considerable intra-urban variability, depending largely on local traffic patterns. In some instances, however, even these relatively small buffer zones might be inadequate,

(vi) the sparse numbers of mortality events for the PM2.5 constituents analysis, and the high inter-pollutant correlations, which together made it difficult to distinguish differences in effect estimates for these pollutants.

(vii) potential exposure misclassification with respect to traffic exposures for women in the CTS cohort who were still actively employed (e.g., due to exposures at work or during commuting) because the underlying CTS database did not include school address information.

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Glossary of terms, abbreviations, and symbols

ACS	American Cancer Society
AHSMOG	Adventist Health and Smog Study
ARB	Air Resources Board
BMI	body mass index (weight/height^2)
CI	confidence interval
CO	carbon monoxide
CHD	coronary heart disease
CP	cardiopulmonary
CPS	Cancer Prevention Study
CTS	California Teachers Study
CV	cardiovascular
EC	elemental carbon
EPA	U.S. Environmental Protection Agency
FRM	Federal reference method
HPMS	Highway Performance Monitoring System
HR	hazard ratio
HSC	Harvard Six Cities (Study)
IHD	ischemic heart disease
IQR	interquartile range
MI	myocardial infarction
NM	nonmalignant
NO	nitric oxide
NOx	nitrogen oxides
NO_2	nitrogen dioxide
O_3	ozone
OC	organic carbon
OSHPD	Office of Statewide Health Planning and Development
PM	particulate matter
PM2.5	PM with a median aerodynamic diameter < 2.5 μ
PM10	PM with a median aerodynamic diameter < 10 μ
RR	relative risk
SHS	second-hand smoke
SO_2	sulfur dioxide
STRS	State Teachers Retirement System
USC	University of Southern California
USPS	United States Postal Service
VMT	vehicle miles traveled

Appendix A: Methods and Results for Main Analysis Using Exposure Assessment Methodology in Original Proposal

As noted in the main text of this report, we used the methodology in our original proposal to estimate individual exposures and the associated hazard ratios for various air pollutants. This Appendix provides a brief description of the relevant aspects of the methodology used, as well as selected illustrative results, which are quite different from those provided in the report. The hazard ratios are markedly elevated for many outcomes and for multiple pollutants. We believe that this is due primarily to the assignment of a summary average exposure of each pollutant to each participant. Because of the marked declines in the ambient concentrations of most air pollutants in California during the relevant periods of exposure (see Figures 2 and 3), those who survived without incident to the end of the study period would have had lower average levels of exposure compared with those who died or were admitted to hospital with an MI or stroke earlier on. This would have resulted in associations of higher levels of exposure with mortality or hospitalization for MI or stroke and lower levels with no events, thereby inflating the hazard ratios.

Air Pollution Exposure Estimates

Monthly average concentrations for PM10, ozone, nitrogen dioxide (NO_2), nitrogen oxides (NOx), carbon monoxide (CO), and sulfur dioxide (SO_2) were calculated from fixed-site monitors, requiring a minimum of 75% completeness in any given month for each monitor to be included. For PM2.5, monthly averages were created from Federal Reference Method monitors that became available from 1999 through 2005. The monitors used in this investigation are part of California's State and Local Air Monitoring Network, which is intended to represent regional population exposures. Pollutant surfaces of monthly average ambient concentrations were developed via inverse distance-weighted (IDW) interpolation, using ArcGIS v. 9.1 (ESRI, Redlands, CA). To maximize spatial coverage, all monitors available each month were used. Most air pollution monitoring stations in California are assigned spatial scale designations (e.g., neighborhood, regional), which define a radial range for which monitors are intended to provide representative data. We utilized this information to include in the analysis women whose residences were within the representative range of a given pollutant monitor (e.g., 20 km for PM2.5), and exclude those whose homes were outside the representative range of any monitor for that pollutant.

Monthly individual exposure estimates were created via spatial linkage of the geocoded residential addresses to the IDW pollutant surfaces. For each individual and each pollutant, the value for all person-months of exposure were summed and then divided by the total months of exposure, to create an average measure of overall long-term exposure until the time of an event or the end of the observation period.

