The Association between Fatal Coronary Heart Disease and Ambient Particulate Air Pollution: Are Females at Greater Risk?

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The purpose of this study was to assess the effect of long-term ambient particulate matter (PM) on risk of fatal coronary heart disease (CHD). A cohort of 3,239 nonsmoking, non-Hispanic white adults was followed for 22 years. Monthly concentrations of ambient air pollutants were obtained from monitoring stations [PM < 10 µm in aerodynamic diameter (PM10), ozone, sulfur dioxide, nitrogen dioxide] or airport visibility data [PM < 2.5 µm in aerodynamic diameter (PM2.5)] and interpolated to ZIP code centroids of work and residence locations. All participants had completed a detailed lifestyle questionnaire at baseline (1976), and follow-up information on environmental tobacco smoke and other personal sources of air pollution were available from four subsequent questionnaires from 1977 through 2000. Persons with prevalent CHD, stroke, or diabetes at baseline (1976) were excluded, and analyses were controlled for a number of potential confounders, including lifestyle. In females, the relative risk (RR) for fatal CHD with each 10-µg/m3 increase in PM2.5 was 1.42 (95% confidence interval (CI), 1.06–1.90) in the single-pollutant model and 2.00 (95% CI, 1.51–2.64) in the two-pollutant model with O3. Corresponding RRs for a 10-µg/m3 increase in PM10,2.5 and PM10 were 1.62 and 1.45, respectively, in all females and 1.85 and 1.52 in postmenopausal females. No associations were found in males. A positive association with fatal CHD was found with all three PM fractions in females but not in males. The risk estimates were strengthened when adjusting for gaseous pollutants, especially O3, and were highest for PM2.5. These findings could have great implications for policy regulations.

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Since the early reports of increased deaths from cardiopulmonary disease (CPD) after serious air pollution episodes (Firket 1931; Logan 1953), studies both within the United States and abroad have found similar short-term effects of air pollution (Dominici et al. 2003; Samet et al. 2000; Zanobetti et al. 2003).

Studies have also found increased risk of CPD, noncancer respiratory, and respiratory cancer deaths with chronic exposure to ambient particulate matter (PM) (Abbey et al. 1999; Dockery et al. 1993; McDonnell et al. 2000; Pope et al. 1995, 2002, 2004a), black smoke (NOx) (Dockery et al. 2002), and nitrogen oxides (Dockery et al. 2002; Nafstad et al. 2004). Four main prospective studies have been conducted in the United States to assess long-term health effects of ambient air pollution in adults [the Six Cities Study, the American Cancer Society (ACS) study, the Adventist Health Study on the Health Effects of Smog (AHSMOG), and the national cohort of male U.S. veterans]. Associations with fine particulates [PM < 2.5 µm in aerodynamic diameter (PM2.5)] have been found for all-cause mortality, CPD mortality, and respiratory/lung cancer mortality in the ACS, Six Cities, and AHSMOG studies and with mortality attributable to ischemic heart disease (IHD), dysrhythmias, heart failure, and cardiac arrest in the ACS study. AHSMOG (Abbey et al. 1999) has also shown positive associations, although not always significant, between PM < 10 µm in aerodynamic diameter (PM10), all-cause mortality and CPD mortality in males but not in females. For fatal lung cancer and any mention of nonmalignant respiratory disease, a positive association was found with PM10 in both sexes. The national cohort of male U.S. veterans, where all subjects were hypertensive at baseline, found no increased mortality with increasing levels of fine particulates (Lipfert et al. 2000).

From Europe, Hoek et al. (2002) reported increased risk of CPD mortality and all-cause mortality with increased concentrations of black smoke and nitrogen dioxide, and Nafstad et al. (2004) found increased risk of noncancer respiratory mortality and CPD mortality with increasing levels of NOx.

Several studies on short-term effects have found that ambient PM increases cardiac arrhythmia (Peters et al. 2000), decreases heart rate variability (Pope et al. 2004b), increases the inflammatory response measured by C-reactive protein (CRP) (Riediker et al. 2004), and increases blood viscosity (Peters et al. 1997) as well as other blood markers (e.g., hemoglobin, fibrinogen, platelet counts, white cell counts) (Riediker et al. 2004). These observed effects would provide a mechanism by which chronic exposure to ambient air pollution is associated with risk of coronary heart disease (CHD).

