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Relationships of mortality with the fine and coarse fractions of long-term ambient PM_{10} concentrations in nonsmokers

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In a cohort of 6338 California Seventh-day Adventists, we previously observed for males associations between long-term concentrations of particulate matter (PM) with an aerodynamic diameter less than 10 μm (PM_{10}) and 15-year mortality due to all natural causes (ANC) and lung cancer (LC) listed as underlying causes of death and due to nonmalignant respiratory disease listed as either the underlying or a contributing (CRC) cause of death. The purpose of this analysis was to determine whether these outcomes were more strongly associated with the fine ($PM_{2.5}$) or the coarse ($PM_{2.5-10}$) fractions of PM_{10}. For participants who lived near an airport (n=3769), daily $PM_{2.5}$ concentrations were estimated from airport visibility, and on a monthly basis, $PM_{2.5-10}$ concentrations were calculated as the differences between PM_{10} and $PM_{2.5}$. Associations between ANC, CRC, and LC mortality (1977–1992) and mean PM_{10}, $PM_{2.5}$, and $PM_{2.5-10}$ concentrations at study baseline (1973–1977) were assessed using Cox proportional hazards models. Magnitudes of the PM_{10} associations for the males of this subgroup were similar to those for the males in the entire cohort although not statistically significant due to the smaller numbers. In single-pollutant models, for an interquartile range (IQR) increase in PM_{10} (29.5 $\mu g/m^3$), the rate ratios (RRs) and 95% confidence intervals (CI) were 1.15 (0.94, 1.41) for ANC, 1.48 (0.93, 2.34) for CRC, and 1.84 (0.59, 5.67) for LC. For an IQR increase in $PM_{2.5}$ (24.3 $\mu g/m^3$), corresponding RRs (95% CI) were 1.22 (0.95, 1.58), 1.64 (0.93, 2.90), and 2.23 (0.56, 8.94), and for an IQR increase in $PM_{2.5-10}$ (9.7 $\mu g/m^3$), corresponding RRs (95% CI) were 1.05 (0.92, 1.20), 1.19 (0.88, 1.62), and 1.25 (0.63, 2.49), respectively. When both $PM_{2.5}$ and $PM_{2.5-10}$ were entered into the same model, the $PM_{2.5}$ estimates remained stable while those of $PM_{2.5-10}$ decreased. We concluded that previously observed associations of long-term ambient PM_{10} concentration with mortality for males were best explained by a relationship of mortality with the fine fraction of PM_{10} rather than with the coarse fraction of PM_{10}. *Journal of Exposure Analysis and Environmental Epidemiology* (2000) **10,** 427–436.

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Introduction

We have previously observed in a cohort (n=6338) of nonsmoking California Seventh-day Adventists (the Adventist Health Air Pollution study, AHSMOG), relationships between long-term ambient concentrations of particulate matter (PM) with an aerodynamic diameter less than 10 μm (PM_{10}) and mortality due to all natural causes, nonmalignant respiratory disease, and lung cancer over a 15-year follow-up period in males (Abbey et al., 1999). Curiously, we observed minimal or no evidence of such relationships for females in the cohort. These findings in males are generally consistent with observations from two other recent cohort studies (Dockery et al., 1993; Pope et al., 1995) in which mortality during follow-up was related to PM concentrations measured early in the study. The observed associations between measures of long-term ambient particle concentration and mortality could potentially be the result of a process by which long-term exposure to either some component of PM or a highly correlated copollutant has an adverse effect upon the initiation or progression of underlying disease processes resulting in early death, or they could be the result of an acute process in which short-term exposure (which is generally related to long-term exposure) has a substantial adverse effect upon survival in some individuals. Little or no information is available to distinguish between these two possibilities, although the latter scenario would be consistent with the large number of studies in which mortality and other measures of health have been related to ambient PM concentrations averaged over a period of 1–5 days (Pope and Dockery, 1992; Schwartz, 1993; Schwartz and Dockery, 1992; Thurston et al., 1994; Gold et al., 1999; Loomis et al., 1999).

Although relationships with mortality and other health effects have been associated with various size fractions and constituents of PM (Dockery et al., 1992, 1993; Thurston et al., 1994; Pope et al., 1995; Lippman and Thurston, 1996),

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much recent attention has been focused upon the role of the smaller combustion-generated particles as being responsible for the observed relationships. Airborne PM is comprised of a large number of compounds and associated with a number of other compounds often produced by the same processes by which PM is produced. Consequently, no consensus has been reached as to which component(s) or characteristic(s) or closely associated pollutant(s) of PM is responsible for the observed associations of mortality with either short-term or long-term exposures. Factors contributing to this uncertainty include the general lack of available exposure data for the various components/characteristics/copollutants of PM for epidemiologic studies, an inability to separate the effects of closely related substances, and the lack of widely accepted mechanistic and toxicologic models for PM-induced mortality.

For a subset of the AHSMOG cohort, however, estimates of the ambient concentrations of the fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) fractions of PM_{10} can be derived, and estimates of other ambient air pollutants are also available. We thus have the opportunity to contribute information on the relative roles that two nominal size fractions of PM_{10} play in the previously observed mortality–PM_{10} relationships in this California-based cohort while controlling for the effects of other routinely monitored pollutants. The specific purpose of this analysis was to determine whether mortality is more closely related to $PM_{2.5}$ or to $PM_{2.5-10}$. Using a subset of the above-mentioned cohort, we found that mortality for males was generally more closely related to $PM_{2.5}$ than to $PM_{2.5-10}$. A secondary purpose of this analysis was to investigate the relative contributions to mortality of recent and long-term ambient PM concentrations.

