# Long-Term Exposure to Air Pollution and Cardiorespiratory Disease in the California Teachers Study Cohort

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*Rationale*: **Several studies have linked long-term exposure to particulate air pollution with increased cardiopulmonary mortality; only two have also examined incident circulatory disease.**

*Objectives*: **To examine associations of individualized long-term exposures to particulate and gaseous air pollution with incident myocardial infarction and stroke, as well as all-cause and cause-specific mortality.**

*Methods*: **We estimated long-term residential air pollution exposure for more than 100,000 participants in the California Teachers Study, a prospective cohort of female public school professionals. We linked geocoded residential addresses with inverse distance-weighted monthly pollutant surfaces for two measures of particulate matter and for several gaseous pollutants. We examined associations between exposure to these pollutants and risks of incident myocardial infarction and stroke, and of all-cause and cause-specific mortality, using Cox proportional hazards models.**

*Measurements and Main Results*: **We found elevated hazard ratios linking long-term exposure to particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), scaled to an increment of 10 $\mu g/m^3$ with mortality from ischemic heart disease (IHD) (1.20; 95% confidence interval [CI], 1.02–1.41) and, particularly among postmenopausal women, incident stroke (1.19; 95% CI, 1.02–1.38). Long-term exposure to particulate matter less than 10 μm in aerodynamic diameter ($PM_{10}$) was associated with elevated risks for IHD mortality (1.06; 95% CI, 0.99–1.14) and incident stroke (1.06; 95% CI, 1.00–1.13), while exposure to nitrogen oxides was associated with elevated risks for IHD and all cardiovascular mortality.**

*Conclusions*: **This study provides evidence linking long-term exposure to $PM_{2.5}$ and $PM_{10}$ with increased risks of incident stroke as well as IHD mortality; exposure to nitrogen oxides was also related to death from cardiovascular diseases.**

## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Several cohort studies have linked long-term air pollution exposure with increased risks of cardiovascular mortality; only two have examined the relationship of air pollution to incident circulatory disease.

### What This Study Adds to the Field

In this study long-term exposures to particulate matter were associated with increased risk of incident stroke as well as death from ischemic heart disease, supporting the notion that such exposures may play a role in the development of circulatory disease.

**Keywords:** particulate matter; cardiovascular diseases; air pollutants; epidemiology

Several cohort studies have linked long-term exposure to air pollution with both all-cause and cardiopulmonary mortality (1–8). All found associations between particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and increased risks of mortality. However, concerns about the extent of exposure misclassification in these studies persist, because several relied on only one or a few years of $PM_{2.5}$ exposure data, and some used data collected in the remote past and imputed data. In addition, most prior cohort studies of $PM_{2.5}$ examined mortality from cardiovascular causes, but not incident disease. Miller and colleagues (5) identified significantly increased risks of incident and fatal cardiovascular events associated with elevated $PM_{2.5}$ exposures in the observational study of the Women's Health Initiative (WHI), using 1 year of annual average $PM_{2.5}$ levels as the principal exposure metric. Using data from the Nurses' Health Study, Puett and colleagues recently found that long-term exposure to estimated $PM_{2.5}$ was associated with death from coronary heart disease (CHD), but not with overall incident CHD (8). In this study we used several years of concurrently monitored pollutant data to examine associations of long-term exposure to $PM_{2.5}$, $PM_{10}$, and several gaseous pollutants with risks of incident myocardial infarction (MI) and stroke, as well as with all-cause and several subcategories of mortality, in a large cohort of predominantly nonsmoking women in California. Some preliminary results from this study were previously reported in an abstract (9).

## METHODS

### Study Population

The California Teachers Study (CTS) is a prospective cohort investigation, initiated in 1995, of 133,479 current and former public school

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professionals who completed baseline questionnaires mailed to approximately 329,000 female enrollees in the State Teachers' Retirement System. A full description of the cohort is available elsewhere (10). Subsequent questionnaires were mailed to the CTS participants in 1997 and 2000. Annual follow-up includes updating names and residential addresses for outcome linkage with hospitalization and mortality databases. All residential addresses were geocoded and linked with pollutant data to generate estimates of long-term exposure. For this analysis, we restricted the study population to the 124,614 women living in California when they joined the study.