Statistical Methods

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between each pollutant and the outcomes of interest. In these analyses, in order to ensure that each participant had a minimum of one year of exposure to the pollutant of interest, we initiated outcome follow-up for the participants who had had at least a year of exposure data. To maintain uniformity of follow-up, this meant that exposure metrics for ozone, NO_2, NOx, CO, SO_2 and PM10 were initiated in June 1996, while outcome follow-up began in June 1997, both of which continued until the end of the observation period (December 31, 2005). For PM2.5, the corresponding start dates for exposure and cohort follow-up were March 1999 and March 2000, respectively, through 2005. HRs and 95% CIs were scaled to interquartile ranges (IQRs), based on pollutant distributions for women who did not experience any events during the study period. For purposes of comparison with other studies of particulate matter, we scaled HRs for PM2.5 and PM10 in relation to increments of 10 $\mu g/m^3$). We initially adjusted for age and race only; then included individual-level risk factors and neighborhood variables in subsequent models.

Results

Table A-1 summarizes the estimated HRs for incident MI and stroke, as well as for mortality from all causes, and cardiovascular, respiratory, non-malignant respiratory, lung cancer, and ischemic heart diseases, per 10 $\mu g/m^3$ increment of the long-term average concentrations of PM2.5 and PM10. The results indicate strong and mostly highly significant associations between PM2.5 and all outcomes, with the strongest associations with IHD and nonmalignant respiratory disease. In contrast, PM10 was associated with fewer outcomes (mortality from all causes, cardiovascular disease and IHD, and incidence of stroke), and the magnitudes of these associations were substantially lower than those for PM2.5.

Table A-2 summarizes the results for the gaseous pollutants, using the IQR of exposure for 1996-2005 for the full cohort. All of the gaseous pollutants except ozone were associated with all-cause mortality, while all but SO_2 were associated with both cardiovascular and IHD mortality. In contrast to the results for PM2.5 and PM10, none was associated with incident MI or stroke. Table A-3 summarizes the results for the runs using summer ozone alone. The HRs were generally similar but slightly higher than those based on analysis of year-round ozone levels, and in addition, the association with non-malignant respiratory disease mortality was close to statistical significant. In two-pollutant models including ozone with PM2.5, NO_2 or CO, however, the ozone coefficients diminished and became nonsignificant, while those for the other pollutants remained elevated and significant (data not shown). The results for analyses restricted to never-smokers are presented in Tables A-2 and A-4. The HRs for all outcomes for PM2.5 were slightly to markedly higher among the never-smokers, while for PM10, the results among the never-smokers were similar to those of the entire cohort, except for nonmalignant respiratory mortality, which increased and attained statistical significance, while the reverse was true for stroke incidence. For the gaseous pollutants, the HRs among never-smokers were generally about the same or higher.

TABLE A-1. HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MI AND STROKE, PER 10 μg/m^3 INCREMENT OF PM2.5 (2000-2005) AND PM10 (1996-2005) FOR THE CALIFORNIA TEACHERS STUDY COHORT.

	PM2.5			PM10		
Outcome	# events	N	HR (95% CI)	# events	N	HR (95% CI)
All-cause mortality	4,147	73,489	1.01 (0.95, 1.09)	4,694	61,181	1.00 (0.97, 1.04)
Cardiovascular mortality	1,630	73,489	1.07 (0.95, 1.19)	1,863	61,181	1.03 (0.98, 1.08)
Respiratory mortality	638	73,489	1.10 (0.92, 1.32)	728	61,181	1.02 (0.94, 1.11)
NM-Respiratory mortality	404	73,489	1.21 (0.97, 1.52)	453	61,181	1.08 (0.98, 1.19)
Lung cancer mortality	234	73,489	0.95 (0.70, 1.28)	275	61,181	0.93 (0.81, 1.07)
IHD mortality	773	73,489	1.20 (1.02, 1.41)	843	61,181	1.06 (0.99, 1.14)
Cerebrovascular mortality	382	73,489	1.16 (0.92, 1.46)	486	61,181	0.99 (0.89, 1.09)
MI incidence	722	72,403	0.98 (0.83, 1.16)	837	60,307	0.98 (0.91, 1.06)

Models adjusted for smoking status, total pack-years, BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period for PM2.5: Mar 1999-Dec 2005; cohort follow-up period: Mar 2000-Dec 2005. Exposure period for PM10: June 1996-Dec 2005; cohort follow-up period: June1997-Dec 2005.

