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Abbreviations and Definitions: body mass index (BMI), cardiovascular disease (CVD), coronary heart disease (CHD), geographic information systems (GIS), hazard ratio (HR), metropolitan statistical areas (MSAs), myocardial infarction (MI), 95% confidence interval (95%CI), odds ratio (OR), PM_{10} (particulate matter less than 10 microns in diameter), $PM_{2.5}$ (particulate matter less than 2.5 microns in diameter), $PM_{10-2.5}$ (particulate matter between 2.5 and 10 microns in diameter), relative risk (RR),

Abstract

Background: The association of all cause mortality and cardiovascular outcomes with air pollution exposures has been well established in the literature. The number of studies examining chronic exposures in cohorts is growing, with more recent studies conducted among women finding risk estimates of greater magnitude. Questions remain regarding gender differences in the relationship of chronic particulate matter exposures with mortality and cardiovascular outcomes. Objectives: The current study explored these associations in the male Health Professionals Follow-Up Study prospective cohort. Methods: The same spatio-temporal exposure estimation models, and similar outcomes and biennially updated covariates were used as those previously applied in the female Nurses' Health Study cohort. Results: Among 17,545 men residing in the Northeastern and Midwestern US, there were 2,813 deaths, including 746 cases of fatal coronary heart disease (CHD). An interquartile range change (4 $\mu g/m^3$) in average $PM_{2.5}$ exposure in the 12 previous months was not associated with all cause mortality (HR: 0.94; 95%CI: 0.87,1.00) or fatal CHD (HR: 0.99; 95%CI: 0.87,1.13) in fully adjusted models. Findings were similar for separate models of PM_{10} and $PM_{10-2.5}$ exposures and for co-pollutant models. Conclusions: Among this cohort of men with high socioeconomic status, living in the Midwestern and Northeastern US, the results did not support an association of chronic particulate matter exposures with all cause mortality and cardiovascular outcomes in models with time-varying covariates. Whether these findings suggest gender differences in susceptibility or the protective impact of healthier lifestyles and higher socioeconomic status requires additional investigation.

Introduction

The association of ambient particulate matter exposures with mortality and cardiovascular outcomes has been well established in studies of short-term exposure (COMEAP and Cardiovascular Disease and Air Pollution 2006; Levy et al. 2000; Samet et al. 2000; Samet et al. 2000; Zanobetti et al. 2000). The literature on health outcomes associated with long-term particulate matter (PM) exposures has been growing. Beginning with the Harvard Six Cities Study and the American Cancer Society Study, researchers have reported increased risks of all cause and cardiopulmonary mortality with chronic exposures(Dockery et al. 1993; Pope et al. 1995). More recent cohort studies have confirmed these findings(Brunekreef et al. 2009; Eftim et al. 2008; Laden et al. 2006; Miller et al. 2007; Pope et al. 2004; Puett et al. 2009; Puett et al. 2008).

A few recently published cohort studies have focused on women and have reported stronger effect estimates for fatal coronary heart disease and all cause mortality than previous studies (Miller et al. 2007; Puett et al. 2009; Puett et al. 2008).

Questions remain regarding gender differences in the associations of chronic PM exposures with all cause and cardiovascular mortality. The current study applies the same spatio-temporal exposure modeling used in the all-female Nurses' Health Study cohort to examine similar relationships among the all-male Health Professionals Follow-Up Study cohort.

Materials and Methods

Study Population

The Health Professionals Follow-Up Study cohort consists of 51,529 male dentists, pharmacists, optometrists, podiatrists, osteopaths and veterinarians residing in the US. The cohort began with a baseline questionnaire in 1986, when participants were aged 40 to 75. The Health Professionals Follow-Up Study was approved by the Harvard School of Public Health Institutional Review Board, and returning the completed questionnaires constituted implied consent to use the data in ongoing research. Follow-up questionnaires are mailed every two years, with response rates of approximately 93%. The current study is limited to participants living in 13 contiguous northeastern and midwestern states (ME, VT, NH, MA RI, CT, NY, NJ, DE, PA, OH, MI, MD) for comparison to our recent studies in the Nurses' Health Study. Health professionals were excluded for any time period during which they lived outside this region.

Outcomes

The outcomes for the current study were all cause mortality (excluding accidental deaths), nonfatal myocardial infarction, fatal coronary heart disease (CHD), and hemorrhagic and ischemic stroke. We also examined total cardiovascular disease (CVD) events including fatal CHD**,** nonfatal myocardial infarction (MI), and total strokes. Deaths were confirmed by families, postal officials and the National Death Index. We included MI's if medical record information met World Health Organization criteria (presence of symptoms and typical electrocardiographic changes or elevated cardiac enzyme levels) or if the patient was hospitalized and additional corroborating correspondence was obtained confirming the

diagnosis(Rose 1982). Men with MI's prior to baseline were excluded. Fatal CHD was confirmed through hospital records or by a death certificate listing CHD as the primary cause or the most plausible cause and previous history of the disease was available. Strokes were included if medical records showed evidence of typical neurologic deficit of sudden or rapid onset lasting 24 hours or more attributed to a cerebrovascular event or if the participant was hospitalized and the supplementary correspondence corroborated the diagnosis. Hemorrhagic and ischemic strokes were categorized using National Survey of Stroke criteria(Walker 1981). Men experiencing strokes prior to baseline were excluded. All medical records were reviewed by physicians blinded to the participants' exposure status.