Use of data on human subjects was approved by the California Health and Human Services Agency's Committee for the Protection of Human Subjects and the institutional review boards for each participating organization.

### Air Pollution Exposure Estimates

Monthly average concentrations for particulate matter with an aerodynamic diameter of 10 μm or less ($PM_{10}$), ozone, nitrogen dioxide ($NO_2$), nitrogen oxides (NOx), carbon monoxide (CO), and sulfur dioxide ($SO_2$) were calculated from fixed-site monitors for the period June 1996 through December 2005. For $PM_{2.5}$, monthly averages were created from Federal Reference Method monitors that became available starting in 1999. Details about the monitoring network and statewide maps showing monitor distributions can be found in the online supplement. Pollutant surfaces of monthly average ambient concentrations were developed with inverse distance-weighted (IDW) interpolation, using the Spatial Analyst extension of ArcVIEW version 9.0 (ESRI, Redlands, CA).

Most California air pollution monitoring stations are assigned spatial scale designations (e.g., neighborhood, regional) defining a radial range for which the monitors are intended to provide representative data. We used this information to include women whose residences were within the representative range of a given pollutant monitor, and exclude those living outside the representative range of any monitor for that pollutant. The representative ranges for neighborhood monitors were designated as 20 km for ozone and $PM_{2.5}$, 10 km for $PM_{10}$, 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 $PM_{2.5}$ and $PM_{10}$, and 5 km for the other gases.

Monthly individual exposure estimates were created via spatial linkage of the geocoded residential addresses to 250-m gridded IDW pollutant surfaces. All residences within a given grid in a given month were assigned the interpolated pollutant value for that grid for that period. At the time of each death or hospital admission, the average long-term pollution exposure for each individual remaining in the cohort was recalculated, allowing comparison between the index case's long-term average exposure and those of all others still in the risk set. Additional details about assignment of long-term air pollution exposure estimates can be found in the online supplement.

### Outcome Assessment and Calculation of Person-time at Risk

CTS records are linked annually to government mortality and hospitalization files. Mortality data were obtained from the California Department of Public Health, the U.S. Social Security Administration death master file, and the National Death Index. Causes of deaths occurring through 1998 were coded using the *International Classification of Diseases*, Ninth Revision (ICD-9); deaths from 1999 through 2005 were coded using ICD-10.

We examined incident myocardial infarction (MI) and stroke among women who reported no prior history of either on the baseline questionnaire. Because initial episodes of MI or stroke are often fatal, we created variables combining hospitalizations and deaths for these outcomes. Principal hospitalization admission diagnoses of MI and stroke were ascertained from cohort inception through December 31, 2005, using probabilistic record linkage with hospital discharge data maintained by the California Office of Statewide Planning and Development (OSHPD) (11). ICD codes used to classify deaths and hospitalizations are presented in the online supplement.

We calculated person-days at risk as the number of days between June 1, 1997, for analyses of all pollutants except $PM_{2.5}$ (or, for analyses involving $PM_{2.5}$, March 1, 2000) and (*1*) the date of death (for mortality analyses), (*2*) the date of hospitalization or death (for MI and stroke incidence analyses), (*3*) the end of the follow-up period (December 31, 2005), or (*4*) the date of first relocation to a non-California address for women who moved out of state for at least 4 months before any of events 1–3 occurred. In incidence analyses, hospital admission for either MI or stroke resulting in death was counted as a single event.

### Covariates

We selected individual-level predictor variables based on risk factors identified in previous observational studies of cardiovascular disease, especially investigations of air pollution and cardiopulmonary mortality (1, 4, 6). Distributions by category are shown in Table 1. The online supplement provides additional information on variables for age, race, smoking status and pack-years, second-hand smoke exposure, body mass index, lifetime physical activity, calories, fat and fiber intake, alcohol consumption, marital status, menopausal status, menopausal hormone therapy use, use of hypertension medication and aspirin, and family history of MI and stroke. Data on all individual-level variables except marital status (which was assessed in the 2000 questionnaire) were obtained from the baseline questionnaire; we did not have repeated measures that would allow us to adjust for covariate changes over time.

Ecological variables at the census block group level were derived from the 2000 Census data to consider "contextual" neighborhood confounding, and included ethnic/racial composition, income, unemployment, population size, income inequality, and education within block groups.