This study reports on the risk of fatal CHD associated with long-term ambient air pollution in AHSMOG.

Materials and Methods

Study population. AHSMOG began in April 1977 by enrolling 6,338 participants from the Adventist Health Study (AHS) (n = 34,198), a large cohort study of the relationship between lifestyle and risk of chronic disease (Beeson et al. 1989). To be included in AHSMOG, subjects must be nonsmoking, non-Hispanic whites ≥ 25 years of age at baseline and must have lived ≥ 10 years within 5 miles of their 1976 neighborhood. All subjects satisfying these criteria were selected from three large metropolitan areas in California: San Francisco, South Coast (i.e., Los Angeles and eastward), and San Diego air basins. In addition, a 13% random sample of 862 AHS subjects was selected from the rest of California assuring large variation and wide ranges in concentrations of different ambient air pollutants.

As part of their enrollment in the AHS in 1976, all participants completed a comprehensive questionnaire that included questions on education, anthropometric data, smoking history, dietary habits, exercise patterns, and previous physician-diagnosed chronic diseases (Beeson et al. 1989). Monthly residence and work location histories were obtained for each subject for the period January 1966 through December 1998, or until date of death or date of last contact, by using mailed questionnaires (1977, 1987, 1992, 2000), tracing by telephone, and interviewing of surrogates (for deceased subjects). Only 29 (< 0.01%) persons were lost to follow-up with respect to vital status, and these were censored at date of last contact for inclusion in risk sets. The follow-up questionnaires contained standardized questions on respiratory symptoms (American Thoracic Society 1995) and questions to determine the status of the 42 health variables.

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ascertain lifestyle and housing characteristics pertinent to relative exposure to ambient air pollutants, as well as occupational exposures to dust and fumes and indoor sources of air pollution, including environmental tobacco smoke (ETS).

Several air pollutants were estimated for study participants using the statewide network of monitoring stations maintained by the California Air Resource Board (CARB) (Abbey et al. 1991). Because estimated PM$_{2.5}$ measures were not available on a statewide basis during follow-up, only the 3,769 (2,422 females and 1,347 males) belonging to the airport subcohort (those who lived within an airshed adjacent to one of nine California airports with available visibility measures: Alameda, Bakersfield, Fresno, Long Beach, Los Angeles, Ontario, Sacramento, San Jose, and San Diego) were included in this study. Of these, 530 ($n = 332$ females, $n = 198$ males) were excluded because of a history of CHD, stroke, or diabetes at baseline, leaving 3,239 subjects for analyses.

**Estimation of ambient air pollution concentrations.** Estimates of monthly ambient concentrations of PM$_{10}$, ozone, sulfur dioxide, and NO$_2$ were formed for study participants for 1973–1998 using fixed-site monitoring stations maintained by CARB. The detailed methods for estimating ambient air pollutants for study participants are described elsewhere (Abbey et al. 1991, 1995a). Briefly, monthly indices of ambient air pollution concentrations at 348 monitoring stations throughout California were interpolated to geographic ZIP code centroids according to home and work location histories of study participants. These were cumulated and then averaged over time. Interpolations were restricted to ZIP code centroids within 50 km of a monitoring station and were not allowed to cross barriers to airflow or other topographic obstructions $> 250$ m above the surrounding terrain. Concentrations of PM$_{10}$ before 1987 were estimated using site- and season-specific regressions based on total suspended particles (TSPs) (Abbey et al. 1995a). Since 1987, directly monitored PM$_{10}$ has been used.

Daily estimates of ambient PM$_{2.5}$ concentration were obtained for 11 airsheds from daily measures of visibility collected at the nine California airports for the years 1973–1998 using regression equations relating PM$_{2.5}$ and visibility. Because of wind patterns, Ontario provided three separate airsheds (East, West, Central). Detailed methods for PM$_{2.5}$ estimation have been described previously (Abbey et al. 1995b). Individual monthly average PM$_{2.5}$ concentrations were calculated as the mean of the daily ambient PM$_{2.5}$ estimates for the airshed in which the participant resided. Any month with PM$_{2.5}$ estimates for $> 75\%$ of the days was considered to have valid data.