Methods

Study Population

A cohort of nonsmoking, California Seventh-day Adventists was recruited in 1977 to participate in the AHSMOG study of the health effects of long-term air pollution exposure. Details of recruitment and follow-up of this cohort have been previously published (Hodgkin et al., 1984; Abbey et al., 1993). Abbey et al. (1999) recently evaluated the relationship between mortality in that cohort and long-term PM_{10} concentrations. In the current analysis we evaluate the relationships of mortality to $PM_{2.5}$ and $PM_{2.5-10}$ for the subgroup of the original participants with available $PM_{2.5}$ data. Participants included in the current analysis were white, non-Hispanic, 27 years of age or older in 1977, and lived within an airshed adjacent to one of nine airports located throughout California for 80% of the months during the study baseline period (1973–1977). Throughout this manuscript we refer to this subset (n=1347 males, 2422 females) as the airport cohort.

Participants completed detailed questionnaires in 1976 and 1977 which ascertained information on past residence and work locations; lifestyle characteristics including tobacco, alcohol, diet, exercise and education; occupational exposures; and history of selected medical conditions. Monthly residence and work locations for the period 1977–1992 (or date of death or loss to follow-up, if earlier) were ascertained by mailed questionnaires (1987, 1992), telephone tracing, or interviewing of surrogates for deceased participants. Ninety-two (2.4%) of the airport cohort participants were lost to follow-up.

Deaths during the follow-up period (1977–1992) were ascertained by searching the California death certificate files for the years 1977–1992 and the National Death Index files for the years 1979–1992 and through cohort tracing procedures including church records. We identified 943 study participants who died during this period and obtained death certificates for all. A state-certified nosologist blinded to pollutant concentration data coded each death certificate according to the Ninth Revision of the International Classification of Disease (ICD-9). For each death, the underlying cause (disease or injury that initiated events resulting in death) and contributing causes were coded.

Air Pollution Estimates

Daily estimates of ambient $PM_{2.5}$ concentration were derived for 11 airsheds from daily measures of visibility collected at nine California airports for the years 1966–1993 using regression equations relating $PM_{2.5}$ and visibility. These regression equations were site- and season-specific and included an adjustment for relative humidity. They were based upon measures of visibility and $PM_{2.5}$ collected on the same days during the years 1979–1993. Details and evaluation of the precision of these methods can be found in Abbey et al. (1995b). For each individual, monthly average $PM_{2.5}$ concentrations were calculated as the means of the daily ambient $PM_{2.5}$ estimates for the airshed in which the participant resided. Any month with nonmissing $PM_{2.5}$ estimates for more than 75% of the days was considered to have valid data. The mean distance of participant residences from the nearest airport varied from 8.6 to 31.8 km across airports, and the maximum distance for individual participants varied from 16.4 to 63.2 km (Abbey et al., 1995b). In a separate analysis, $PM_{2.5}$ concentrations adjusted for the amount of time reportedly spent outdoors at baseline were calculated using an indoor/outdoor ratio of 0.80 (Winer et al., 1989).

Estimates of monthly ambient air pollutant concentrations were formed for study participants for ozone (O_3), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) for the period 1966–1992, for PM_{10} for the years 1973–1992, and for suspended sulfates (SO_4) for the period 1977–1992 by

interpolating measures from fixed site monitoring stations maintained by the California Air Resources Board to zip code centroids of home and work locations for each participant. Details of these methods have been published elsewhere (Abbey et al., 1991, 1995a). For the years prior (1973–1986) to routine measurement of PM_{10}, concentrations of PM_{10} were estimated using site- and season-specific regressions based on total suspended PM (Abbey et al., 1995a). Monthly estimates of $PM_{2.5-10}$ were calculated for each volunteer as the monthly mean PM_{10} value minus the monthly mean $PM_{2.5}$ value.

Statistical Analysis

Gender-specific adjusted mortality rate ratios (RRs) were estimated using Cox regression models (Kleinbaum, 1996) for the three outcomes which we previously identified to be related to ambient PM_{10} concentrations. These were mortality due to all natural causes (ANC, ICD-9: 001–799) and to lung cancer (LC, ICD-9: 162) listed as the underlying cause of death and to nonmalignant respiratory disease (ICD-9: 460–519) listed as either the underlying or a contributing cause of death (CRC). Model structure and covariates for each outcome are those which were previously identified in the larger cohort (Abbey et al., 1999). Briefly, in that earlier work, a large number of characteristics which might be predictors of mortality or effect modifiers of the mortality–PM_{10} relationship were considered for inclusion in the models. Any factor whose inclusion substantially changed the pollutant regression coefficient or significantly improved the fit of the model was retained as a covariate (Maldonado and Greenland, 1993). Model covariates ultimately used for each outcome are listed in the Results section of this manuscript. For CRC mortality, the data were stratified into individuals less than or equal to, and those greater than, age 65 years at baseline because the proportional hazards assumption was violated for the covariate age at baseline (Kleinbaum, 1996). A third stratum consisting of individuals over the age of 85 years at baseline was excluded from further analyses of CRC mortality because the coefficients of model variables for this stratum were dissimilar from those of the other two strata, and the number of subjects was small.

The primary analyses for this manuscript utilized mean ambient pollutant concentrations during the baseline period (1973–1977) as fixed measures of exposure. Survival times of participants who did not die were censored at the end of the follow-up period or at the time of last contact if they were lost to follow-up (N=92). Time-on-study was used as the time variable for ANC and CRC mortality so that potential effects of short-term exposures could be better captured while age was used as the time variable for LC mortality to enhance the control of age effects (Breslow et al., 1983). The effects reported in this manuscript were generally insensitive to choice of time variable or to stratification. The proportional hazards assumption was tested (Kleinbaum, 1996) and found to be met for all final models. Adjusted RRs were calculated and reported for increments of mean ambient pollutant concentration equal to the interquartile range (IQR) of the mean 1973–1977 pollutant concentration across the airport cohort. Two-pollutant models, separate models for various subgroups of the sample, and models using ambient concentration adjusted for time spent outdoors were also fit to evaluate the stability of the associations.