### Statistical Methods

Of the 124,614 women living in California at baseline, we excluded those who had no available pollutant data; had less than 12 months of exposure data or were younger than age 30 years at the start of follow-up; had consented to participate only in studies of breast cancer; moved out of California or died before the beginning of follow-up; or were missing information for continuous variables used in the regression models. The numbers excluded were different for $PM_{2.5}$ versus the other pollutants because of the difference in follow-up start times: details are provided in Table E3 in the online supplement. These exclusions left 101,784 women in the analytic cohort for the mortality analyses of all pollutants other than $PM_{2.5}$ and 73,489 for the $PM_{2.5}$ analyses. Women included in analyses of incident MI ($n = 100{,}340$ for all pollutants except $PM_{2.5}$, and 72,403 for $PM_{2.5}$) and stroke ($n = 100{,}223$ for all pollutants except $PM_{2.5}$, and 72,230 for $PM_{2.5}$) were further restricted to those who reported no history of these events on the baseline questionnaire and had no prior outcome-specific occurrence in the OSHPD database.

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. Per-subject exposure in the regression models was represented as a time-dependent function $x(m)$, where the value at month $m$ was calculated as the average of available monthly pollutant levels between the exposure start month and $m$, inclusive. To ensure that we would be examining primarily associations with chronic rather than acute or subacute exposures, we limited outcome follow-up to women for whom we had at least 12 months of exposure data. Thus, whereas exposure metrics for ozone, $NO_2$, NOx, CO, $SO_2$, and $PM_{10}$ began in June 1996, outcome follow-up started in June 1997; both continued until December 31, 2005. For $PM_{2.5}$, the start dates for exposure and cohort follow-up were March 1999 and March 2000, respectively. HRs and 95% CIs were scaled to interquartile ranges (IQRs), based on pollutant distributions for women during the study period. For purposes of comparison with other studies of particulate matter, we scaled HRs for $PM_{2.5}$ and $PM_{10}$ to increments of 10 $\mu g/m^3$.

We conducted several sensitivity and stratified analyses. First, we analyzed associations with ozone measured only in the third quarter (summer) rather than year-round. Additional analyses involved restricting the $PM_{2.5}$ analysis to women who were postmenopausal at baseline, never-smokers, or never-movers. To be able to better compare our results with those of other studies in which $PM_{2.5}$ exposures were assigned before follow-up, we conducted analyses in which the participants' exposures were estimated only from the year prior to outcome follow-up (i.e., $PM_{2.5}$ averages from March 1999 through February

**TABLE 1. PERCENTAGE DISTRIBUTIONS OF COVARIATES AMONG ELIGIBLE PARTICIPANTS IN THE CALIFORNIA TEACHERS STUDY RESIDING IN CALIFORNIA AT COHORT INCEPTION IN 1995***

| | Percent |
|---|---|
| Age, yr | |
| 20–29 | 4 |
| 30–39 | 13 |
| 40–49 | 26 |
| 50–59 | 24 |
| 60–69 | 17 |
| 70–79 | 11 |
| ⩾80 | 5 |
| Race/ethnicity | |
| Non-Hispanic white | 87 |
| Other | 11 |
| Unknown | 2 |
| Smoking status | |
| Never-smoker | 67 |
| Current smoker | 5 |
| Former smoker | 28 |
| Total smoking pack-years among current and former smokers, mean | 15.3 |
| Body mass index, kg/m$^2$ | |
| <20.0 (underweight) | 10 |
| 20.0–24.9 (normal weight) | 48 |
| 25.0–29.9 (overweight) | 24 |
| 30.0–39.9 (obese) | 12 |
| ⩾40.0 (extremely obese) | 2 |
| Unknown | 4 |
| Marital status† | |
| Married/living with partner | 44 |
| Not married | 21 |
| Unknown | 35 |
| Alcohol consumption | |
| No alcohol consumption | 33 |
| Beer (yes) | 24 |
| Wine (yes) | 57 |
| Liquor (yes) | 30 |
| Unknown | 6 |
| Second-hand smoke (SHS) exposure at home (during both childhood and adulthood) | |
| No SHS exposure | 45 |
| SHS exposure | 49 |
| Unknown | 6 |
| Dietary fat, g/d | |
| <41.64 | 30 |
| 41.64–63.00 | 31 |
| ⩾63.01 | 30 |
| Unknown | 9 |
| Dietary fiber, g/d | |
| <11.81 | 30 |
| 11.81–17.04 | 31 |
| ⩾17.05 | 30 |
| Unknown | 9 |
| Dietary calories, kcal/d | |
| <1,300.17 | 30 |
| 1,300.17–1,749.30 | 31 |
| ⩾1,749.31 | 30 |
| Unknown | 9 |
| Physical activity, h/wk | |
| <1.99 (low) | 32 |
| 1.99–4.93 (medium) | 34 |
| ⩾4.94 (high) | 33 |
| Unknown | 1 |
| Menopausal status/hormone therapy (HT) use | |
| Premenopausal | 38 |
| Peri/postmenopausal and no HT use | 13 |
| Peri/postmenopausal and past HT use | 8 |
| Peri/postmenopausal and current use of estrogen | 13 |
| Peri/postmenopausal and current use of estrogen plus progestin | 14 |
| Unknown menopausal status or HT use | 14 |
| Parental history of myocardial infarction | |
| No | 67 |
| Yes | 33 |
| Parental history of stroke | |
| No | 79 |
| Yes | 21 |
| Hypertension medication use | |
| No regular use | 80 |
| 1–3 d/wk (intermittent) | 1 |
| 4–7 d/wk (regular) | 15 |
| Unknown | 4 |
| Aspirin use | |
| No regular use | 76 |
| 1–3 d/wk (intermittent) | 10 |
| 4–7 d/wk (regular) | 11 |
| Unknown | 3 |