**Ascertainment of deaths.** Fatal CHD, defined by codes 410–414 of the International Classification of Diseases, 9th Revision (ICD-9) (World Health Organization 1977) as either “definite fatal myocardial infarction” or “other definite fatal CHD,” as underlying or immediate cause of death was used to assess fatal CHD. Deaths were ascertained through 1998 using record linkage with both the California death certificate files and the National Death Index (Centers for Disease Control and Prevention, National Center for Health Statistics, Atlanta, GA, USA). In addition, our tracing procedures, which included church records, were used (Beeson et al. 1989). Thus, among the airport subcohort free of CHD, stroke, and diabetes at baseline, we identified 1,054 total deaths during follow-up. Death certificates were obtained, and a state-certified nosologist, blinded to the exposure status, coded each death certificate according to the ICD-9 codes.

**Statistical analysis.** Sex-specific comparisons of baseline descriptive information between CHD mortality cases and noncases were made using the Student $t$-test or chi-square test. Time-dependent Cox proportional-hazards regression modeling was used to study associations between pollutants (PM$_{2.5}$, PM$_{10}$, O$_3$, SO$_2$, and NO$_2$) and CHD mortality with attained age as the time variable (Greenland 1989). This was further augmented by adding the sandwich variance estimate (Lin 1994) to adjust for correlated observations within each airshed. All 11 airsheds around the nine airports were included in the model. We also included the airports as dummy variables stratified with the Cox model. Rate ratios were calculated for an increment of $10 \mu g/m^3$ for each of the particular pollutants and 10 ppb for each of gaseous pollutants, except SO$_2$, which was calculated for an increment of 1 ppb. Because measures for most of the pollutants were available only from 1973, we had 4-year monthly averages for these pollutants at baseline in 1977. To standardize the exposure window preceding events, we therefore selected 4-year average as our moving time period of exposure, but excluded the last month before the event to avoid measuring short-term effects. Participants who did not die were censored at end of follow-up, or at time of last contact if they were lost to follow-up (394 females, 166 males). The different pollutants were entered into the model as continuous variables.

The basic multivariable model included past cigarette smoking, body mass index (BMI), years of education, and frequency of meat consumption. We added an interaction term between sex and pollutant to this basic model that was significant, and therefore, all analyses were sex specific. Additional candidate variables for inclusion in the final model were ETS (years lived or worked with a smoker), total physical activity at baseline, history of hypertension at baseline, exposure to dust/fumes at work, frequency of eating nuts (Fraser et al. 1992), number of glasses of water per day (Chan et al. 2002), time spent outdoors, and hormone replacement therapy (HRT) (female models). In addition, we found that the levels of PM pollutants used in this study have declined from 1973 to 1998 (Figure 1), and we therefore included calendar

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**Figure 1.** Mean concentration over time, 1973–1998: (A) PM$_{10}$ (B) PM$_{2.5}$ and (C) O$_3$. (A and B) Sexes combined: AHSMOG cohort (solid line), Ontario East air basin (dashed line), and San Diego air basin (dotted line). (C) AHSMOG cohort (solid line), mountain areas (dashed line), and coastal areas (dotted line). The $y$-axis scales differ among the three panels.
time as a candidate variable to adjust for possible changes in PM composition over time. All candidate variables were entered into the basic multivariable model one at a time to assess their impact on the main effect. Only calendar year changed the relative risks (RRs) > 10% (actually 16%) and was retained in the final model (Greenland 1989).

The proportional hazards assumption was checked by examining log (–log[survival]) curves versus the time (attained age) as well as the product term of each respective variable in the final model with the log of the time variable (Greenland 1989). Each of these interaction terms produced a p-value > 0.05 based on the Wald statistic, indicating that the proportional hazards assumptions were not seriously violated. This was supported further by visual inspection.

The same sex-specific, time-dependent multivariable Cox proportional-hazards regression models with and without the sandwich variance estimate, airport dummy variables, and stratified analysis were further used to study associations in two-pollutant models for particulates (PM2.5, PM10–2.5, or PM10) with each of the gases (O3, SO2, and NO2) and CHD mortality. We evaluated the interactions between two individual pollutants for inclusion in the final model based on whether they changed the RRs > 10%. None of the terms met this criterion (Greenland 1989). All analyses were repeated for postmenopausal females separately.