Exposure Assessment

Spatio-temporal models were developed to estimate monthly $PM_{2.5}$ (particulate matter 2.5 microns in diameter or less) and PM_{10} (particulate matter 10 microns in diameter or less) exposures for each address of each participant. $PM_{10-2.5}$ exposures were estimated, for each month and location, by subtracting the modeled $PM_{2.5}$ estimates from the PM_{10} modeled estimates. These models allowed us to predict chronic PM exposure levels for all individuals with a geocoded address, even those living in areas with no nearby monitors. The models are described in detail elsewhere (Paciorek et al. 2009; Yanosky et al. 2009; Yanosky et al. 2008). Briefly, the models use a Geographic Information System (GIS)-based spatial smoothing model and include pollution data from monitoring sites in the US Environmental Protection Agency's Air Quality System (AQS; U.S. EPA 2009), the Visibility Information Exchange Web System (VIEWS), the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, Stacked Filter Unit (a predecessor to

IMPROVE), Clean Air Status and Trends (CASTNet) networks, and Harvard research studies (Spengler et al. 1996; Suh et al. 1997) as well as GIS-derived covariates including population density, distance to nearest road, elevation, urban land use, point- and area-source primary emissions and meteorological information. To allow for sparse $PM_{2.5}$ monitoring prior to 1999, separate generalized additive mixed models were constructed for the time periods from 1988 to 1998 and from 1999 to 2002. To compensate for the relative lack of $PM_{2.5}$ data, the pre-1999 model added extinction coefficients and a simpler spatio-temporal structure to estimate the $PM_{2.5}$ to PM_{10} ratio seasonally. Point-source $PM_{2.5}$ emissions were included in the post-1999 $PM_{2.5}$ model. The models were evaluated using cross-validation and were shown to exhibit little bias and high precision(Paciorek et al. 2009; Yanosky et al. 2009; Yanosky et al. 2008).

Evaluation of confounders and effect modifiers

Questionnaires were originally mailed in January of 1986 and follow-up questionnaires were sent in January of subsequent even-numbered years. Data from these biennial questionnaires were used to assess potential confounding and effect modification by covariates. We selected covariates a priori based on known risk factors for mortality and cardiovascular disease in the general population and specific to this cohort (Chiuve et al. 2008; Cho et al. 2002; Pischon et al. 2005). We examined confounding by adjustment and effect modification through the use of interaction terms and stratification for: hypertension (yes, no), hypercholesterolemia (yes, no), diabetes mellitus (yes, no), physical activity (less than three, three to less than nine, nine to less than 18, 18 to less than 27, or greater than or equal to 27 metabolic equivalents (MET) hours per week), alcohol consumption (0, 0.1-

4.9, 5.0-14.9, 15 plus grams per day), body mass index (BMI, continuous), smoking status (never, former, or current), smoking pack years, and low versus high risk diet. A low risk diet was assessed as a diet with a high ratio of polyunsaturated to saturated fat, high in cereal fiber and low in trans fat and glycemic load (details described elsewhere)(Hu et al. 2001). Family history of MI was examined on the baseline questionnaire. On the baseline questionnaire, information was also available to determine if the mailing address provided was a residential or business location.

Statistical Analysis

Time-varying Cox proportional hazards models were used to assess the relationships of all cause mortality and cardiovascular outcomes with predicted PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ exposures averaged over the 12 months prior to each outcome. All survival models were based on a monthly time scale and were used to estimate hazard ratios (HRs) and 95% confidence intervals (95%CIs). Person-years of follow-up time were calculated from baseline (January,1989) until the end of follow-up (January, 2003). Person-time spent living outside the geographic region of interest was excluded, as were men with cardiovascular outcomes prior to baseline. Incidence rates were estimated as the number of new cases divided by person-years of follow-up. Each particulate size fraction was assessed in separate and combined models. Cox models were stratified by age in months, in order to control finely for age in a nonparametric way. Models were also adjusted for year (linear term), season (indicator variables), and for state of residence (indicator variables), rather than stratifying by these covariates in order to maximize the number of cases in strata. Effect modification was assessed through the use of interaction terms in the models, as well as through likelihood ratio tests (LRT). In a sensitivity analysis, we

compared model results for each size fraction of PM for additional time windows of exposure: 24, 36 and 48 months. We also conducted sensitivity analyses excluding participants who resided outside Metropolitan Statistical Areas (MSAs). All statistical analyses used SAS version 9.2 (Cary, NC).