*n = 124,614.
† Determined on the basis of data collected in the 2000 survey.

2000); unlike all the other analyses, these did not involve time-dependent exposure recalculations for the cohort at the time of each event. We also examined whether individuals who had diabetes or were overweight or obese at baseline were at greater risk. For outcomes with elevated HRs for more than one pollutant, we ran two-pollutant models. Last, we reran the incidence analyses using only OSHPD hospitalization data.

We conducted proportional hazards analyses with SAS software (SAS Institute, Inc., version 9.3, Cary, NC).

## RESULTS

The median durations of follow-up were 8.3 years for $PM_{10}$ and the gases, and 5.6 years for $PM_{2.5}$. Table 1 presents the covariate distributions for the members of the study population. Participants were predominantly non-Hispanic white (87%); two-thirds were never-smokers, with 5% current smokers. Most were postmenopausal at baseline. Table 2 provides descriptive statistics for the exposure data used in the study. Of the 124,614 CTS participants who had a California address at cohort inception, there were 77,390 never-movers, whereas 47,224 (38%) moved at least once, 15,824 (13%) moved at least twice, and 4,818 (4%) moved at least three times. Exposure estimates for those who moved within California include monthly estimates at each residence. Aggregating over all of the individual estimates, the mean concentration of $PM_{2.5}$ for the period March 1999 through 2005 was 15.6 $\mu g/m^3$, with an IQR of 8.0 $\mu g/m^3$.

Online supplement Tables E5a and E5b summarize interpollutant correlations during the study period. $PM_{2.5}$ was strongly

**TABLE 2. DESCRIPTIVE STATISTICS FOR AIR POLLUTANTS USED TO ESTIMATE LONG-TERM EXPOSURES AT PARTICIPANTS' RESIDENCES IN THE CALIFORNIA TEACHERS STUDY, JUNE 1996–DECEMBER 2005***

| Pollutant | Units | Mean (SD) | IQR | Min–Max |
|---|---|---|---|---|
| Ozone | ppb | 48.11 (8.72) | 11.02 | 25.39–82.63 |
| $PM_{2.5}$* | $\mu g/m^3$ | 15.64 (4.48) | 8.02 | 3.11–28.35 |
| $PM_{10}$ | $\mu g/m^3$ | 29.21 (9.73) | 15.05 | 9.19–82.64 |
| $NO_2$ | ppb | 33.59 (9.63) | 10.29 | 5.24–67.19 |
| NOx | ppb | 95.60 (34.5) | 48.31 | 7.31–221.4 |
| $SO_2$ | ppb | 1.72 (0.62) | 0.43 | 0.21–3.65 |
| CO | ppm | 1.05 (0.36) | 0.49 | 0.28–3.34 |

*Definition of abbreviations*: IQR = interquartile range; NOx = nitrogen oxides; $PM_{2.5}$ = particulate matter less than 2.5 $\mu$m in aerodynamic diameter; $PM_{10}$ = particulate matter less than 10 $\mu$m in aerodynamic diameter.
* $PM_{2.5}$ data were limited to the period March 1999–December 2005.