A second set of analyses was conducted utilizing mean ambient pollutant concentration from 1973 through the time of each event (a death or censoring within the cohort) as a time-dependent measure of exposure. Survival times were censored at the earliest of end of study, time of death, time of last contact if lost to follow-up, or the date of moving from one of the airport airsheds if the participant remained outside of any study airshed for more than 9 months. The numbers of person–years of follow-up and deaths in these analyses were smaller than for the fixed exposures because a number of participants had moved away from airport areas during the follow-up period (1977–1992). Analyses for SO_4 could only be conducted using these time-dependent exposure models since SO_4 data were not routinely collected throughout California until 1977. Mean ambient SO_4 concentrations were calculated from 1977 through the date of each event. The RRs reported for these time-dependent analyses were calculated using the same increments of exposure as were used for the time-invariant analyses.

In an attempt to separately evaluate effects of long-term exposure and those associated with more recent exposure, a short-term exposure variable was created by subtracting the mean pollutant concentration from 1973 through the date of each event from the pollutant concentration during the month preceding each event. This new variable reflects any deviation in ambient concentration during the month preceding each event from the long-term average concentration. Time-dependent models were fit using both the long- and short-term variables including a variable reflecting season of the year for outcomes with seasonal effects.

Results

The baseline characteristics of the cohort (airport cohort) for which $PM_{2.5}$ estimates for the years 1973–1977 are available are listed in Table 1. These characteristics are generally consistent with those of the larger, previously reported upon cohort (Abbey et al., 1999), suggesting that the airport cohort is representative of the larger cohort with regard to individual characteristics and ambient pollutant concentrations (Table 2). Frequency histograms of the individual mean ambient concentrations (1973–1977) of

Table 1. Number of cause-specific deaths and baseline (1977) characteristics for airport cohort (2422 females, 1347 males).

Female	Male	
568	375	Total deaths 1977–1992
557	359	All natural cause deaths (ICD-9: 001–799)
146	98	Deaths with any mention of nonmalignant respiratory disease as underlying or contributing cause of death (ICD-9: 460–519)[a]
10	14	Lung cancer deaths (ICD-9: 162)
59.3	58.3	Age in years, mean
14.3	36.5	% smoked in the past
11.7	20.1	Pack-years of smoking, mean for past smokers
48.3	37.0	% ever lived with smoker
20.0	16.2	Years lived with smoker, mean[b]
38.4	49.4	% ever worked with smoker
11.2	15.8	Years worked with smoker, mean[b]
0.4	10.1	% occupational exposure to fumes or dust for more than 10 years
13.2	14.4	Years education, mean
24.6	25.0	Body mass index [(weight in kg)/(height in m)^2]), mean
6.1	9.0	% currently use alcoholic beverages
33.4	43.0	% high total exercise level
8.9	17.3	Hours outdoors per week, mean
45.6	40.2	% high antioxidant vitamin consumption from pills[c]
33.0	28.7	% prior heart attack, stroke, diabetes, or high blood pressure

[a]All death counts except this one are for underlying cause only.
[b]Mean of nonzero values.
[c](At least daily consumption of vitamin A) or (>1000 mg vitamin C per week) or (≥200 U vitamin E per week) or (1 or 2 multivitamin pills daily).

$PM_{2.5}$, PM_{10} and $PM_{2.5-10}$ are presented in Figure 1. The individuals exposed to the lowest ambient $PM_{2.5}$ concentrations in this cohort lived in the airsheds represented by the San Diego, San Jose, Sacramento, and Alameda airports (1973–1977 estimated mean $PM_{2.5}$ concentration at the airports=17.3, 17.7, 19.1, and 19.5 $\mu g/m^3$, respectively). Airsheds with moderate levels of $PM_{2.5}$ (in $\mu g/m^3$) were: Fresno (22.2), Los Angeles International (27.6), Bakersfield (28.6), Long Beach (30.4), Ontario West (30.7), and Ontario Central (37.9). The airshed with the highest ambient $PM_{2.5}$ concentrations was to the east of the Ontario airport (45.5 $\mu g/m^3$). During the study follow-up period, ambient $PM_{2.5}$ concentrations decreased slightly in the areas with the highest concentrations while no consistent change was observed in the cleaner areas. The mean concentrations of pollutants of interest for this airport cohort at baseline

Table 2. Descriptive statistics and correlations for long-term average concentrations of pollutants estimated for study participants, 1973 through 1977.[a]

	PM_{10} ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	$PM_{2.5-10}$ ($\mu g/m^3$)	Ozone (ppb)	SO_2 (ppb)	NO_2 (ppb)	SO_4 ($\mu g/m^3$)
Number[b]	3727	3769	3727	3766	2685	3765	3311
Mean	59.2	31.9	27.3	25.3	10.1	40.0	7.3
Std dev	16.8	10.7	8.6	6.2	5.4	11.6	2.4
IQR	29.5	24.3	9.7	12.3	6.8	19.5	2.0
PM_{10}	1.00	0.90	0.83	0.79	0.29	0.07	0.45
$PM_{2.5}$	–	1.00	0.50	0.68	0.18	−0.08	0.33
$PM_{2.5-10}$	–	–	1.00	0.70	0.31	0.23	0.47
Ozone	–	–	–	1.00	−0.13	−0.16	0.25
SO_2	–	–	–	–	1.00	0.86	0.36
NO_2	–	–	–	–	–	1.00	0.33

Abbreviations: PM_{10}=particles less than 10 μm; $PM_{2.5}$=particles less than 2.5 μm; $PM_{2.5-10}$=coarse fraction of PM_{10}; std dev=standard deviation; IQR=interquartile range; ppb=parts per billion.
[a]Except SO_4: 1977 through censor date.
[b]Number of subjects having at least 80% nonmissing monthly values for calculation of correlations between two pollutants varies from 2397 to 3766.