In addition, we repeated sex-specific analyses using cumulative monthly averages of each particulate pollutant from 1973 to censoring and also for each of the PM fractions using three levels of exposure (< 25, 25–38, > 38 µg/m3) rather than as a continuous variable. We used the SAS statistical package (version 9.1; SAS institute, Cary, NC) for all analyses.

Results

During 22-year follow-up (1977–1998), there were 155 CHD deaths in females and 95 among males, 23.7% of all deaths in this group. Those who died of CHD were older at baseline, had fewer years of education, and were more likely to have hypertension; a larger proportion of females were postmenopausal, and of these, fewer had used HRT (Table 1). A higher proportion of female noncases had lived or worked with a smoker (ETS), and noncases tended to drink more water than did cases. The mean concentrations and correlations of pollutants for this airport subcohort from 1973 through the month of censoring are provided in Table 2. Frequency histograms of the individual mean ambient concentrations of each of the PM fractions from 1973 to censoring month are given in Figure 2. Those in the lowest distribution of PM2.5 lived in the airsheds represented by the San Diego, San Jose, Sacramento, and Alameda airports; medium levels were found in Fresno, Los Angeles International, Bakersfield, Long Beach, Ontario West, and Ontario Central; and the highest distribution represents Ontario East. Figure 1 shows the secular trends in PM10, PM2.5, and O3 during the study for the Ontario East and San Diego air basins and for the study population as a whole.

Risk of fatal CHD. All results presented are from the time-dependent Cox model without and with the inclusion of the sandwich variance estimate. For females, in age-adjusted single-pollutant models, a positive but nonsignificant relationship was found between each of the three PM fractions and risk of fatal CHD (Table 3). This association became stronger in multivariate analyses, with PM2.5 having the highest RR of 1.42 [95% confidence interval (CI), 1.11–1.81] for each increment of 10 µg/m3.

In two-pollutant models with O3 (Table 4), the associations with each of the PM fractions became stronger and statistically significant both in age-adjusted and in multivariable-adjusted models, with the strongest relationship for PM2.5 (RR = 1.99; 95% CI, 1.37–2.88). NO2 did not change the associations between PM and fatal CHD, whereas SO2 strengthened the association some, but not to the same degree as did O3. Point estimates remained virtually unchanged both in single-pollutant and in multipollutant models when including the sandwich variance estimate. When airports were included as dummy variables or in stratified analyses, the risk estimates either remained the same or were strengthened. Limiting the analyses to postmenopausal females resulted in small increases in risk estimates.

Using cumulative monthly averages from 1973 to censoring instead of the 4-year moving average gave similar but somewhat weaker associations. Using PM2.5 estimates as tertiles (Figure 3 for females) showed that those exposed to levels > 38 µg/m3 were 2.3 times more likely to die of CHD than were those living in areas where concentrations were ≤ 25 µg/m3 (p-value for trend = 0.007). After adjusting for O3 in two-pollutant models, the risk estimates for PM2.5 increased to 2.03 and