**TABLE 3. HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MYOCARDIAL INFARCTION AND STROKE, PER 10-μg/m³ INCREMENT OF $PM_{2.5}$ (1999–2005) AND $PM_{10}$ (1996–2005) FOR THE CALIFORNIA TEACHERS STUDY COHORT**

| | $PM_{2.5}$ | | | $PM_{10}$ | | |
|---|---|---|---|---|---|---|
| Outcome | No. of Events | n | HR* (95% CI) | No. of 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) |
| 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) |

*Definition of abbreviations*: CI = confidence interval; HR = hazard ratio; IHD = ischemic heart disease; MI = myocardial infarction; NM = nonmalignant; $PM_{2.5}$ = particulate matter less than 2.5 μm in aerodynamic diameter.

*Models adjusted for age, race, 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 therapy use, family history of MI or stroke, blood pressure medication, and aspirin use, and for contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period for $PM_{2.5}$, March 1999–December 2005; cohort follow-up period, March 2000–December 2005. Exposure period for $PM_{10}$, June 1996–December 2005; cohort follow-up period, June 1997–December 2005.

correlated with all of the other pollutants ($r = 0.52$–$0.91$) except $SO_2$. Ozone was correlated with both particulate metrics and with $NO_2$, but only weakly or not at all with the other gases.

Table 3 summarizes the estimated HRs for incident MI and stroke, as well as for mortality from all causes, and from cardiovascular, cerebrovascular, and nonmalignant respiratory diseases, ischemic heart disease (IHD), and lung cancer, per 10-μg/m³ increment of the long-term average concentrations of $PM_{2.5}$ and $PM_{10}$. Although most HR point estimates for $PM_{2.5}$ 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 $PM_{10}$ were, with the exception of incident MI, uniformly lower than those for $PM_{2.5}$. The outcomes with the strongest association with $PM_{10}$ were IHD mortality (HR, 1.06; 95% CI, 0.99–1.14) and incident stroke (HR, 1.06; 95% CI, 1.00–1.13).

Table 4 summarizes the results for the gaseous pollutants, using the IQR of exposure for 1996–2005 for the full cohort. Fewer outcome events were included in the analyses of $NO_2$, NOx, $SO_2$, and CO because (*1*) the representative spatial ranges designated for these pollutant monitors were much smaller than for the ozone, $PM_{2.5}$, and $PM_{10}$ monitors, which meant that fewer participants' residences were included, and (*2*) there were substantially fewer monitors for these pollutants than for $PM_{10}$ and ozone. The associations identified were primarily with IHD mortality, although ozone was also associated with nonmalignant respiratory disease (HR, 1.07; 95% CI, 0.97–1.19) and $SO_2$ with all-cause mortality (HR, 1.11; 95% CI, 1.00–1.23), based on 257 deaths. 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; $P = 0.10$). When the ozone analysis was restricted to summers only, however, the HR for IHD mortality was significantly elevated (HR, 1.09; 95% CI, 1.01–1.19) (Table 5).

In the $PM_{2.5}$ analysis restricted to women who were postmenopausal at baseline, the results were similar to those for the cohort as a whole, except that the HR for stroke incidence increased significantly (HR, 1.19; 95% CI, 1.02, 1.38, based on 907 events) (*see* Table E6). In the $PM_{2.5}$ analysis for never-movers, the results were generally similar in direction and magnitude, but probably because they were based on far fewer events none of the HRs was significant (Table E7). For the $PM_{2.5}$ analysis in which the exposure was assigned only on the basis of the average estimated exposure in the year before follow-up, the results were similar to those using the time-dependent models (Table 6). 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 (Table E8). Among the findings of interest among never-smokers, $PM_{10}$ was associated with nonmalignant respiratory disease mortality (HR, 1.15; 95% CI, 1.00–1.33), $PM_{2.5}$ was more strongly associated with cardiovascular mortality (HR, 1.13; 95% CI, 0.98–1.29, as well as with IHD mortality: HR, 1.28; 95% CI, 1.05–1.57), and summer-only ozone with IHD mortality (HR, 1.12; 95% CI, 1.01–1.23). In addition, long-term exposures to NOx continued to be associated with IHD mortality (HR, 1.40; 95% CI, 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 (body mass index $\geq$ 25.0 kg/m²) at baseline) were at greater pollutant-related risk than those who were not. Similarly, subjects with diabetes were not at increased risk of any of the pollutant-related outcomes examined compared with nondiabetics; however, these analyses in general involved relatively few events (<200) among participants with diabetes.