TABLE A-2. HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MI AND STROKE FOR THE CALIFORNIA TEACHERS STUDY COHORT, BASED ON ESTIMATED LONG-TERM EXPOSURES AT PARTICIPANTS' RESIDENCES, SCALED TO POLLUTANT INTERQUARTILE RANGES (1996 – 2005)

		Full cohort				Never-smokers only			
Pollutant	Outcome	# events	N	IQR	HR* (95% CI)	# events	N	IQR	HR* (95% CI)
Ozone	All-cause mortality	7,381	101,784	11.02	0.97 (0.94, 1.00)	4,426	68,611	10.65	0.97 (0.93, 1.00)
	Cardiovascular mortality	2,919	101,784	11.02	1.00 (0.95, 1.05)	1,921	68,611	10.65	1.00 (0.95, 1.06)
	Respiratory mortality	1,135	101,784	11.02	1.02 (0.94, 1.11)	435	68,611	10.65	1.07 (0.95, 1.21)
	NM-Respiratory mortality	702	101,784	11.02	1.07 (0.97, 1.19)	332	68,611	10.65	1.10 (0.95, 1.27)
	Lung Cancer mortality	433	101,784	11.02	0.96 (0.84, 1.09)	103	68,611	10.65	0.98 (0.76, 1.27)
	IHD mortality	1,358	101,784	11.02	1.06 (0.99, 1.14)	892	68,611	10.65	1.08 (0.99, 1.18)
	MI incidence	728	101,784	11.02	0.97 (0.88, 1.07)	818	67,775	10.65	1.03 (0.94, 1.13)
	Stroke incidence	1,317	100,340	11.02	1.03 (0.95, 1.11)	1,138	67,628	10.63	1.03 (0.95, 1.11)
NOx	All-cause mortality	1,208	15,397	49.31	1.04 (0.95, 1.15)	758	10,549	49.19	1.10 (0.98, 1.24)
	Cardiovascular mortality	499	15,397	49.31	1.13 (0.98, 1.31)	343	10,549	49.19	1.23 (1.03, 1.47)
	Respiratory mortality	198	15,397	49.31	0.88 (0.70, 1.12)	86	10,549	49.19	0.82 (0.57, 1.20)
	NM-Respiratory mortality	128	15,397	49.31	0.86 (0.64, 1.17)	64	10,549	49.19	0.89 (0.57, 1.41)

		Full cohort				Never-smokers only			
Pollutant	Outcome	# events	N	IQR	HR* (95% CI)	# events	N	IQR	HR* (95% CI)
	Lung Cancer mortality	70	15,397	49.31	0.92 (0.60, 1.40)	22	10,549	49.19	0.89 (0.41, 1.92)
	IHD mortality	238	15,397	49.31	1.25 (1.00, 1.55)	156	10,549	49.19	1.40 (1.07, 1.83)
	MI incidence	118	15,397	49.31	1.03 (0.77, 1.39)	125	10,393	48.84	1.10 (0.82, 1.47)
	Stroke incidence	188	15,149	48.82	1.02 (0.80, 1.29)	195	10,364	49.20	1.04 (0.83, 1.31)
NO_2	All-cause mortality	1,010	12,366	10.29	0.97 (0.91, 1.04)	609	8,224	10.51	0.99 (0.91, 1.08)
	Cardiovascular mortality	408	12,366	10.29	0.98 (0.88, 1.09)	265	8,224	10.51	0.96 (0.85, 1.10)
	Respiratory mortality	174	12,366	10.29	0.95 (0.81, 1.13)	68	8,224	10.51	1.01 (0.78, 1.33)
	NM-Respiratory mortality	107	12,366	10.29	0.93 (0.75, 1.15)	48	8,224	10.51	1.15 (0.82, 1.61)
	Lung Cancer mortality	67	12,366	10.29	1.00 (0.75, 1.33)	20	8,224	10.51	0.96 (0.54, 1.71)
	IHD mortality	193	12,366	10.29	1.07 (0.92, 1.25)	118	8,224	10.51	1.11 (0.91, 1.35)
	MI incidence	104	12,366	10.29	0.86 (0.70, 1.06)	100	8,106	10.57	1.21 (0.98, 1.49)
	Stroke incidence	161	12,172	10.27	1.05 (0.90, 1.24)	160	8,077	10.59	0.93 (0.78, 1.10)
CO	All-cause mortality	997	11,412	0.49	0.93 (0.84, 1.02)	616	7,584	0.50	0.93 (0.82, 1.05)
	Cardiovascular mortality	409	11,412	0.49	0.95 (0.81, 1.11)	279	7,584	0.50	0.98 (0.81, 1.19)