### Table 1. Selected characteristics of study population at baseline.

| Characteristic                        | Male (n = 1,149) | Female (n = 2,090) |
|---------------------------------------|------------------|--------------------|
|                                       | Cases (n = 95)   | Noncases (n = 1,054) | Cases (n = 155) | Noncases (n = 1,935) |
| Age (years [mean ± SD])               | 66.7 ± 11.5      | 55.8 ± 12.9**      | 72.3 ± 8.9      | 56.6 ± 13.4**        |
| Years of education (mean ± SD)        | 13.5 ± 3.5       | 14.6 ± 3.2*        | 12.6 ± 2.8      | 13.4 ± 2.6**         |
| Never smokers                         | 51 (53.7)        | 717 (68.0)*        | 133 (85.6)      | 1,055 (85.5)         |
| BMI at or above median                | 46 (48.4)        | 477 (45.3)         | 76 (49.0)       | 875 (45.2)           |
| Meat consumption a,b                  |                 |                    |                 |                    |
| ≤ 1 week                              | 40 (42.1)        | 496 (47.1)         | 88 (56.8)       | 913 (47.2)           |
| 1 week                                | 50 (52.6)        | 516 (49.0)         | 57 (36.8)       | 917 (47.4)           |
| Total exercise                        |                 |                    |                 |                    |
| Low                                   | 25 (26.3)        | 344 (32.6)         | 67 (43.2)       | 937 (48.4)           |
| Moderate and high                    | 70 (73.7)        | 709 (67.3)         | 83 (56.8)       | 990 (51.2)           |
| History of hypertension               | 32 (33.7)        | 171 (16.2)**       | 70 (45.2)       | 444 (22.9)**         |
| ETS                                   | 57 (60.0)        | 619 (58.7)         | 77 (49.7)       | 1,208 (62.5)*        |
| Nuts a                                |                 |                    |                 |                    |
| ≤ 2/month                             | 29 (30.5)        | 331 (31.4)         | 60 (38.7)       | 684 (35.3)           |
| 1–4/week                              | 37 (38.9)        | 428 (40.6)         | 51 (32.9)       | 736 (38.0)           |
| ≥ 5/week                              | 23 (24.2)        | 255 (24.2)         | 33 (21.3)       | 397 (20.5)           |
| Water c                                |                 |                    |                 |                    |
| ≤ 2 glasses                           | 6 (6.3)          | 119 (11.3)         | 26 (16.8)       | 351 (18.1)           |
| 3–4 glasses                           | 44 (46.3)        | 369 (35.0)         | 49 (31.8)       | 708 (38.6)           |
| ≥ 5 glasses                           | 42 (44.2)        | 546 (51.8)         | 79 (51.0)       | 833 (43.0)           |
| Postmenopausal                        |                 |                    |                 |                    |
| HRT in postmenopausal females         | 138 (89.0)       | 1,323 (68.4)**     | 20 (14.5)       | 431 (32.6)**         |

Values are presented as % (or mean ± SD).

aSome columns do not add to 100% because of missing data. bSignificant at p < 0.01 for females only. *Significant at p < 0.05 for males only. **p < 0.01, ***p < 0.001.

### Table 2. Descriptive statistics and correlations between long-term averages of pollutants estimated for study participants, 1973 through month of censoring, females and males combined (n = 3,239).

| PMi (µg/m3) | PMi,0 (µg/m3) | PMi,0–2.5 (µg/m3) | O3 (ppb) | NO2 (ppb) | SO2 (ppb) |
|-------------|---------------|-------------------|----------|-----------|-----------|
| Mean ± SD   | 52.6 ± 16.9   | 29.0 ± 9.8        | 25.4 ± 8.5| 26.2 ± 7.3| 34.9 ± 9.7| 4.5 ± 2.7  |
| PM10        | 1.00          | 0.83*             | 0.91*     | 0.79*     | 0.50*     | 0.36*      |
| PM2.5       | 1.00          | 1.00              | 0.59*     | 0.60*     | 0.50*     | 0.30*      |
| PM10,0      | 1.00          | 1.00              | 0.75      | 0.51*     | 0.31*     | 0.11*      |
| PM10,0–2.5  | 1.00          | 1.00              | 0.52*     | 0.31*     | 0.11*     | 0.07*      |
| O3          | 1.00          | 1.00              | 1.00      | 1.00      | 1.00      | 1.00       |
| NO2         | 1.00          | 1.00              | 1.00      | 1.00      | 1.00      | 1.00       |
| SO2         | 1.00          | 1.00              | 1.00      | 1.00      | 1.00      | 1.00       |

*p < 0.01.
5.35 in the medium and highest tertiles, respectively (p-value for trend = 0.006).

No significant associations were found between any of the gaseous pollutants and fatal CHD in either the age-adjusted or multivariable-adjusted analyses in single-pollutant or in two-pollutant models with PM. However, the association with NO$_2$ was elevated for both males and females in single-pollutant models (Table 3). In males, no association was found between particulate pollutants and fatal CHD either as continuous or as categorical (tertiles) variables in single- or two-pollutant models (Tables 3, 4).

### Discussion

Most studies of the association between ambient particulate air pollution and cardiovascular disease (CVD) have been limited to effects of short-term increases in PM on hospital admissions for CVD (Zanobetti et al. 2000) and total mortality (Dominici et al. 2003;...
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Samet et al. 2000). Of the particulate pollutants, PM$_{2.5}$ seems to show the strongest association with CVD outcomes (Pope et al. 2002, 2004a).