In a two-pollutant model including year-round ozone and $PM_{2.5}$, the HR for IHD mortality in association with $PM_{2.5}$ remained elevated (HR, 1.27; 95% CI, 1.03–1.56), whereas that for ozone declined to a null result (HR, 0.99; 95% CI, 0.88–1.11) (Table E10). Results were similar using $PM_{2.5}$ and third-quarter ozone. The HR for IHD mortality in association with ozone likewise decreased to nonsignificance in a two-pollutant model with $PM_{10}$. Hospitalizations accounted for the majority of events in the incidence analyses for MI (933/1,317 or 71%) and stroke (1,396/1,875 or 74%). When these analyses were restricted to hospitalizations only, there were no significant associations of any pollutants with incident MI. With respect to incident stroke, HR point estimates were greater than unity for all pollutants except CO; however, only that for $PM_{10}$ was significantly increased (HR, 1.09; 95% CI, 1.01–1.17, per 10-μg/m³ increment).

## DISCUSSION

In this study we found associations between IHD mortality and $PM_{2.5}$, $PM_{10}$, NOx, and ozone. The associations with $PM_{2.5}$ and NOx were modestly greater among never-smokers, as were

**TABLE 4. HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MYOCARDIAL INFARCTION 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 | No. of 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) |
| | 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) |
| | 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) |
| $NO_2$ | 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) |
| | 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) |
| | 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) |
| $SO_2$ | 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) |
| | 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) |

*Definition of abbreviations*: CI = confidence interval; HR = hazard ratio; IHD = ischemic heart disease; IQR = interquartile range; MI = myocardial infarction; NM = nonmalignant; NOx = nitrogen oxides.

Units of analysis: ppb for ozone, $NO_2$, NOx, and $SO_2$; ppm for CO.

*Models adjusted for age, race, 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 therapy use, family history of MI or stroke, blood pressure medication, and aspirin use, and for 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.

associations with cardiovascular disease mortality as a whole. Incident stroke (combining fatal and nonfatal events) was associated with $PM_{10}$ and with $PM_{2.5}$, particularly among women who were postmenopausal at baseline, whereas analyses focusing only on nonfatal incident stroke (i.e., hospitalizations only) identified associations with multiple pollutants, especially $PM_{10}$.

This investigation represents one of the largest prospective air pollution studies undertaken to date (1, 3, 5, 12). Unlike most prior studies, we developed individualized estimates of long-term exposure to $PM_{2.5}$ 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), in combination with previously collected data on household second-hand smoke exposure, 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., American Cancer Society Cancer Prevention Study [ACS CPS] II, 22% active smokers; Harvard Six Cities [HSC] study, 33–40% active smokers). 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 design and population characteristics included an individualized exposure assessment and diminished the potential for confounding and effect modification by nonpollutant variables.

Several other long-term air pollution studies have found associations of $PM_{2.5}$ with increased risk of all-cause mortality, and greater risks with either cardiopulmonary or cardiovascular disease. We found no associations with all-cause mortality in any analysis except for NOx and $SO_2$, and these results were based on few events. Although our results are different from those of several other U.S. cohorts, they are generally consistent with the Dutch study by Beelen and colleagues, who reported no significant increases in all-cause or cardiovascular mortality associated with measured $PM_{2.5}$ (12). However, those investigators reported

**TABLE 5. HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MYOCARDIAL INFARCTION AND STROKE IN THE CALIFORNIA TEACHERS STUDY COHORT, BASED ON SUMMER OZONE INTERQUARTILE RANGES (1996–2005)**

| Outcome | No. of Events | n | IQR (ppb) | 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) |
| 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) |

*Definition of abbreviations*: CI = confidence interval; HR = hazard ratio; IHD = ischemic heart disease; IQR = interquartile range; MI = myocardial infarction; NM = nonmalignant.