Results

17,545 men were included at baseline, with a mean age of approximately 57 years (Table 1). Most were never or former smokers at baseline, with current smokers decreasing to about 5% of the study population by the end of follow-up. The percentages of men who reported hypertension, hypercholesterolemia or diabetes increased considerably from baseline (26.5%, 24.3%, and 4.3% respectively) to the end of follow-up (47.5%, 56.6%, 9.8% respectively). About 33% of the men reported 27 or more MET/hours per week of physical activity in 1989, with the percent of respondents in this category growing by the end of follow-up. About 23% of the study population lived in NY, with 15% in PA, 14% in MI, 13% in OH and 10% in NJ. At the beginning of the study, the average annual estimated exposure to PM_{10} was 27.9 $\mu g/m^3$, 17.8 $\mu g/m^3$ for $PM_{2.5}$, and 10.1 $\mu g/m^3$ for $PM_{10-2.5}$. In general, annual predicted PM exposures decreased over the follow-up period, with PM_{10} showing the largest decline (Figure 1). We performed correlations among various time windows of average exposure (12, 24, 36, and 48 months) for each PM fraction. All time windows were highly correlated ($\rho > 0.86$).

There were 2,813 deaths, 746 cases of fatal CHD, 646 cases of nonfatal MI, 1,661 cases of total CVD, 230 ischemic strokes, and 70 hemorrhagic strokes (Table 2). An interquartile range (4 $\mu g/m^3$) change in average $PM_{2.5}$ exposure in the 12 previous months was not

associated with all cause mortality (HR: 0.96; 95%CI: 0.90, 1.03) or ischemic strokes (HR: 0.84; 95%CI: 0.67, 1.06) in basic models adjusting for time and state of residence and stratified by age. The HR for fatal CHD was 1.01 (95%CI: 0.89, 1.15), 1.02 for total CVD (95%CI 0.94, 1.11), and 1.06 for nonfatal MI (95%CI: 0.92, 1.22) in similar models. For comparison purposes with other studies, translating these relative risks to a 10 $\mu g/m^3$ unit change in $PM_{2.5}$ exposure results in an HR for all cause mortality of: 0.90 (95%CI: 0.76,1.06), HR for fatal CHD: 1.02 (95%CI: 0.74,1.41) and HR for total CVD: 1.05 (95%CI: 0.85,1.30). The relative risk for an interquartile range change in average $PM_{2.5}$ exposure hemorrhagic strokes was highest, but the number of cases was small (HR: 1.14; 95%CI: 0.79, 1.65). The HRs were very similar in fully adjusted models with additional adjustment for BMI, hypertension, hypercholesterolemia, diabetes, family history of MI, smoking (status and pack years), physical activity, healthy diet, and alcohol consumption. For example, the fully adjusted HR for total CVD was 1.01 (95%CI: 0.93, 1.10). Results were similar for interquartile range increases in PM_{10} (7 $\mu g/m^{3)}$ and $PM_{10-2.5}$ (4 $\mu g/m^3$) separately, as well as in co-pollutant models with $PM_{2.5}$ and $PM_{10-2.5}$ (Table 3).

Effect modification was evident for $PM_{2.5}$ associations (Table 4). Men without a family history of MI were at significantly lower risk for all cause mortality associated with an interquartile range increase in chronic fine particulate exposure compared to men with such a history. Analysis of $PM_{2.5}$ exposures and fatal CHD stratified by smoking status show an increased risk for fatal CHD associated with chronic fine particulate exposure among never smokers. Though the relative risk for current smokers was higher than that estimated for never smokers, there were only a small number of current smokers with fatal CHD, and there was no apparent relationship for former smokers.

Sensitivity analyses showed that model results were stable using different time windows of average exposure for each size fraction of particulate matter, as well as excluding state of residence from the final models. Findings also did not change when participants residing outside of MSAs were excluded or when the addresses used for exposure assessment were limited to those we were able to confirm as residential (data not shown). Finally, we conducted sensitivity analyses excluding men with prior cancers (other than non-melanoma skin cancer) as well as including men with prior stroke and coronary heart disease, and these results were also comparable (data not shown).

Discussion

Among men participating in the Health Professionals Follow-up Study cohort, living in the Northeastern and Midwestern US, we found no evidence of an association between all cause mortality and an interquartile range increase in estimated exposure to $PM_{2.5}$, $PM_{10-2.5}$ or PM_{10} averaged over the prior 12 months. We observed similar results for total CVD and fatal CHD with all size fractions of particulate exposures and with $PM_{2.5}$ and PM_{10} for ischemic strokes. Risk of ischemic stroke and risk of nonfatal MI were slightly elevated with increases in $PM_{10-2.5}$ and with all sizes of particulate exposures, respectively.