The Six Cities and the ACS studies have reported a positive association between CPD and cardiovascular deaths and long-term exposure to ambient PM. The association was strongest for fine particles, with RR varying between 1.06 for CPD deaths (Pope et al. 2002) and 1.12 for cardiovascular deaths (Pope et al. 2004a) for each increment of 10 µg/m$^3$ after adjusting for age, sex, diet, and other demographic covariates. When comparing most-polluted with least-polluted areas, the RR for CPD death was 1.31 for a difference of 24.5 µg/m$^3$ in the ACS study (Pope et al. 1995) and 1.37 for a difference of 18.6 µg/m$^3$ in the Six Cities Study (Dockery et al. 1993). Pope et al. (2004a) reported a somewhat higher risk estimate for mortality from IHD, with an RR of 1.18 for an increment of 10 µg/m$^3$, and concluded that “predominant PM mortality associations” were with IHD. The effect of fine particles on CPD mortality has not been reported from AHSMOG to date. For PM$_{2.5}$ and CPD mortality, no significant relationships were found, but males had higher estimates than did females (Abbey et al. 1999).

Two European cohort studies have both looked at traffic-related pollution (Hoek et al. 2002; Naftsd et al. 2004). Hoek et al. (2002) found that persons living near a major road had a 1.95 greater risk of CPD death than did others and, that for each increase of 10 µg/m$^3$ in black smoke, the RR increased by 34%. Among Norwegian men, Naftsd et al. (2004) found that for each increase of 10 µg/m$^3$ in nitrogen oxides (markers of traffic pollution), the risk increased by 8% for fatal IHD and by 16% for respiratory deaths.

We found significant relationships between ambient PM and fatal CHD only in females. To our knowledge, no other cohort study on the health effects of ambient air pollution has reported sex-specific risks for CHD mortality. Therefore, we cannot readily compare our findings with others. However, the ACS study did find a slightly higher, although not significant, risk of CPD mortality among never-smoking females versus males in the most-polluted cities compared with the least polluted (RR = 1.57 in females vs. 1.24 in males) (Pope et al. 1995). As far as we have been able to assess, neither the Six Cities Study nor the Dutch study (Hoek et al. 2002) have reported sex-specific findings on CPD mortality. The Norwegian cohort included only males (Naftsd et al. 2004), so did the male U.S. veterans cohort mortality study (Lipfert et al. 2000). In a study of short-term effects, Peters et al. (1997) reported a stronger effect of TSPs on blood viscosity in females than males during episodes of high air pollution in Augsburg, Germany.

Several experimental studies of pulmonary deposition of inhaled particles in healthy adults showed that particle deposition characteristics differ between males and females under controlled breathing conditions. Kim and Hu (1998) found that deposition in females is greater than that in males and that the deposition was more localized within the lung in females. The authors suggest that regional deposition enhancement in women may lead to a greater health risk in females than in males. This is consistent with the hypothesized mechanism in which the deposition of particles in the lung could elicit inflammatory responses resulting in a systemic signal (Seaton et al. 1995).

An experimental study of 50 persons (Sorensen et al. 2003) showed significant positive associations between personal PM$_{2.5}$ exposure and oxidation products [e.g., plasma malondialdehyde, red blood cells (RBCs), and hemoglobin concentrations] in females but not in males. The authors suggest that females possibly are more sensitive to airborne pollution than are males because they have fewer RBCs and thus may be more sensitive to toxicologic influences of air pollutants.

A recent study supporting our sex-differential findings assessed the relationship between ambient levels of PM$_{2.5}$ at place of residence and degree of intima media thickness as measured by ultrasound (Künzli et al. 2005). Cross-sectional analyses of baseline data from two clinical trials in Los Angeles showed that the association was statistically significant among women but not among men. Also, the associations were stronger among older persons who had never smoked or who reported using lipid-lowering treatment at baseline. The strongest association, however, was found among older women (≥ 60 years of age). These findings corroborate with our findings from AHSMOG, which is also an older population, with mean age at fatal CHD of 67.6 years in men and 72.3 years in women.