*Models adjusted for age, race, 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 therapy use, family history of MI or stroke, blood pressure medication, and aspirin use, and for 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.

**TABLE 6. HAZARD RATIOS FOR MORTALITY AND FOR INCIDENT MYOCARDIAL INFARCTION AND STROKE, PER 10-$\mu g/m^3$ INCREMENT OF $PM_{2.5}$ FOR THE CALIFORNIA TEACHERS STUDY COHORT BASED ON EXPOSURE DATA FROM 1999–2000**

| Outcome | No. of Events | n | HR* (95% CI) |
|---|---|---|---|
| All-cause mortality | 4,147 | 73,489 | 1.02 (0.95, 1.09) |
| Cardiovascular mortality | 1,630 | 73,489 | 1.07 (0.96, 1.19) |
| NM respiratory mortality | 404 | 73,489 | 1.16 (0.94, 1.44) |
| Lung cancer mortality | 234 | 73,489 | 0.98 (0.73, 1.31) |
| IHD mortality | 773 | 73,489 | 1.17 (1.00, 1.37) |
| Cerebrovascular mortality | 382 | 73,489 | 1.17 (0.93, 1.46) |
| MI incidence | 722 | 72,403 | 0.99 (0.84, 1.17) |
| Stroke incidence | 969 | 72,230 | 1.15 (1.00, 1.33) |

*Definition of abbreviations*: CI = confidence interval; HR = hazard ratio; IHD = ischemic heart disease; MI = myocardial infarction; NM = nonmalignant; $PM_{2.5}$ = particulate matter less than 2.5 $\mu$m in aerodynamic diameter.

*Models adjusted for age, race, 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 therapy use, family history of MI or stroke, blood pressure medication, and aspirin use, and for contextual variables (income, income inequality, education, population size, racial composition, and unemployment). Exposure period, March 1999–February 2000; cohort follow-up period, March 2000–December 2005.

slightly increased risks for these outcomes in relation to traffic intensity on the nearest road. 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 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 $PM_{2.5}$ exposure for IHD mortality that are of the same magnitude as those reported here (13).

Several prior California-specific studies of air pollutant exposure and mortality have produced mixed results. Enstrom found essentially no relationship between exposure to fine PM and all-cause mortality among elderly California participants in the ACS CPS I from 1973 to 2002, although the relative risk (RR) for the 20,210 women was slightly elevated (RR, 1.027; 95% CI, 1.005–1.050) (14). Chen and colleagues reported in 2005 that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with an RR of 1.42 (95% CI, 1.11–1.81) for fatal CHD in a cohort of 2,090 women participating in the Adventist Health Study (15). In an analysis of the ACS CPS II data for 22,905 Los Angeles residents, Jerrett and colleagues (6) reported that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with HRs of 1.11 (95% CI, 0.99–1.25) for all-cause and 1.25 (95% CI, 0.99–1.59) for IHD mortality, using a model with 44 individual-level and parsimonious contextual covariates. In a more recent analysis of these data using land use regression, these estimates were only slightly greater (13).

Although we found no relationship of $PM_{2.5}$ with all-cause mortality, the association between a 10-$\mu g/m^3$ increase in $PM_{2.5}$ and increased risk of fatal IHD (HR, 1.20; 95% CI, 1.02–1.41) was of similar magnitude to that reported by Jerrett and colleagues (6). In an analysis of the national ACS CPS II cohort from 1983 to 1998, average $PM_{2.5}$ was also associated with IHD mortality (HR, 1.18; 95% CI, 1.14–1.23) (3). Other, more recent studies of PM and mortality from CHD in women have produced higher risk estimates. For instance, in the WHI, the risk of CHD death associated with a 10-$\mu g/m^3$ increase in estimated $PM_{2.5}$ was more than doubled (HR, 2.21; 95% CI, 1.17–4.16) (5). Using modeled $PM_{2.5}$ data to estimate 10-year exposures to participants in the Nurses' Health Study, Puett and colleagues reported a similarly elevated risk of death from CHD (HR, 2.02; 95% CI, 1.07–1.54), although 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) (8). 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 main $PM_{2.5}$ analysis, far more than in these other recent studies); methods of estimating exposure; particle composition and relative toxicity; and measurement and control of potential confounders. When exposures were assigned using only the average $PM_{2.5}$ concentrations estimated for the participants during the year preceding follow-up, our results remained consistent with those from the time-dependent exposure models (Table 6).