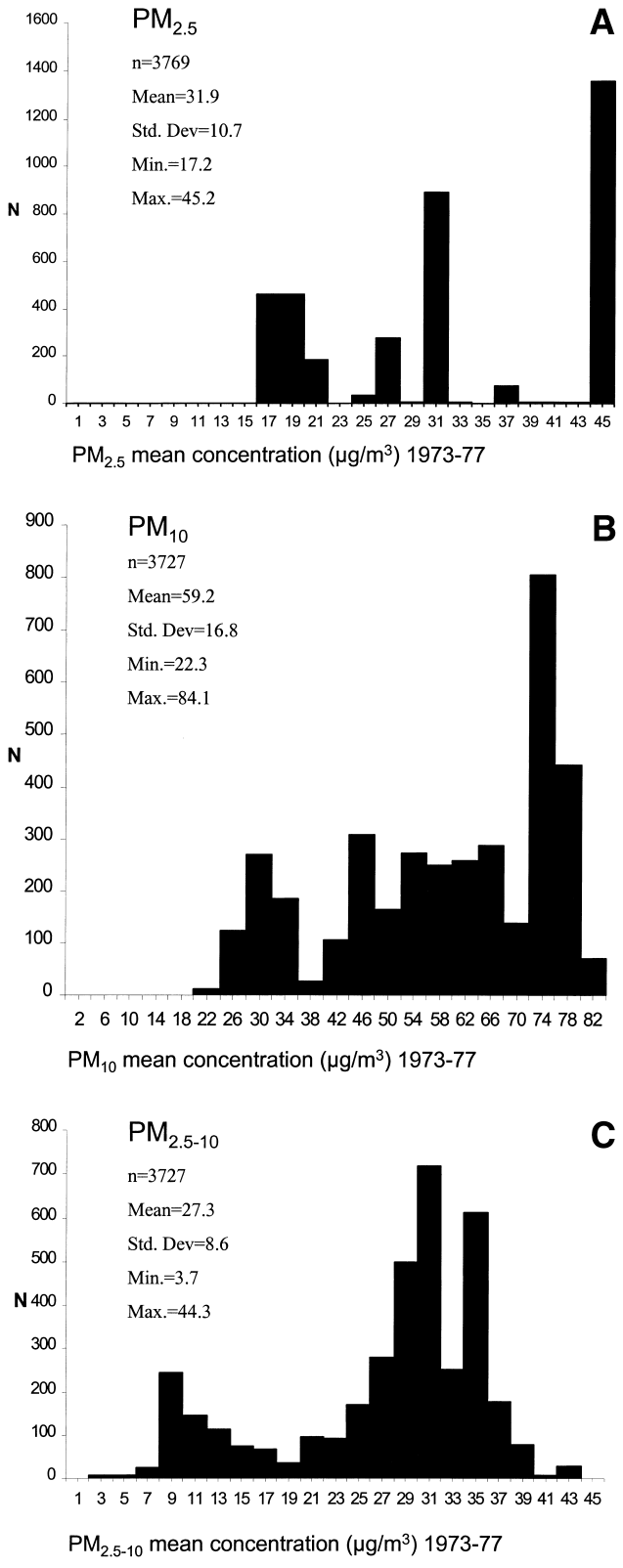

Figure 1. (A), (B), (C) Frequency distributions of mean ambient concentrations of $PM_{2.5}$, PM_{10}, and $PM_{2.5-10}$ for participants at study baseline (1973–1977).

(1973–1977) are provided in Table 2. The correlations of PM_{10} with $PM_{2.5}$ and $PM_{2.5-10}$ were high, while $PM_{2.5}$ and $PM_{2.5-10}$ were only modestly correlated. The correlations of $PM_{2.5}$ with SO_2 and SO_4 were weak (Table 2).

The adjusted mortality RRs for ANC, CRC, and LC mortality for single pollutant models (PM_{10}, $PM_{2.5}$, or $PM_{2.5-10}$) and for models containing both $PM_{2.5}$ and $PM_{2.5-10}$ are presented in Table 3 for males. Covariates included in the models for each outcome are the same as described for the previous PM_{10} models (Abbey et al., 1999) and are listed in the footnotes to Table 3. Both the estimated values of the coefficients of the covariates (data not presented) and the RRs for an incremental increase in PM_{10} concentration for this smaller airport cohort are comparable to those previously reported for the larger cohort if the same exposure increment is used, suggesting that the airport cohort is representative of the larger cohort also with regard to both covariate and PM–mortality relationships. The wider confidence intervals for the airport cohort reflect the smaller number of deaths and person–years of follow-up. For females, relationships between PM_{10} or $PM_{2.5}$ concentrations and mortality for the airport cohort are uniformly weak or inverse as had been previously reported for PM_{10} (Abbey et al., 1999). Data for females are therefore not presented, and the following results are applicable only to males.

For both ANC and CRC mortality in males, $PM_{2.5}$ is more strongly related in the single-pollutant models to mortality than is $PM_{2.5-10}$ (Table 3). In the models containing both $PM_{2.5}$ and $PM_{2.5-10}$, any relationship of mortality with $PM_{2.5-10}$ disappears while that of mortality with $PM_{2.5}$ remains stable. A similar pattern appears to hold for LC mortality although one should draw conclusions with caution due to the small number of LC deaths ($n=13$) used for this model.

The relationship between ANC mortality and $PM_{2.5}$ was not changed meaningfully by addition of either mean ambient concentration of ozone, sulfur dioxide, or nitrogen dioxide to the $PM_{2.5}$ model. In the two-pollutant models, the RRs for an IQR increase in $PM_{2.5}$ are 1.26 (0.89, 1.80), 1.23 (0.89, 1.71), and 1.27 (0.98, 1.65), respectively. For CRC mortality, addition of either sulfur dioxide or nitrogen dioxide to the $PM_{2.5}$ model did not result in a change in the RRs for $PM_{2.5}$. In the two-pollutant models the RRs for an IQR increment in $PM_{2.5}$ are 1.57 (0.77, 3.18) and 1.56 (0.89, 2.72), respectively. Inclusion of ozone mean concentration in a two-pollutant model for CRC resulted in a decrease in the RR for $PM_{2.5}$ (1.39 [0.65, 2.99]) with a resulting RR for an IQR increase of 12.3 ppb in ozone of 1.26 (0.64, 2.47). Inclusion of ozone, SO_2 or NO_2 in two-pollutant models for LC resulted in either minimal reductions or increases in the RR for $PM_{2.5}$.