In contrast to other cohort studies of chronic exposures among men and women combined, the present study showed essentially no association. Both the original and extended follow-up of the Harvard Six Cities Study found all cause and cardiopulmonary mortality significantly associated with long-term exposures to $PM_{2.5}$, with increased risks for all cause mortality ranging from 13 to 16% and cardiopulmonary risks from 18 to 28% for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Dockery et al. 1993; Laden et al. 2006). The original and extended American Cancer Society Study included data collected as part of the nationwide Cancer Prevention Study II, restricting the approximately 1.2 million participants to those living in metropolitan areas with available pollution data. Reported risks associated with $PM_{2.5}$ were lower than those from the Harvard Six Cities Study but still statistically significant (ranging from 4 to 6% for all cause and 6 to 9% for cardiopulmonary mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$) (Pope et al. 2002; Pope et al. 1995). A recent reanalysis of the American Cancer Society Study exploring adjustment for

ecologic covariates also found an increase when adjusting for median household income (per 10μg/m^3 increase in $PM_{2.5}$ relative risk (RR) for all cause mortality: 1.05; 95%CI: 1.03,1.07) compared with no adjustment for ecologic covariates (RR for $PM_{2.5}$: 1.03; 95%CI: 1.02,1.05)(Krewski et al. 2009). In the Medicare Cohort Air Pollution Study, Zeger and colleagues examined the relationship of all cause mortality with a 6 year average exposure to fine particulates in zip code regions of the eastern region of the US, which encompassed our study's geographic area (Zeger et al. 2008). The risk associated with a 10μg/m^3 increase in PM2.5 exposure was 6.8% (95%CI: 4.9 to 8,7%), adjusting for socioeconomic status (education, poverty, unemployment, income) and chronic obstructive pulmonary disease. Results were stronger for the Central US (13.2; 95%CI: 9.5 to 16.9) and lower for the Western US (-1.1; 95%CI: -3.0 to 0.8). Results from the Netherlands Cohort Study (NCLS) of men and women were similar to American Cancer Society Study findings(Brunekreef et al. 2009). The risk of CVD mortality was 1.04(95%CI: 0.90 , 1.21) with a 10 μg/m^3 increase in $PM_{2.5.}$ However, the same risk for an embedded case-cohort study was 0.83 (95%CI: 0.60, 1.15), adjusting for a much larger number of potential confounders. Lastly, similar to our findings, a study of male veterans (Lipfert et al. 2006) did not find evidence of an association between $PM_{2.5}$ in μg/m^3 (mean 14.3 μg/m^3; standard deviation 3.0μg/m^3) and all cause mortality , however the study found an association with traffic density suggesting that traffic-related pollution may be more important in men.

Differences between our study findings and previously published results may stem from differences in the populations examined, pollution measures and covariates that were considered in analyses. For example, city specific $PM_{2.5}$ averages in the Harvard Six Cities

Study ranged from 11.4 to 29.0 $\mu g/m^3$ in the original time period (Dockery et al. 1993) and from 10.2 to 22.0 $\mu g/m^3$ in the extended period (Dockery et al. 1993; Laden et al. 2006), which includes our range of average estimated exposure from baseline: 17.8$\mu g/m^3$ to the final year of follow-up:12.5$\mu g/m^3$. However, the Harvard Six Cities Study population exhibited higher percentages of smokers, a lower level of educational attainment, and between 28 to 53% occupationally exposed to dust/fumes, factors that may increase susceptibility to ambient air pollution exposures. Metropolitan area $PM_{2.5}$ measures were used to estimate exposure in the American Cancer Society Study (Pope et al. 2002) which reported an average participant exposure of 17.7$\mu g/m^3$, similar to our study average. As with the Harvard Six Cities Study (Dockery et al. 1993; Laden et al. 2006) and the American Cancer Society Study (Pope et al. 2002), pollution levels did not differ greatly between our study and the Medicare Cohort Air Pollution Study(Zeger et al. 2008). Using a 6 year average exposure estimated at the zip code level, the interquartile range of $PM_{2.5}$ exposure (12.3-15.3 for Eastern region $\mu g/m^3$) was lower than our baseline interquartile range (15.6-19.9 $\mu g/m^3$). Reported relative risks in this study were higher than those in our study, with models adjusting for fewer and area level covariates: socioeconomic status and chronic obstructive pulmonary disease. The Medicare Cohort Study population was also of lower socioeconomic status than the health professionals, however the authors report that analyses stratified by the national median of socioeconomic status were similar. Results from the NCLS (Brunekreef et al. 2009) were more comparable to our findings; and similar to our study, they adjusted for a much larger number of potential confounders than previous studies. Full cohort analyses were adjusted for age, gender, smoking, area level income, and area. Case-cohort analyses, which showed lower relative risks, were adjusted for age, sex, weight/height squared, smoking, marital status, diet, alcohol use,

education, occupation, and area level income. In addition, pollution exposure methods included the use of updated residential addresses. Lastly, we also note that though we have presented major findings in interquartile range change as well as 10 $\mu g/m^3$ some direct comparisons between previously published study findings and ours are limited due to differences in the units used for incremental change.

Few studies of chronic air pollution exposures have examined cerebrovascular outcomes. In the American Cancer Society Study, Pope and colleagues reported an increased risk of 2% (95%CI: -5%, 10%) for cerebrovascular death associated with a 10 $\mu g/m^3$ increase in fine particulate exposures, falling between our risk estimates for incident ischemic and hemorrhagic strokes with an interquartile range change in average $PM_{2.5.}$ (4 $\mu g/m^3$) (Pope et al. 2004). Among a national cohort of women (the Women's Health Initiative [WHI]), findings for first stroke associated with $PM_{2.5}$ exposures were stronger, with a reported risk of 1.28 (95%CI: 1.02, 1.61) for a 10 $\mu g/m^3$ increase(Miller et al. 2007).