		Full cohort				Never-smokers only			
Pollutant	Outcome	# events	N	IQR	HR* (95% CI)	# events	N	IQR	HR* (95% CI)
	Respiratory mortality	155	11,412	0.49	0.83 (0.65, 1.07)	61	7,584	0.50	0.81 (0.54, 1.22)
	NM-Respiratory mortality	103	11,412	0.49	0.83 (0.60, 1.14)	46	7,584	0.50	1.03 (0.64, 1.65)
	Lung Cancer mortality	52	11,412	0.49	0.89 (0.57, 1.39)	15	7,584	0.50	0.37 (0.13, 1.06)
	IHD mortality	198	11,412	0.49	0.90 (0.72, 1.13)	133	7,584	0.50	1.04 (0.79, 1.37)
	MI incidence	92	11,412	0.49	0.78 (0.55 1.11)	97	7,478	0.50	1.04 (0.77, 1.41)
	Stroke incidence	163	11,234	0.49	0.90 (0.71, 1.14)	153	7,455	0.50	0.86 (0.67, 1.09)
SO_2	All-cause mortality	257	3,428	0.43	1.11 (1.00, 1.23)	152	2,170	0.46	1.18 (1.02, 1.36)
	Cardiovascular mortality	107	3,428	0.43	1.07 (0.91, 1.25)	69	2,170	0.46	1.27 (1.01, 1.60)
	Respiratory mortality	29	3,428	0.43	1.03 (0.70, 1.52)	7	2,170	0.46	----
	NM-Respiratory mortality	16	3,428	0.43	-	5	2,170	0.46	----
	Lung Cancer mortality	13	3,428	0.43	-	2	2,170	0.46	----
	IHD mortality	49	3,428	0.43	1.03 (0.80, 1.32)	31	2,170	0.46	1.33 (0.83, 2.14)
	MI incidence	23	3,428	0.43	1.22 (0.79, 1.87)	28	2,140	0.46	0.87 (0.54, 1.42)
	Stroke incidence	43	3,375	0.43	1.06 (0.80, 1.42)	35	2,125	0.47	1.23 (0.86, 1.76)

* Models adjusted for smoking status, total pack-years BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period: June 1996-Dec 2005; cohort follow-up period: June1997-Dec 2005.

TABLE A-3. HAZARD RATIOS* FOR AND FOR INCIDENT MI AND STROKE IN THE CALIFORNIA TEACHERS STUDY COHORT, BASED ON SUMMER OZONE INTERQUARTILE RANGES (1996 – 2005)

Pollutant	Outcome	# events	N	IQR	HR* (95% CI)
Ozone	All-cause mortality	7,381	101,784	22.96	0.97 (0.94, 1.01)
	Cardiovascular mortality	2,919	101,784	22.96	1.02 (0.96, 1.07)
	Respiratory mortality	1,135	101,784	22.96	1.03 (0.94, 1.12)
	NM-Respiratory mortality	702	101,784	22.96	1.09 (0.97, 1.21)
	Lung cancer mortality	433	101,784	22.96	0.95 (0.82, 1.10)
	IHD mortality	1,358	101,784	22.96	1.09 (1.01, 1.19)
	Cerebrovascular mortality	728	101,784	22.96	0.99 (0.88, 1.10)
	MI incidence	1,317	100,340	22.95	1.04 (0.96, 1.12)

* Models adjusted for smoking status, total pack-years BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period: June 1996-Dec 2005; cohort follow-up period: June1997-Dec 2005.