Because of 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 $PM_{2.5}$, $PM_{10}$, and ozone. Moreover, these gases are subject to considerable intraurban variability, depending largely on local traffic patterns; this variability may have been underestimated by IDW interpolation. $NO_2$ levels may vary significantly over a distance of a few hundred meters (16). Therefore, our NOx results should be interpreted with caution. Last, 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.

Only one prospective investigation of long-term exposure to $PM_{2.5}$ has reported associations with incident MI and stroke (5). The investigators followed nearly 66,000 participants in the WHI observational study without a history of cardiovascular disease for a median of 6 years, using as the exposure metric a 1-year average of $PM_{2.5}$ 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 $PM_{2.5}$ (5). Our results are similar in that we found associations of $PM_{2.5}$ and $PM_{10}$ with stroke, but not MI. In our incidence analysis that included only hospital admissions, stroke was also positively associated with both $PM_{2.5}$ (HR, 1.10; 95% CI, 0.93–1.31) and $PM_{10}$ (HR, 1.09; 95% CI, 1.01–1.17).

Puett and colleagues modeled monthly $PM_{2.5}$ 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 to 2002 (8). They found significantly elevated HRs for all-cause mortality, but the risk of incident CHD (including nonfatal MI) was not significantly elevated overall (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 and colleagues with respect to the lack of association with incident MI and CHD. Although $PM_{10}$ and $PM_{2.5}$ were highly correlated in our data set, $PM_{2.5}$ showed somewhat stronger associations with IHD mortality and stroke. This may be due in part to the likelihood of greater exposure misclassification for $PM_{10}$ than for $PM_{2.5}$, as the former exhibits greater spatial heterogeneity.

Using year-round and summer ozone levels, we found positive associations with IHD mortality, but not overall cardiovascular mortality. In two-pollutant models, however, there was no association of IHD mortality with ozone, whereas the HRs for $PM_{2.5}$ and $PM_{10}$ remained elevated, suggesting that the results for ozone were most likely explicable by its positive correlation with particulate matter. 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 (1, 4, 6). However, Jerrett and colleagues 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 $PM_{2.5}$ (7).

Jerrett and colleagues also reported associations of respiratory mortality with long-term ozone exposure nationwide, but when they stratified on geographic area, they found no association of ozone with respiratory mortality in Southern California (7). Both measures of ozone in our study suggested associations with nonmalignant respiratory mortality (Tables 4 and 5, and Table E10), which were of comparable magnitude to the ozone-associated relative risk for nonmalignant respiratory mortality among women in the Adventist Health Study (17). Our results also suggest associations between both particulate matter metrics and nonmalignant respiratory disease mortality, especially among nonsmokers, although the latter HRs were based on relatively few events (203 deaths for $PM_{10}$ and 191 for $PM_{2.5}$; Table E8). Nonetheless, the estimated HRs were of comparable magnitude to that identified for deaths due to lower respiratory infections in the ACS CPS II analysis among never-smokers (HR, 1.20; 95% CI, 1.02–1.41) (3).

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. Although some of these participants may have experienced silent events, 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 such 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 (18–21). 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 postmenopausal women) far exceed those reported in time-series investigations (e.g., 3% for stroke mortality [21]). 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 $PM_{2.5}$ (6-mo study average, 15 $\mu g/m^3$) was associated with enhanced progression of disease, increased vasomotor tone, and vascular inflammation (22). 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 $PM_{2.5}$ (23) and, more recently, in pooled data from five clinical studies conducted in the Los Angeles basin (24). Thus, although 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 (25).

This study provides evidence that long-term exposures to $PM_{2.5}$, $PM_{10}$, and NOx were associated with increased risks for IHD mortality. The increased risk of IHD mortality associated with long-term ozone exposure was most likely explicable by its correlation with particulate matter, whereas that for NOx was based on relatively small numbers of observations. These data also suggest associations of long-term ozone and particulate matter exposure with mortality from nonmalignant respiratory disease. That both measures of PM were associated with incident stroke provides support for the notion that these pollutants may play an etiological role in the development of circulatory disease.

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