Though some studies have not found significant differences between men and women, others have reported estimated effects of greater magnitude for women (Brunekreef et al. 2009; Chen et al. 2005; Miller et al. 2007; Zeger et al. 2008). Though the Medicare cohort study did not find significant gender differences, the reported mortality risks in the Eastern US associated with a 10$\mu g/m^3$ increase in PM2.5 exposure were slightly higher for women (8.5%; 95%CI: 6.3, 10.6%) than men(7.0%;95%CI: 5.2, 8.8%) (Zeger et al. 2008). Risks for cardiovascular outcomes were much higher for the Women's Health Initiative study which showed risks of 2.21 (95%CI: 1.17, 4.16) for fatal CHD (definite diagnosis) and 1.24(95%CI: 1.09, 1.41) for total CVD with a 10$\mu g/m^3$ change in $PM_{2.5}$ (Miller et al. 2007).

Average $PM_{2.5,}$ exposure (13.5 µg/m^3) and educational level were lower among this population than for our study of men, but they were comparable overall for many other health risks and behaviors. Relative risks were also stronger in the Nurses' Health Study, which used the same exposure estimation methods and geographic area as the current study, though the women generally showed worse health indicators (e.g. less physically active, more current smokers) and lived in areas of lower socioeconomic status (Puett et al. 2009; Puett et al. 2008). The HRs for all cause mortality were 1.26 (95%CI: 1.02, 1.54), 1.03 (95%CI: 0.89,1.18), 1.07 (95%CI: 0.97,1.18) with a 10µg/m^3 change in $PM_{2.5,}$ $PM_{10-2.5}$ and PM_{10} respectively and 2.02 (95%CI: 1.07, 3.78) for fatal CHD with a 10µg/m^3 change in $PM_{2.5,}$ in models adjusting for similar potential confounders(Puett et al. 2009). Relative risks for nonfatal MI appear to be stronger in the current study of men (Nurses' Health Study HR: 0.73; 95%CI: 0.48, 1.12 for a 10µg/m^3 change in $PM_{2.5}$). The Adventist Health Study on the Health Effects of Smog (AHSMOG) cohort study of men and women also reported stronger estimated effects among women for fatal CHD with higher overall levels of PM_{10} and $PM_{2.5}$ exposure than those in the current study (Chen et al. 2005). For a 10µg/m^3 change in $PM_{2.5}$, the risk for women was 1.42 (95%CI: 1.06, 1.90) and 0.90 (95%CI: 0.76, 1.05) for men. Relative risks associated with PM_{10} and $PM_{10-2.5}$ were also higher than comparable risks for men; however given the differences in exposure contrasts, results are not directly comparable. However, as for the Nurses and Health Professionals air pollution study comparisons, we cannot rule out the impact of education and lifestyle differences. Men in the AHSMOG study exhibited slightly higher levels of education and physical activity than the women.

Modification of air pollution associated outcomes by gender is biologically plausible based on studies that have shown greater fractions of deposition for inhaled particles among women(Bennett et al. 1996; Jaques and Kim 2000). As Dockery and Stone (Dockery and Stone 2007) suggest, the evidence may also point to increased susceptibility to air pollution due to an underlying cardiac profile that is more common among women, given that gender differences in the studies described appear more consistent with respect to cardiovascular outcomes and studies have shown gender differences in the cardiovascular pathways that air pollution may impact (Krishnan et al. 2009, Kublickiene and Luksha 2008; Mizia-Stec et al. 2007, Noon et al. 2008). However, the specific biological mechanisms through which particulate matter air pollution effects all cause mortality and cerebrovascular and cardiovascular disease outcomes have not been fully elucidated. Proposed pathways include endothelial dysfunction, oxidative stress and inflammation (Donaldson et al. 2001; Pope et al. 2004; Pope and Dockery 2006; Utell et al. 2002).

Our GIS-based temporal spatial smoothing models of PM exposures resulted in estimates that fell into the range of exposures reported by previous studies. As previously reported, our models showed high predictive accuracy and precision with R^2 ranging from 0.62 to 0.77 (Yanosky et al. 2008, Yanosky et al. 2009). However the possibility of residual confounding exists as we did not include such environmental covariates as temperature. However, given that the risk sets in the Cox model are updated monthly and we control for state and season in the model, the level of residual confounding is likely to be negligible. We also did not have information on behavioral covariates, such as time spent outside or proportion of time spent at the address, which may lead to misclassification in the personal

exposure estimate. Part of the difference between these results and those from the Nurses' Health Study may be due to residential addresses being used for the nurses while a mixture of occupational and residential addresses were available for the health professionals. However, results did not change for the men when the analysis was restricted to known residential addresses.