TABLE A-4. HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MI AND STROKE, PER 10 μg/m^3 INCREMENT OF PM2.5 (2000-2005) AND PM10 (1996-2005) FOR THE CALIFORNIA TEACHERS STUDY COHORT, ANALYSIS RESTRICTED TO NEVER-SMOKERS

	PM2.5			PM10		
Outcome	# events	N	HR (95% CI)	# events	N	HR (95% CI)
All-cause mortality	2,513	50,229	1.03 (0.94, 1.13)	2,821	41,209	1.00 (0.96, 1.04)
Cardiovascular mortality	1,074	50,229	1.13 (0.98, 1.29)	1,256	41,209	1.02 (0.95, 1.08)
Respiratory mortality	241	50,229	1.30 (0.97, 1.74)	265	41,209	1.11 (0.97, 1.26)
NM-Respiratory mortality	191	50,229	1.26 (0.91, 1.76)	203	41,209	1.15 (1.00, 1.33)
Lung Cancer mortality	50	50,229	1.62 (0.83, 3.16)	62	41,209	1.00 (0.75, 1.31)
IHD mortality	513	50,229	1.28 (1.05, 1.57)	564	41,209	1.06 (0.97, 1.16)
MI incidence	460	49,585	1.03 (0.83, 1.27)	534	40,694	1.03 (0.94, 1.13)
Stroke incidence	592	49,453	1.17 (0.97, 1.41)	734	40,601	1.05 (0.97, 1.14)

Models adjusted for smoking status, total pack-years, BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication and aspirin use; and contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period for PM2.5: Mar 1999-Dec 2005; cohort follow-up period: Mar 2000-Dec 2005. Exposure period for PM10: June 1996-Dec 2005; cohort follow-up period: June1997-Dec 2005.

Appendix B: Results of Alternative Approaches to Address the Issue of Missing Covariates

Table 10 in the report indicates that there are a number of variables used in the regression equations that had substantial numbers of missing data, particularly marital status, exposure to second-hand smoke, and menopausal status/hormone therapy. We created an "unknown" category for each of these variables, so that the individuals for whom the data were missing would not be dropped in the regression analyses. However, several simulation studies have shown that using an "unknown" category for potential confounders can compromise the ability to control confounding due to those variables (Vach and Blettner 1991; Knol et al. 2010; Gorelick 2006). Two approaches that we used to examine the potential effects of such missing data were to re-run the regressions for PM10, PM2.5 and NOx: (1) dropping each one of the above potential confounding variables from the models; and (2) including only those individuals for whom the data for those variables were not missing. These exclusions reduce the number of events (incident cases or deaths) in the analysis. For example, excluding subjects with unknown secondhand smoke exposure from the PM2.5 analysis reduces the number of events by 5%, excluding unknown menopause status by 20%, and excluding unknown marital status by 50% or more for some outcomes. Hence, the analysis restricted to complete cases can result in loss of power and wider confidence intervals. As indicated in Tables B-1 and B-2, below, while the results for some outcomes changed slightly, our overall conclusions remain the same.

TABLE B-1: HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MI AND STROKE IN RELATION TO PM2.5, PM10, AND NOx FOR THE CALIFORNIA TEACHERS STUDY COHORT, WITH VARIABLES CONTAINING SUBSTANTIAL MISSING DATA DROPPED FROM REGRESSION MODELS