Our findings and those of other studies show that particulate air pollution seems to have a stronger effect on fatal CHD than on other fatal CPD end points. The ACS study found a somewhat higher RR associated with an increase in PM$_{2.5}$ of 10 µg/m$^3$ for fatal IHD (RR = 1.18; 95% CI 1.14–1.23) (Pope et al. 2004a) than what they had previously found for CPD mortality (RR = 1.09; 95% CI 1.03–1.16) (Pope et al. 2002). In females, our findings for fatal CHD and PM are stronger than those we have previously reported for CPD mortality in the total AHSMOG cohort (Abbey et al. 1999) and in the airport cohort (McDonnell et al. 2000). Also, in a previous report we found positive associations with CPD mortality only in males (Abbey et al. 1999). In extended follow-up of CPD mortality in the total AHSMOG cohort through 1998 using the same models as previously, we continue to find a slightly stronger association in males than in females (unpublished data). However, when we exclude baseline CHD, stroke, and diabetes, these sex differences disappear, and when we limit our analyses to the airport cohort, CPD mortality is actually significantly increased in females but not in males (RR = 1.14 vs. 1.02 in males). These findings warrant further study of the effect of PM in sensitive subgroups and in densely populated areas (e.g., airport cohort) versus less densely populated areas. It also suggests that health effects of air pollution are different in males and females.

Even though we found the strongest association with PM$_{2.5}$, the coarse fraction was also associated with significant risk. One possible explanation for the higher risk estimates for all three PM fractions in our study could be more precise estimates of ambient air pollution and thus less exposure misclassification. AHSMOG is the only study with monthly estimates of ambient air pollution for each subject throughout the entire follow-up period. Other reasons could be the homogeneity of the population (see “Strengths and limitations,” below). Because different components of air pollution frequently occur together and are highly correlated (Table 2), the U.S. Environmental Protection Agency (EPA) has suggested that the association observed with PM could instead be due to gaseous pollutants (U.S. EPA 1989). We found no significant association between fatal CHD and gaseous pollutants in single- or two-pollutant models. However, in two-pollutant models, both O$_3$ and SO$_2$ strengthened the relationship between PM and fatal CHD, whereas NO$_2$ had no effect. The modifying effect of O$_3$ can possibly be explained by findings indicating that lung epithelial permeability increases with exposure to O$_3$ (Blomberg et al. 2003), thus making the body more susceptible to intrusion of particulate matter. The proposed mechanisms for
Although we have shown cardiovascular effects of particulate air pollution in this study, we have unknown amounts of measurement error in both the estimated long-term ambient concentrations of pollutants and other covariates. One source of measurement error derives from interpolating ambient concentrations (PM$_{10}$, O$_3$, NO$_2$, SO$_2$) from fixed-site monitoring stations to ZIP code centroids of work and home locations of study participants (Abby et al. 1991, 1995a). Another source of measurement error is that ambient PM$_{2.5}$ concentration was not measured directly for the duration of this study, but estimated from airport visibility, temperature, and humidity (Abby et al. 1995b). The precision of the PM$_{10-2.5}$ is unknown because it is calculated as the difference between PM$_{10}$ and PM$_{2.5}$. Use of ambient concentrations rather than measures of personal exposure could be one limitation in this study, but it is unlikely that we have selective bias in the females only. Further, we cannot rule out the possibility that the observed sex difference in effect could be due to measurement error. Males, more than females, reported working > 5 miles from their residence and thus may have spent more time in heavy traffic (more commutes and longer commuter distances). We have not been able to take this into consideration when estimating each subject’s ambient air pollution levels.

Conclusions

In summary, in this study we found an elevated risk of fatal CHD associated with ambient levels of PM$_{10}$, PM$_{10-2.5}$, and PM$_{2.5}$ in females but not in males. The risk estimates were strengthened when adjusting for gaseous pollutants and were highest for PM$_{2.5}$. Our findings are in line with findings by others of an effect of PM on CPD mortality, but are of greater magnitude, possibly because the outcome was limited to fatal CHD with better control of confounding factors such as alcohol and tobacco.

Further studies are needed from larger cohorts and/or with longer follow-up to support our findings of a sex-differential effect of PM on risk of fatal CHD. Developing more accurate ways to assess an individual’s exposure to ambient levels of PM will improve precision of risk estimates. Further, it is important to study whether the effects of air pollution are reversible in a manner similar to that found when smokers stop smoking. The effect of different exceedance frequencies should also be explored as well as the effect of different chemical compositions of PM.
Kiechl S, Werner P, Egger G, Oberhollenzer F, Mayr M, Xu Q, et al. 2002. Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. Stroke 33(9):2170–2176.