The relationship of mortality to $PM_{2.5}$ was further explored by dividing the cohort into three groups based

Table 3. Adjusted mortality rate ratios by cause of death (1977–1992) for specific PM components from single- and two-pollutant models.

PM component average 1973–1977	Increment[a] ($\mu g/m^3$)	RR (95% CI) single-pollutant	RR (95% CI) $PM_{2.5}+PM_{2.5-10}$
All natural cause mortality for males[b] (n=1266; 316 deaths)			
$PM_{2.5}$	24.3	1.22 (0.95–1.58)	1.24 (0.91–1.67)
PM_{10}	29.5	1.15 (0.94–1.41)	
$PM_{2.5-10}$	9.7	1.05 (0.92–1.20)	0.99 (0.84–1.16)
Any mention of nonmalignant respiratory mortality for males[c] (n=1171; 72 deaths)			
$PM_{2.5}$	24.3	1.64 (0.93, 2.90)	1.55 (0.80, 3.03)
PM_{10}	29.5	1.48 (0.93, 2.34)	
$PM_{2.5-10}$	9.7	1.19 (0.88, 1.62)	1.06 (0.74, 1.52)
Lung cancer mortality for males[d] (n=1228; 13 deaths)			
$PM_{2.5}$	24.3	2.23 (0.56, 8.94)	2.10 (0.45, 9.90)
PM_{10}	29.5	1.84 (0.59, 5.67)	
$PM_{2.5-10}$	9.7	1.25 (0.63, 2.49)	1.07 (0.49, 2.31)

Abbreviations: PM=particulate matter; RR=rate ratio; 95% CI=95% confidence interval; $PM_{2.5}$=particles less than 2.5 μm; PM_{10}=particles less than 10 μm; $PM_{2.5-10}$=coarse fraction of PM_{10}.

[a]IQRs were used as increments.

[b]Covariates included age, years of education, pack-years of past smoking, history of high blood pressure, years lived with a smoker, and total exercise level.

[c]Covariates included pack-years of past smoking, body mass index, total physical exercise, and age within age stratum. Models were stratified by age (<65 vs. ≥65) and excluded over age 85 in 1977.

[d]Covariates included years of education, pack-years of past smoking, and alcohol use.

upon ambient $PM_{2.5}$ concentration (low $\leq 22\ \mu g/m^3$ < medium $\leq 40\ \mu g/m^3$ < high). For ANC, the RRs for those living in the areas of medium and high $PM_{2.5}$ concentrations are 1.23 (0.92, 1.64) and 1.29 (0.97, 1.71), respectively, compared to those living in the low areas. For CRC, the corresponding RRs are 1.03 (0.54, 1.95) and 1.64 (0.89, 3.04). Results for LC are not reported due to the small number of cases in each group.

We investigated the robustness of the observed relationships of $PM_{2.5}$ with ANC and CRC mortality by refitting the Cox models for various subgroups of male participants. We do not present the results for subgroups which include less than 20% of the total deaths for ANC and CRC mortality, nor do we present any results for LC mortality because of the small number of LC deaths. As can be seen in Table 4, the RR for an IQR increase in $PM_{2.5}$ for each subgroup is generally similar to the RR for the overall airport cohort of males indicating that the observed mortality–$PM_{2.5}$ relationships are not due to uncontrolled confounding by the variables in Table 4. Although some small differences in RR were observed between the two levels of a given variable (e.g. history of respiratory disease for CRC mortality), the 95% confidence intervals overlap considerably, and we cannot identify with any certainty a subgroup for which mortality may be more strongly related to $PM_{2.5}$ concentration. In a further analysis, $PM_{2.5}$ concentrations were adjusted downward by a factor of 0.8 based upon the amount of time participants reported spending indoors at baseline. Refitting these adjusted data resulted in RRs for ANC, CRC, and LC which are similar to and slightly larger than those reported for the unadjusted concentrations reported in Table 3.

Because some individuals moved from and among airsheds and because, on a yearly basis, pollutant levels in a given airshed may change, we decided to also conduct analyses in which pollutant concentration was treated as a time-dependent variable and was calculated for each individual as the mean of monthly data from 1973 (from 1977 for SO_4) through the time of each event in the risk set. Because some participants moved from the airport areas during the period 1977–1992, the person–years of follow-up and the numbers of events which could be analyzed were smaller (male ANC deaths=174, male CRC deaths=46, male LC deaths=7). The confidence intervals are generally wider due to the reduced numbers of events, and the point estimates of the RRs for ANC (1.48 [1.03, 2.12]) and for CRC (2.06 [0.96, 4.44]) mortality for the same $PM_{2.5}$ exposure increment (24.3 $\mu g/m^3$) are somewhat larger than those reported in Table 3 for the analyses using 1973–1977 mean concentration as the exposure variable. Data for LC mortality are not presented due to the small number of LC deaths (n=7). In two-pollutant models containing both $PM_{2.5}$ and $PM_{2.5-10}$, ANC mortality is related to $PM_{2.5}$ (RR=1.46, CI=0.90, 2.38), but not to $PM_{2.5-10}$ (RR=1.00, CI=0.77, 1.31). Similarly, CRC mortality is related to $PM_{2.5}$ (RR=1.85, CI=0.69, 4.95), but not $PM_{2.5-10}$ (RR=1.08, CI=0.63, 1.86).