Findings from the current study may not be generalizeable to other populations of men. Our study population represented a narrower range of socioeconomic status and fewer occupational exposures to dust and fumes than the US population as a whole. The Health Professionals Follow-Up Study consisted of health professionals with high levels of educational attainment, physical activity, never smokers, and low risk diets. Therefore, they are likely to be much healthier than average. The death rate in the general population of US men aged 65 to 69 has been estimated to be 2,125 deaths per 100,000 person years (Centers for Disease Control and Prevention August 21, 2007), while the rate of nonaccidental deaths in the Health Professionals Follow-up Study is 1,275 per 100,000 person years. Similarly, the incidence rate of cardiovascular disease in this cohort (7.8 cases per 1,000 person years) (National Heart Lung and Blood Institute National Institutes of Health May 2006) is lower than that reported by the Framingham Heart Study (34.6 cases per 1,000 person years for men aged 65 to 74), a study more representative of the general population. However, it should be noted that rates could be somewhat more similar than those reported here, due to our inability to make exact comparisons to our age strata and time period.

Findings have been somewhat inconsistent regarding the impact of socioeconomic status on relationships between mortality(Bateson and Schwartz 2004; Krewski et al. 2000; Pope et al. 2002), cardiovascular disease and air pollution exposures; however as Bateson and Schwartz (Bateson and Schwartz 2004)suggest, inconsistencies may be due somewhat to differences in the geographic scale of these measures with individual level measures showing higher risk for lower educational attainment. In the reanalysis of the American Cancer Society Study, men with education above high school showed risks of all cause mortality comparable to those found in our study (1.02; 95%CI: 0.89, 1.17) (Krewski et al. 2000). Healthier lifestyles may also reduce risks from air pollution, as demonstrated by increased risks of air pollution-associated cardiovascular outcomes among those with larger BMIs(Miller et al. 2007; Puett et al. 2009; Puett et al. 2008). The impact of health behaviors in this population will be examined in detail in further work. In addition, the current study was restricted to the Northeastern and Midwestern US and the addresses used for assigning air pollution exposure estimates were a mixture of work and residential addresses. Differences in findings from the current study compared with some other cohort studies may be partially due to the differences in regional pollutant mixtures, given that other cohort studies covered larger or dissimilar geographic areas of the US (Dockery et al. 1993; Laden et al. 2006; Pope et al. 2002; Zeger et al. 2008). For example, Zeger et al. (Zeger et al. 2008) reported stronger risks for the Central versus Eastern regions of the US. However, this does not account for the stronger risks found among Nurses' Health Study Cohort participants, as those studies were conducted in the same geographic region as the current study(Puett et al. 2009; Puett et al. 2008).

Conclusion

Overall, associations of chronic particulate matter exposures with all cause mortality or cardiovascular disease outcomes were not evident in this population of male health professionals living in the Northeastern and Midwestern US. The lower relative risks found in this study should be explored further to ascertain whether men with high SES and healthy lifestyles are less susceptible to cardiovascular outcomes associated with long-term particle exposure.

References

Bateson TF, Schwartz J. 2004. Who is sensitive to the effects of particulate air pollution on mortality? A case-crossover analysis of effect modifiers. Epidemiology 15(2):143-149.

Bennett WD, Zeman KL, Kim C. 1996. Variability of fine particle deposition in healthy adults: effect of age and gender. Am J Respir Crit Care Med 153(5):1641-1647.

Brunekreef B, Beelen R, Hoek G, Schouten L, Bausch-Goldbohm S, Fischer P, et al. 2009. Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: the NLCS-AIR study. Res Rep Health Eff Inst(139):5-71; discussion 73-89.

Centers for Disease Control and Prevention. August 21, 2007. National Vital Statistics Reports. Deaths: Final Data for 2004.

Chen LH, Knutsen SF, Shavlik D, Beeson WL, Petersen F, Ghamsary M, et al. 2005. The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk? Environ Health Perspect 113(12):1723-1729.

Chiuve SE, Rexrode KM, Spiegelman D, Logroscino G, Manson JE, Rimm EB. 2008. Primary prevention of stroke by healthy lifestyle. Circulation 118(9):947-954.

Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB. 2002. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. J Am Coll Cardiol 40(5):954-960.

COMEAP, Cardiovascular Disease and Air Pollution. 2006. A Report by the Committee on the Medical Effects of Air Pollutant's Cardiovascular Sub-Group. London, United Kingdom: United Kingdom Department of Health.

Dockery DW, Pope ACd, Xu X, Spengler JD, Ware JH, Fay ME, et al. 1993. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329(24):1753-1759.

Dockery DW, Pope CA, 3rd, Xu X, Spengler JD, Ware JH, Fay ME, et al. 1993. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329(24):1753-1759.

Dockery DW, Stone PH. 2007. Cardiovascular risks from fine particulate air pollution. N Engl J Med 356(5):511-513.

Donaldson K, Stone V, Seaton A, MacNee W. 2001. Ambient particle inhalation and the cardiovascular system: potential mechanisms. Environ Health Perspect 109 Suppl 4:523-527.

Eftim SE, Samet JM, Janes H, McDermott A, Dominici F. 2008. Fine particulate matter and mortality: a comparison of the six cities and American Cancer Society cohorts with a medicare cohort. Epidemiology 19(2):209-216.

Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. 2001. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345(11):790-797.

Jaques PA, Kim CS. 2000. Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. Inhal Toxicol 12(8):715-731.

Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, et al. 2000. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality: A Special Report of the Institute's Particle Epidemiology Reanalysis Project. Cambridge, MA: Health Effects Institute.

Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, et al. 2009. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Res Rep Health Eff Inst(140):5-114; discussion 115-136.

Laden F, Schwartz J, Speizer FE, Dockery DW. 2006. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 173(6):667-672.

Levy JI, Hammitt JK, Spengler JD. 2000. Estimating the mortality impacts of particulate matter: what can be learned from between-study variability? Environ Health Perspect 108(2):109-117.

Lipfert FW, Baty JD, Miller JP, Wyzga RE. 2006. PM2.5 constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans. Inhal Toxicol 18(9):645-657.

Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356(5):447-458.

National Heart Lung and Blood Institute National Institutes of Health. May 2006. Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases.

Paciorek CJ, Yanosky JD, Puett RC, Laden F, Suh H. 2009. Practical large-scale spatio-temporal modeling of particulate matter concentrations. Annals of Applied Statistics 3:369-396.

Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. 2005. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 112(22):3375-3383.

Pope CA, 3rd, 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, 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. 2004. 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, 3rd, Dockery DW. 2006. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 56(6):709-742.

Pope CA, 3rd, 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(3 Pt 1):669-674.

Puett RC, Hart JE, Yanosky JD, Paciorek C, Schwartz J, Suh H, et al. 2009. Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. Environ Health Perspect 117(11):1697-1701.

Puett RC, Schwartz J, Hart JE, Yanosky JD, Speizer FE, Suh H, et al. 2008. Chronic particulate exposure, mortality, and coronary heart disease in the nurses' health study. Am J Epidemiol 168(10):1161-1168.

Rose G, Blackburn, H. . 1982. Cardiovascular Survey Methods. Geneva: World Health Organization.

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(24):1742-1749.

Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW, et al. 2000. The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality

from air pollution in the United States. Res Rep Health Eff Inst 94(Pt 2):5-70; discussion 71-79.

Spengler J, Koutrakis P, Dockery D, Raizenne M, Speizer F. 1996. Health effects of acid aerosols on North American children: air pollution exposures. Environ Health Perspect 104:492–499.

Suh H, Nishioka Y, Allen G, Koutrakis P, Burton R. 1997. The Metropolitan Acid Aerosol Characterization Study: results from the summer 1994 Washington, D.C. field study. Environ Health Perspect 105:826–834.

Utell MJ, Frampton MW, Zareba W, Devlin RB, Cascio WE. 2002. Cardiovascular effects associated with air pollution: potential mechanisms and methods of testing. Inhal Toxicol 14(12):1231-1247.

Walker A, Robins, M,Weinfeld, FD. :I13-44. 1981. The national survey of stroke: clinical findings. . Stroke 12(2 pt 2 suppl 1):13-44.

Yanosky J, Paciorek C, Suh H. 2009. Predicting Chronic Fine and Coarse Particulate Exposures Using Spatio-temporal Models for the Northeastern and Midwestern US Environ Health Perspect 117:522-529.

Yanosky JD, Paciorek CJ, Schwartz J, Laden F, Puett RC, Suh H. 2008. Spatio-temporal modeling of chronic PM10 exposure for the Nurses' Health Study. Atmos Environ 42(18):4047-4062.

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(11):1071-1077.

Zeger SL, Dominici F, McDermott A, Samet JM. 2008. Mortality in the Medicare population and chronic exposure to fine particulate air pollution in urban centers (2000-2005). Environ Health Perspect 116(12):1614-1619.

Table 1. Characteristics for the Health Professionals Follow-up Study at baseline for the current study in 1989

Variable	Mean (SD) or Proportion
N	17,545
Mean (SD) Age	57.4 (9.8)
Mean (SD) BMI	25.8 (3.4)
Smoking Status	
Never	44.9%
Current	9.5%
Former	45.5%
Mean (SD) Pack Years	25.2(19.4)
Hypertension	26.5%
Hypercholesterolemia	24.3%
Diabetes	4.3%
Family History of MI	14.0%
Low risk diet	42.5%
Alcohol consumption	
0	20.8%
0.1-4.9 g/d	27.5%
5.0-14.9 g/d	28.1%
15.0 plus g/d	23.6%
Physical Activity	
less than 3 MET hrs/week	14.9%
3 to less than 9	19.1%
9 to less than 18	19.0%
18 to less than 27	13.8%
27+	33.2%
Mean (SD) Predicted PM_{10} μ g/m3	27.9(5.8)
interquartile range Predicted PM_{10} μ g/m3	7.4
Mean (SD) Predicted $PM_{2.5}$ μ g/m3	17.8(3.4)
interquartile range Predicted $PM_{2.5}$ μ g/m3	4.3
Mean (SD) Predicted $PM_{10-2.5}$ μ g/m3	10.1(3.3)
interquartile range Predicted $PM_{10-2.5}$ μ g/m3	4.3

[a] Percentages are based on complete data for participants

Table 2: Hazard ratios and 95% CIs for associations of an interquartile range change in average predicted particulate matter exposure adjusting for covariates