Kim CS, Hu SC. 1998. Regional deposition of inhaled particles in human lungs: comparison between men and women. J Appl Physiol 84(6):1834–1844.

Koenig V, Sund M, Filippi B, Doring A, Lowel H, Ernst E. 1998. Plasma viscosity and the risk of coronary heart disease: results from the M0NICA-Augsburg Cohort Study. 1984 to 1992. Arterioscler Thromb Vasc Biol 18(5):768–772.

Künzli N, Jerrett M, Mack WJ, Beckerman B, Doring A, Lowel H, Ernst E. 2005. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 113:201–206.

Lin D. 1994. Cox regression analysis of multivariate failure time data: the marginal approach. Stat Med 13:2233–2247.

Lipfert FW, Perry HM Jr, Miller JP, Baty JD, Wyzga RE, Carmody SE. 2000. The Washington University–EPRI Veterans’ Cohort Mortality Study: preliminary results. Inhal Toxicol 12(suppl 4):41–73.

Logan WP. 1953. Mortality in the London fog incident, 1952. Lancet 1:336–338.

Mack WJ, Islam T, Lee Z, Selzer RH, Hodis HN. 2000. Environmental tobacco smoke and carotid arterial stiffness. Prev Med 31(2):148–154.

McDonnell WF, Nishino-Ishikawa N, Petersen FF, Chen LH, Abbey DE. 2000. Relationships of mortality with the fine and coarse fractions of long-term ambient PM2.5 concentrations in nonsmokers. J Exp Anal Environ Epidemiol 10(5):427–436.

Nafstad P, Haheim L, Wulff T, Gram F, Offedal B, Holme I, et al. 2004. Urban air pollution and mortality in a cohort of Norwegian men. Environ Health Perspect 112:619–625.

Panagiotakos DB, Prisavos C, Chrysohoou C, Skoumas J, Masoura C, Toutouzas P, et al. 2004. Effect of exposure to secondhand smoke on markers of inflammation: the ATTICA study. Am J Med 116(3):145–150.

Peters A, Doring A, Wichmann HE, Koenig W. 1997. Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349(9065):1582–1587.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, et al. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11(1):11–17.

Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287(9):1132–1141.

Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. 2004a. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109(1):71–77.

Pope CA III, Hansen ML, Long RW, Nielsen KR, Etoough NL, Wilson WE, et al. 2004b. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ Health Perspect 112:339–345.

Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, et al. 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151:669–674.

Riediker M, Cassio WE, Griggs TR, Herbst MC, Bromberg PA, Neas L, et al. 2004. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. Am J Respir Crit Care Med 169(8):934–940.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. N Engl J Med 343:1742–1749.

Seaton A, MacNee W, Donaldson K, Godden D. 1995. Particulate air pollution and acute health effects. Lancet 345:176–178.

Sorensen M, Daneshvar B, Hansen M, Dragsted LO, Hertel O, Knudsen L, et al. 2003. Personal PM10 exposure and markers of oxidative stress in blood. Environ Health Perspect 111:161–166.

U.S. EPA. 1989. Assessing Multiple Pollutant Multiple Source Cancer Risks from Urban Air Toxics. EPA-450/2-89-010. Research Triangle Park, NC.U.S. Environmental Protection Agency, Office of Air Quality, Planning and Standards.

Wichers LB, Nolan JP, Winsett DW, Ledbetter AD, Kodavanti UP, Schladweiler MC, et al. 2004. Effects of instilled combustion-derived particles in spontaneously hypertensive rats. Part II: pulmonary responses. Inhal Toxicol 16(6–7):407–419.

World Health Organization. 1977. International Classification of Diseases. Manual of the International Statistical Classification of Disease, Injuries, and Causes of Death, 9th Revision. Geneva:World Health Organization.

Zanobetti A, Schwartz J, Dockery DW. 2000. Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ Health Perspect 108:1071–1077.

Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Peacock J, et al. 2003. The temporal pattern of respiratory and heart disease mortality in response to air pollution. Environ Health Perspect 111:1188–1193.