Table 4. Adjusted ANC and CRC mortality rate ratios for males for a 24.3-$\mu g/m^3$ increment in mean $PM_{2.5}$ (1973–1977) for various subgroups of participants.

Independent variable		ANC mortality[a]		CRC mortality[b]	
		Deaths/*n*	RR (95% CI)	Deaths/*n*	RR (95% CI)
Overall		321/1283	1.24 (0.96, 1.60)	73/1187	1.66 (0.94, 2.92)
Past smoking	Never	191/839	1.23 (0.89, 1.70)	40/774	1.50 (0.71, 3.19)
	Ever	130/450	1.31 (0.87, 1.99)	33/419	1.73 (0.72, 4.17)
Tobacco smoke exposure	None	133/449	1.25 (0.85, 1.84)	31/415	1.29 (0.56, 2.96)
	Some	188/837	1.22 (0.87, 1.71)	43/780	1.81 (0.85, 3.85)
Occupational exposure	$\leq$10 years	284/1158	1.33 (1.01, 1.75)	64/1070	2.02 (1.08, 3.75)
Alcohol use	None	271/1114	1.34 (1.01, 1.77)	65/1040	1.68 (0.92, 3.04)
Housing density	High	283/1145	1.39 (1.06, 1.82)	65/1065	2.03 (1.11, 3.71)
Antioxidant pills	None/low	143/720	1.12 (0.77, 1.65)	30/668	1.91 (0.75, 4.84)
	High	160/519	1.31 (0.91, 1.88)	40/486	1.32 (0.63, 2.79)
CV disease history	No	158/913	1.19 (0.82, 1.72)	36/845	2.24 (0.95, 5.24)
	Yes	159/362	1.30 (0.91, 1.85)	37/327	1.38 (0.62, 3.08)
Resp disease history	No	262/1043	1.25 (0.94, 1.65)	58/969	1.80 (0.94, 3.45)
	Yes	58/234	1.26 (0.68, 2.31)	15/213	1.15 (0.36, 3.68)

Abbreviations: $PM_{2.5}$=particles less than 2.5 μm; ANC=all natural cause; CRC=underlying or contributing nonmalignant respiratory cause; RR=rate ratio; 95% CI=95% confidence interval; CV disease history=history of myocardial infarction, high blood pressure, stroke, or diabetes at baseline; resp disease history=history of chronic bronchitis, asthma, or emphysema at baseline.

[a]Covariates included age, years of education, pack-years of past smoking, history of high blood pressure, years lived with a smoker, and total exercise level.

[b]Covariates included pack-years of past smoking, body mass index, total physical exercise, and age within age stratum. Models were stratified by age (<65 vs. $\geq$65) and excluded over age 85 in 1977.

For ANC mortality, addition of either ozone or SO_2 to a model containing $PM_{2.5}$ did not result in a reduction in the RR for $PM_{2.5}$. In the two-pollutant model containing both $PM_{2.5}$ and SO_2, the RR for an IQR increment in SO_2 is 1.29 (0.86, 1.91) suggesting a possible independent effect of SO_2 on mortality. For the two-pollutant model containing $PM_{2.5}$ and SO_4, the RR for $PM_{2.5}$ dropped to 1.33 (0.86, 2.05) while the RR for SO_4 was 1.06 (0.88, 1.28). For CRC mortality, addition of either SO_2 or SO_4 to a model containing $PM_{2.5}$ resulted in no change in the $PM_{2.5}$ coefficient, and no independent positive association of either SO_2 or SO_4 with CRC mortality was observed. Ozone, however, is related to CRC mortality in both the single-pollutant ozone model (RR=2.02, CI=1.13, 3.60) and in the two-pollutant model (RR=1.91, CI=0.87, 4.18) with $PM_{2.5}$. Also the $PM_{2.5}$ RR was much reduced in the two pollutant model (RR=1.11, CI=0.41, 3.04) with ozone. This analysis in which pollutant concentration is treated as a time-dependent variable suggests that CRC mortality is more strongly related to ozone concentration than to $PM_{2.5}$ concentration.

In order to explore the question of whether mortality may be more closely related to recent $PM_{2.5}$ concentrations compared to long-term concentrations, we reran the models including as time-dependent variables both long-term $PM_{2.5}$ concentration (1973 to time of each event) and the difference between long-term $PM_{2.5}$ concentration and the $PM_{2.5}$ concentration for the month preceding each event. We thus simultaneously evaluated the effect of long-term ambient concentration and the effect of recent (one month) deviations from the long-term average. The addition of the short-term concentration deviation did not result in a meaningful change (>10%) in the coefficient for the long-term $PM_{2.5}$ concentration, nor was the short-term deviation term significant for either ANC or CRC mortality. Similar results were observed for 2- and 3-month deviations from the long-term average.

Discussion

In a previous analysis of the AHSMOG cohort (Abbey et al., 1999), we observed that long-term ambient PM_{10} concentration was significantly, positively related to ANC, CRC, and LC mortality in males, but not in females. In this smaller airport cohort we have found PM_{10} relationships of similar magnitude for males and no relationships for females. Upon dividing PM_{10} into fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) fractions, we observed for males that the relationships of $PM_{2.5}$ with ANC, CRC, and LC mortality were of similar or greater magnitude than the PM_{10} relationships (on the basis of an IQR increment in concentration), and we observed that $PM_{2.5-10}$ was not related to these outcomes. We consistently found similar relationships between $PM_{2.5}$ and mortality in models containing both $PM_{2.5}$ and $PM_{2.5-10}$, in models in which

ambient concentration was treated as a time-invariant and as a time-dependent exposure variable, in analyses of various subgroups of the cohort, and when adjusting ambient concentrations for amount of time spent indoors. Consistent with the weak correlations of $PM_{2.5}$ with SO_2 and SO_4 in this cohort, we found no evidence that the observed relationships of $PM_{2.5}$ with mortality could be accounted for by confounding by SO_2 or SO_4. In the time-dependent, but not the time-invariant analyses, we did see some evidence for an independent association of SO_2 with ANC mortality. In the time-dependent analyses we also saw indications that CRC mortality may have been more strongly related to long-term concentrations of ozone than to $PM_{2.5}$. With this possible exception for CRC mortality, we interpret this body of evidence to indicate one of two things. Either the constituent(s) of PM_{10} that is responsible for the observed mortality associations in this cohort is contained primarily in the fine fraction of PM_{10} or these observations are the result of a relationship between mortality and an unmeasured compound(s) closely correlated with $PM_{2.5}$ or visibility.