OMITTING MARITAL STATUS

	PM2.5			PM10			NOx		
Outcome	# events	N	HR (95% CI)	# events	N	HR (95% CI)	# events	N	HR (95% CI)
All-cause mortality	4,147	73,489	1.02 (0.95, 1.10)	4,694	61,181	1.00 (0.97, 1.04)	1,208	15,397	1.04 (0.95, 1.14)
Cardiovascular mortality	1,630	73,489	1.08 (0.96, 1.20)	1,863	61,181	1.03 (0.98, 1.08)	499	15,397	1.13 (0.98, 1.31)
Respiratory mortality	638	73,489	1.12 (0.93, 1.33)	728	61,181	1.02 (0.94, 1.11)	198	15,397	0.90 (0.71, 1.15)
NM-Respiratory mortality	404	73,489	1.23 (0.98, 1.54)	453	61,181	1.08 (0.97, 1.19)	128	15,397	0.88 (0.65, 1.19)
Lung cancer mortality	234	73,489	0.95 (0.71, 1.29)	275	61,181	0.93 (0.81, 1.07)	70	15,397	0.93 (0.61, 1.41)
IHD mortality	773	73,489	1.21 (1.03, 1.42)	843	61,181	1.06 (0.98, 1.14)	238	15,397	1.25 (1.01, 1.55)
Cerebrovascular mortality	382	73,489	1.17 (0.92, 1.47)	486	61,181	0.98 (0.89, 1.09)	118	15,397	1.01 (0.75, 1.35)
MI incidence	722	72,403	0.98 (0.83, 1.16)	837	60,307	0.98 (0.91, 1.06)	188	15,149	1.02 (0.80, 1.29)
Stroke incidence	969	72,230	1.14 (0.99, 1.32)	1,179	60,204	1.06 (1.00, 1.13)	310	15,117	1.05 (0.88, 1.27)

Models adjusted for personal risk factors and contextual variables. HRs scaled to increments of 10 $\mu g/m^3$ increment of PM2.5 (2000-2005) and PM10 (1997-2005), and the interquartile range for NOx.

OMITTING PASSIVE SMOKING

	PM2.5			PM10			NOx		
Outcome	# events	N	HR (95% CI)	# events	N	HR (95% CI)	# events	N	HR (95% CI)
All-cause mortality	4,147	73,489	1.01 (0.95, 1.09)	4,694	61,181	1.00 (0.97, 1.04)	1,208	15,397	1.04 (0.95, 1.15)
Cardiovascular mortality	1,630	73,489	1.07 (0.96, 1.20)	1,863	61,181	1.03 (0.97, 1.08)	499	15,397	1.13 (0.98, 1.31)
Respiratory mortality	638	73,489	1.10 (0.92, 1.32)	728	61,181	1.02 (0.94, 1.11)	198	15,397	0.91 (0.72, 1.16)
NM-Respiratory mortality	404	73,489	1.22 (0.97, 1.52)	453	61,181	1.08 (0.98, 1.19)	128	15,397	0.90 (0.67, 1.22)
Lung cancer mortality	234	73,489	0.95 (0.70, 1.28)	275	61,181	0.93 (0.81, 1.07)	70	15,397	0.93 (0.62, 1.40)
IHD mortality	773	73,489	1.19 (1.01, 1.41)	843	61,181	1.06 (0.98, 1.14)	238	15,397	1.24 (1.00, 1.54)
Cerebrovascular mortality	382	73,489	1.17 (0.93, 1.47)	486	61,181	0.99 (0.89, 1.10)	118	15,397	1.01 (0.75, 1.35)
MI incidence	722	72,403	0.98 (0.83, 1.16)	837	60,307	0.98 (0.91, 1.06)	188	15,149	1.02 (0.80, 1.29)
Stroke incidence	969	72,230	1.14 (0.99, 1.32)	1,179	60,204	1.06 (0.99, 1.13)	310	15,117	1.06 (0.88, 1.28)

Models adjusted for personal risk factors and contextual variables. HRs scaled to increments of 10 $\mu g/m^3$ increment of PM2.5 (2000-2005) and PM10 (1997-2005), and the interquartile range for NOx.