			$PM_{2.5}$ (interquartile range=4 μg/m^3)		PM_{10} (interquartile range=7 μg/m^3)		$PM_{10-2.5}$ (interquartile range=4 μg/m^3)	
Outcome	**Cases**	**Person Years**	**Basic Model[a]**	**Full Model[b]**	**Basic[a]**	**Full[b]**	**Basic[a]**	**Full[b]**
All Cause Mortality	2,813	220,552	0.96 (0.90,1.03)	0.94 (0.87,1.00)	0.97 (0.91,1.03)	0.94 (0.89,1.00)	0.98 (0.93,1.04)	0.96 (0.91,1.02)
Fatal CHD	746	220,562	1.01 (0.89,1.15)	0.99 (0.87,1.13)	1.04 (0.93,1.16)	1.01 (0.90,1.14)	1.05 (0.94,1.16)	1.02 (0.92,1.14)
Nonfatal MI	646	214,919	1.06 (0.92,1.22)	1.06 (0.92,1.22)	1.05 (0.92,1.18)	1.04 (0.92,1.18)	1.03 (0.92,1.15)	1.02 (0.91,1.15)
Total CVD	1,661	212,649	1.02 (0.94,1.11)	1.01 (0.93,1.10)	1.04 (0.96,1.12)	1.02 (0.95,1.10)	1.04 (0.97,1.11)	1.03 (0.96,1.11)
Ischemic Strokes	230	218,944	0.84 (0.67,1.06)	0.86 (0.68,1.08)	0.97 (0.79,1.19)	0.98 (0.80,1.21)	1.08 (0.90,1.29)	1.08 (0.90,1.30)
Hemorrhagic Strokes	70	220,292	1.14 (0.79,1.65)	1.17 (0.81,1.69)	0.99 (0.70,1.41)	1.01 (0.71,1.44)	0.88 (0.63,1.24)	0.90 (0.64,1.26)

[a] stratified by age in months, adjusting for year, season, and state of residence
[b] stratified by age in months, adjusting for year, season, state of residence, BMI, hypertension, hypercholesterolemia, diabetes, family history of MI, smoking (status and pack years), physical activity, healthy diet, and alcohol consumption

Table 3: Hazard ratios and 95% CIs for associations of interquartile range (4 μg/m^3) changes in average predicted copollutant ($PM_{2.5}$ and $PM_{10-2.5}$) exposures adjusting for covariates

Covariates included	All Cause Mortality	Fatal CHD	Nonfatal MI	Total CVD	Ischemic Strokes	Hemorrhagic Strokes
	2,813 Cases	746 Cases	646 Cases	1,661 Cases	230 Cases	70 Cases
	220,552 Person Years	220,562 Person Years	214,919 Person Years	212,649 Person Years	218,944 Person Years	220,292 Person Years
Basic[a]						
$PM_{2.5}$	0.96 (0.89,1.04)	0.97 (0.83,1.13)	1.06 (0.90,1.25)	0.99 (0.90,1.10)	0.74 (0.56,0.96)	1.33 (0.86,2.06)
$PM_{10-2.5}$	1.00 (0.94,1.06)	1.06 (0.94,1.20)	1.00 (0.88,1.14)	1.04 (0.96,1.13)	1.24 (0.99,1.54)	0.77 (0.52,1.15)
Full[b]						
$PM_{2.5}$	0.94 (0.87,1.02)	0.97 (0.83,1.13)	1.06 (0.90,1.25)	0.99 (0.90,1.10)	0.76 (0.58,0.99)	1.35 (0.87,2.09)
$PM_{10-2.5}$	0.98 (0.92,1.05)	1.04 (0.92,1.17)	1.00 (0.87,1.14)	1.03 (0.95,1.12)	1.22 (0.98,1.52)	0.78 (0.53,1.16)

[a] stratified by age in months, adjusting for year, season and state of residence
[b] stratified by age in months, adjusting for year, season, state of residence, BMI, hypertension, hypercholesterolemia, diabetes, family history of MI, smoking (status and packyears), physical activity, healthy diet and alcohol consumption

TABLE 4. Hazard Ratios for all cause mortality and fatal CHD associated with an interquartile range (4 µg/m^3) change in average 12 month PM2.5 exposure, stratified by MI family history and smoking status, respectively.[ab]

Variable	Cases	Person-Years	HR (95%CI)	LRT pvalue[c]
Family History of MI	All cause mortality			
No	2439	189619	0.91 (0.85,0.98)	<0.01
Yes	374	30933	1.08 (0.91,1.29)	
Smoking Status	Fatal CHD			
Never	195	86571	1.28 (1.01,1.63)	0.04
Former	398	95384	0.90 (0.77,1.06)	
Current	47	13550	1.40 (0.88,2.21)	

[a] Modeled stratifying by age in months, adjusting for state of residence, year and season, smoking status, hypercholesterolemia, diabetes, hypertension, BMI, diet, alcohol consumption and physical activity
[b] Results presented for complete smoking data.
[c] Likelihood Ratio Test pvalue

Figure 1. Mean annual estimated particulate matter exposures from 1988 to 2002 in the Northeastern and Midwestern US