The $PM_{2.5}$–mortality relationships for the males in this cohort are generally consistent with the reported findings from the Six Cities Study (Dockery et al., 1993) in which a cohort of 8111 individuals were followed for approximately 15 years. In that study, $PM_{2.5}$ was found in a combined-gender analysis to be related to ANC (RR=1.35 using the 24.3-$\mu g/m^3$ increment of the AHSMOG study) and to LC (RR=1.51 for a 24.3-$\mu g/m^3$ increment) mortality. Although we did not find a statistically significant relationship between PM_{10} and cardiopulmonary mortality in our previous paper, in the current analysis of the airport cohort, for cardiopulmonary mortality as the underlying cause of death we observed a RR=1.25 (CI=0.92, 1.71) for an IQR increment of $PM_{2.5}$, also consistent with that observed by Dockery *et al.* In contrast to our findings, mortality in the Six Cities Study was found to also be related to SO_4 in single-pollutant models. In that study, however, SO_4 and $PM_{2.5}$ were highly correlated while for the AHSMOG study, these two pollutants were poorly correlated (r=0.33). Similarly, the $PM_{2.5}$ findings for males from the AHSMOG airport cohort were generally consistent with those from the American Cancer Society (ACS) cohort in which the 7-year mortality of 552,138 adults living in 151 metropolitan areas was ascertained (Pope et al., 1995). In that study, for an equivalent increment (24.3 $\mu g/m^3$) in $PM_{2.5}$, for males, RRs of 1.18 for ANC, 1.10 for LC, and 1.24 for cardiopulmonary mortality were observed. Again, in contrast to the AHSMOG results, Pope et al. (1995) observed that in single-pollutant models SO_4 was significantly related to ANC, LC, and cardiopulmonary mortality for males.

In the previous manuscript, PM_{10} was not found to be significantly related to mortality for females of the AHSMOG cohort (Abbey et al., 1999). In general, the observed relationships for specific causes of death were inverse or small. We observed the same phenomenon in the airport cohort, and did not observe any meaningful relationships between mortality and either PM_{10} or $PM_{2.5}$ for females. No such gender differences were found in the Six Cities Study. In the ACS study, the particle–mortality relationship was present in males but not females for LC, but no gender differences were observed for the other outcomes. Although males in the AHSMOG study cohort spent more time outdoors than females, fine particles generally penetrate well into living spaces, and a significant difference in exposure based upon time outdoors is probably not the explanation. Males in this cohort did have a history of greater past smoking and had more occupational exposures than did females, and females tended to have diets higher in antioxidants than males. We have no convincing explanation, however, for the differences in the PM associations between the males and females of the AHSMOG cohort. This is an area in which further investigation is warranted.

In view of the frequent observations that short-term elevations of PM are associated with mortality (Dockery et al., 1992; Schwartz, 1993; Schwartz and Dockery, 1992; Loomis et al., 1999), and knowing that level of short-term PM exposure is usually well correlated with long-term ambient concentration, we wondered to what extent our findings of relationships between long-term exposure and mortality might reflect mechanisms or associations which were more short-term in nature. Although we did not attempt to estimate ambient $PM_{2.5}$ concentrations for the 1–5 days immediately preceding death, we did add to the long-term model a variable which estimated the deviation of the ambient $PM_{2.5}$ concentration for the month prior to which death occurred from the long-term average concentration. We did not observe any meaningful relationships between the variable representing short-term deviations in $PM_{2.5}$ concentrations and mortality, nor did we see a meaningful change in the RR for the long-term ambient $PM_{2.5}$ concentration when we added the short-term variable. While we cannot rule out the presence of very short-term effects (e.g. 1–5 days), we found no evidence in this cohort that mortality was related to anything other than long-term concentration of $PM_{2.5}$. It is still not clear, however, whether exposure which occurs in the remote past or at an earlier stage of life is more or less strongly related to mortality than exposure which may have occurred more recently. This is an area in which further research is needed.

A limitation of this study is that ambient $PM_{2.5}$ concentration was not measured directly for the duration of this study but was estimated from airport visibility which is also correlated with other pollutants including particles with diameter somewhat larger than 2.5 μm. The estimates of daily $PM_{2.5}$ used for this study, however, were based