OMITTING MENOPAUSAL STATUS

	PM2.5			PM10			NOx		
Outcome	# events	N	HR (95% CI)	# events	N	HR (95% CI)	# events	N	HR (95% CI)
All-cause mortality	4,147	73,489	1.01 (0.94, 1.09)	4,694	61,181	1.00 (0.97, 1.04)	1,208	15,397	1.04 (0.95, 1.14)
Cardiovascular mortality	1,630	73,489	1.07 (0.95, 1.19)	1,863	61,181	1.03 (0.97, 1.08)	499	15,397	1.12 (0.97, 1.29)
Respiratory mortality	638	73,489	1.10 (0.92, 1.32)	728	61,181	1.02 (0.94, 1.11)	198	15,397	0.93 (0.73, 1.17)
NM-Respiratory mortality	404	73,489	1.21 (0.97, 1.52)	453	61,181	1.08 (0.98, 1.19)	128	15,397	0.92 (0.68, 1.23)
Lung cancer mortality	234	73,489	0.95 (0.70, 1.28)	275	61,181	0.93 (0.81, 1.07)	70	15,397	0.91 (0.61, 1.35)
IHD mortality	773	73,489	1.19 (1.01, 1.40)	843	61,181	1.06 (0.98, 1.14)	238	15,397	1.27 (1.03, 1.56)
Cerebrovascular mortality	382	73,489	1.16 (0.92, 1.46)	486	61,181	0.99 (0.89, 1.09)	118	15,397	0.96 (0.72, 1.29)
MI incidence	722	72,403	0.98 (0.82, 1.15)	837	60,307	0.98 (0.91, 1.06)	188	15,149	1.02 (0.80, 1.29)
Stroke incidence	969	72,230	1.14 (0.99, 1.32)	1,179	60,204	1.06 (1.00, 1.13)	310	15,117	1.07 (0.89, 1.28)

Models adjusted for personal risk factors and contextual variables. HRs scaled to increments of 10 $\mu g/m^3$ increment of PM2.5 (2000-2005) and PM10 (1997-2005), and the interquartile range for NOx.

TABLE B-2: HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MI AND STROKE IN RELATION TO PM2.5, PM10, AND NOx FOR THE CALIFORNIA TEACHERS STUDY COHORT, USING REGRESSION MODELS IN WHICH PARTICIPANTS WITH MISSING DATA FOR MARITAL STATUS, SECOND-HAND SMOKE EXPOSURE OR MENOPAUSAL STATUS WERE EXCLUDED.

			Marital status known		**SHS exposure known**		**Menopausal status known**
Pollutant	Outcome	# events	HR (95% CI)	# events	HR (95% CI)	# events	HR (95% CI)
PM2.5			N=49,384; IQR=10.0		N=70,128; IQR=10.0		N=66,173; IQR=10.0
	All-cause	2,095	1.06 (0.96, 1.17)	3,923	1.01 (0.94, 1.08)	3,508	1.02 (0.95, 1.10)
	Cardiovascular	746	1.10 (0.93, 1.30)	1,550	1.05 (0.94, 1.18)	1,352	1.09 (0.97, 1.24)
	Respiratory	334	1.14 (0.89, 1.47)	591	1.12 (0.93, 1.35)	552	1.10 (0.91, 1.34)
	NM-Respiratory	198	1.16 (0.84, 1.60)	372	1.21 (0.95, 1.53)	342	1.20 (0.94, 1.53)
	Lung Cancer	136	1.12 (0.75, 1.65)	219	1.00 (0.73, 1.36)	210	0.97 (0.71, 1.34)
	IHD	349	1.28 (1.00, 1.63)	731	1.17 (0.99, 1.38)	629	1.29 (1.08, 1.55)
	Cerebrovascular	161	1.16 (0.81, 1.68)	367	1.14 (0.90, 1.44)	320	1.12 (0.87, 1.45)
	MI incidence	443/ 48.684	1.05 (0.85, 1.30)	686/ 69,088	0.99 (0.83, 1.17)	624/ 65,239	1.02 (0.85, 1.22)
	Stroke incidence	576/ 48,667	1.09 (0.90, 1.32)	930/ 68,921	1.09 (0.94, 1.27)	848/ 65,096	1.11 (0.95, 1.29)
PM10			N=40,389; IQR=10.0		N=58,418; IQR=10.0		N=54,835; IQR=10.0
	All-cause	1,805	1.02 (0.97, 1.07)	4,428	1.00 (0.96, 1.03)	3,920	1.01 (0.97, 1.04)
	Cardiovascular	668	1.03 (0.95, 1.12)	1,772	1.02 (0.97, 1.07)	1,514	1.04 (0.98, 1.10)
	Respiratory	307	0.96 (0.85, 1.10)	677	1.02 (0.94, 1.11)	624	1.01 (0.93, 1.11)

	NM-Respiratory	184	1.00 (0.84, 1.18)	423	1.07 (0.96, 1.19)	379	1.08 (0.97, 1.21)
	Lung Cancer	123	0.91 (0.74, 1.12)	254	0.94 (0.81, 1.08)	245	0.92 (0.79, 1.07)
	IHD	302	1.07 (0.94, 1.21)	797	1.06 (0.98, 1.15)	667	1.09 (1.00, 1.18)
	Cerebrovascular	164	1.06 (0.88, 1.26)	466	0.98 (0.88, 1.09)	402	1.00 (0.89, 1.12)
	MI incidence	452/ 39,895	1.02 (0.92, 1.13)	797/ 57,578	0.98 (0.91, 1.06)	721/ 54,107	0.97 (0.90, 1.06)
	Stroke incidence	622/ 39,897	1.05 (0.96, 1.15)	1,131/ 57,490	1.05 (0.98, 1.12)	1,013/ 54,021	1.05 (0.98, 1.12)
NOx			N=10,165; IQR=50.61		N=14,717; IQR=48.57		N=13,787; IQR=49.38
	All-cause	451	1.09 (0.92, 1.28)	1,135	1.04 (0.94, 1.14)	1,010	1.08 (0.97, 1.19)
	Cardiovascular	172	1.01 (0.78, 1.32)	477	1.13 (0.97, 1.31)	411	1.18 (1.00, 1.39)
	Respiratory	80	1.16 (0.77, 1.75)	182	0.91 (0.72, 1.16)	173	0.89 (0.69, 1.16)
	NM-Respiratory	52	1.07 (0.64, 1.81)	117	0.89 (0.66, 1.21)	109	0.89 (0.64, 1.24)
	Lung Cancer	28	1.38 (0.65, 2.93)	65	0.90 (0.59, 1.39)	64	0.92 (0.59, 1.44)
	IHD	85	1.17 (0.79, 1.73)	226	1.23 (0.99, 1.53)	191	1.40 (1.10, 1.79)
	Cerebrovascular	38	0.79 (0.45, 1.38)	113	1.00 (0.74, 1.34)	102	1.11 (0.81, 1.52)
	MI incidence	118/ 10,015	1.10 (0.80, 1.50)	178/ 14,483	1.03 (0.81, 1.31)	162/ 13,583	0.94 (0.73, 1.22)
	Stroke incidence	162/ 10,021	0.99 (0.78, 1.27)	295/ 14,447	1.01 (0.84, 1.21)	271/ 13,560	1.10 (0.91, 1.34)

Appendix C: Crude Mortality and Incidence Rates Among California Teachers Study Participants for March 2000 – December 2005 (outcome follow-up period for PM2.5 analyses) and June 1997 – December 2005 (outcome follow-up period for all other pollutants)

3/00 – 12/05

N	Outcome	# events	Person-time years	Crude rate per 100,000
73,489	all-cause	4,147	409,079	1014
73,489	cardiovascular	1,630	409,079	398
73,489	NM-respiratory	404	409,079	99
73,489	lung cancer	234	409,079	57
73,489	IHD	773	409,079	189
73,489	cerebrovascular	382	409,079	93
72,403	MI incidence	722	403,825	179
72,230	Stroke incidence	969	403,007	240

6/97 – 12/05

N	Outcome	# events	Person-time years	Crude rate per 100,000
101,784	all-cause	7,381	820,049	900
101,784	cardiovascular	2,919	820,049	356
101,784	NM-respiratory	702	820,049	86
101,784	lung cancer	433	820,049	53
101,784	IHD	1,358	820,049	166
101,784	cerebrovascular	728	820,049	89
100,340	MI incidence	1,317	810,124	163
100,223	Stroke incidence	1,875	809,396	232