upon site- and season-specific regression equations in which actual measures of ambient $PM_{2.5}$ were used to scale the daily measures of visibility. The methods and precision of using airport visibility for estimating ambient $PM_{2.5}$ concentrations have been described for an earlier subset of these data (Abbey et al., 1995b). Using updated (1979–1993) $PM_{2.5}$ and visibility data, we calculated a split-halves correlation coefficient of 0.72 between daily measured and estimated $PM_{2.5}$ at the monitoring sites. Another weakness in comparing the relative roles that $PM_{2.5}$ and $PM_{2.5-10}$ play in mortality associations is that the relative precision with which our estimates of ambient $PM_{2.5}$ and $PM_{2.5-10}$ reflect actual exposure to individuals is unknown. Estimation of ambient PM_{10} concentrations for individual participants has been discussed in detail in the previous manuscript (Abbey et al., 1999) and in an earlier methods paper (Abbey et al., 1995a), and a correlation coefficient (r) of 0.86 was found between estimated and measured monthly mean PM_{10} concentrations at monitoring stations located throughout the study area. The precision of the $PM_{2.5-10}$ estimates across airsheds is unknown, however. Because $PM_{2.5-10}$ is calculated as the difference of PM_{10} and $PM_{2.5}$ concentrations, both estimated with error, under most circumstances one might expect ambient $PM_{2.5-10}$ concentration to be estimated with less precision than ambient $PM_{2.5}$ concentration. Furthermore, because small particles penetrate more effectively into indoor spaces than larger particles, one would expect personal exposure to be more precisely estimated by ambient $PM_{2.5}$ concentrations than by ambient $PM_{2.5-10}$ concentrations. Such imprecision in estimation of $PM_{2.5-10}$ exposure could result in a bias towards the null and a finding of no relationship between the coarse fraction of PM_{10} and mortality where one actually exists. We thus cannot conclude with certainty that $PM_{2.5-10}$ has no relationship to mortality. However, because the relationships of both PM_{10} and $PM_{2.5}$ to mortality are of similar magnitude for equivalent IQR increments in concentration, and because addition of $PM_{2.5-10}$ and other pollutants to the $PM_{2.5}$ models does not change the $PM_{2.5}$ association, we can conclude that the previously observed relationships of mortality with PM_{10} can be explained by an underlying relationship of mortality with the fine fraction of PM_{10}. As in any observational study, we cannot rule out the possibility that the associations observed with $PM_{2.5}$ are the result of confounding by unmeasured pollutants which are closely correlated with $PM_{2.5}$ or visibility, nor can we speculate about the characteristics or the specific size limits of the fine particle fraction which are most closely related to mortality. Other limitations of this study such as possible confounding by past tobacco smoke exposure, possible underreporting of current smoking, use of ambient concentrations rather than measures of personal exposure, and measurement error of concentrations of pollutants other than $PM_{2.5}$ and $PM_{2.5-10}$ have been previously discussed (Abbey et al., 1999).

We concluded that the previously observed relationships between long-term PM_{10} concentrations and mortality in male members of the AHSMOG cohort can be explained by underlying relationships of ANC, CRC, and LC mortality with the fine fraction of PM_{10} (represented by $PM_{2.5}$ in this analysis). Although neither sulfate nor SO_2 concentration appeared to be responsible for the $PM_{2.5}$–mortality associations, the $PM_{2.5}$–CRC mortality relationship may have been due to an underlying association between ozone and CRC mortality. We saw no evidence that the coarse fraction of PM_{10} was related to mortality. We could find no evidence that the association of long-term $PM_{2.5}$ concentration to mortality was the result of an underlying relationship of short-term concentration to mortality, although our methods for testing this may have lacked sensitivity.

Disclaimer

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References

Abbey D.E. et al. Estimating cumulative ambient concentrations of air pollutants: description and precision of methods used for an epidemiological study. *Arch. Environ. Health* 1991: 46 (5): 281–287.

Abbey D.E. et al. Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a non-smoking population. *Arch. Environ. Health* 1993: 48: 33–46.

Abbey D.E. et al. Estimated long-term ambient concentrations of PM_{10} and development of respiratory symptoms in a nonsmoking population. *Arch. Environ. Health* 1995a: 50 (2): 139–152.

Abbey D.E. et al. Estimating fine particulates less than 2.5 microns in aerodynamic diameter (PM2.5) from airport visibility data in California. *J. Exposure Anal. Environ. Epidemiol.* 1995b: 5: 161–180.

Abbey D.E. et al. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am. J. Respir. Crit. Care Med.* 1999: 159: 373–382.

Breslow N.E. et al. Multiplicative models and cohort analysis. *J. Am. Stat. Assoc.* 1983: 78: 1–12.

Dockery D.W. et al. Air pollution and daily mortality: associations with particulates and acid aerosols. *Environ. Res.* 1992: 59: 362–373.

Dockery D.W. et al. An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med.* 1993: 329: 1753–1759.

Gold D.R. et al. Particulate and ozone pollutant effects on the respiratory function of children in southwest Mexico City. *Epidemiology* 1999: 10: 8–16.

Hodgkin J.E. et al. COPD prevalence in nonsmokers in high and low photochemical air pollution areas. *Chest* 1984: 86 (6): 830–838.

Kleinbaum D.G. Survival Analysis: A Self-Learning Text. Springer-Verlag, New York, 1996.

Lippman M., and Thurston G.W. Sulfate concentrations as an indicator of ambient particulate matter air pollution for health risk evaluations. *J. Expos. Anal. Environ. Epidemiol.* 1996: 6: 123–146.

Loomis D. et al. Air pollution and infant mortality in Mexico City. *Epidemiology* 1999: 10: 118–123.

Maldonado G., and Greenland S. Simulation study of confounder-selection strategies. *Am. J. Epidemiol.* 1993: 138 (11): 923–936.

Pope C.A., and Dockery D.W. Acute health effects of PM_{10} pollution on symptomatic and asymptomatic children. *Am. Rev. Respir. Dis.* 1992: 145: 1123–1128.

Pope C.A. et al. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am. J. Respir. Crit. Care Med.* 1995: 151: 669–674.

Schwartz J. Air pollution and daily mortality in Birmingham, Alabama. *Am. J. Epidemiol.* 1993: 137: 1136–1147.

Schwartz J., and Dockery D.W. Increased mortality in Philadelphia associated with daily air pollution concentrations. *Am. Rev. Respir. Dis.* 1992: 145: 600–604.

Thurston G.D. et al. Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. *Environ. Res.* 1994: 65: 271–290.

Winer A.M. et al. Characterization of air pollution exposures in the California South Coast Air Basin: application of a new regional human exposure (REHEX) model. In: Final Report, Contract # TSA 106-01-88, South Coast Air Quality Management District, Statewide Air Pollution Research Center, University of California, Riverside, CA, 1989, pp. 33–47.