Journal of Exposure Science and Environmental Epidemiology (2007) 17, 279–287

www.nature.com/jes

Association between $PM_{2.5}$ and all-cause and specific-cause mortality in 27 US communities

MEREDITH FRANKLIN, ARIANA ZEKA AND JOEL SCHWARTZ

Exposure, Epidemiology and Risk Program, Department of Environmental Health, Harvard School of Public Health, 401 Park Drive, Boston, MA, USA

While fine mode particulate matter ($PM_{2.5}$) forms the basis for regulating particles in the US and other countries, there is a serious paucity of large population-based studies of its acute effect on mortality. To address this issue, we examined the association between $PM_{2.5}$ and both all-cause and specific-cause mortality using over 1.3 million deaths in 27 US communities between 1997 and 2002. A two-stage approach was used. First, the association between $PM_{2.5}$ and mortality in each community was quantified using a case-crossover design. Second, meta-analysis was used to estimate a summary effect over all 27 communities. Effect modification of age and gender was examined using interaction terms in the case-crossover model, while effect modification of community-specific characteristics including geographic location, annual $PM_{2.5}$ concentration above $15\,\mu g/m^3$ and central air conditioning prevalence was examined using meta-regression. We observed a 1.21% (95% CI 0.29, 2.14%) increase in all-cause mortality, a 1.78% (95% CI 0.20, 3.36%) increase in respiratory related mortality and a 1.03% (95% CI 0.02, 2.04%) increase in stroke related mortality with a $10\,\mu g/m^3$ increase in previous day's $PM_{2.5}$. The magnitude of these associations is more than triple that recently reported for PM_{10}, suggesting that combustion and traffic related particles are more toxic than larger sized particles. Effect modification occurred in all-cause and specific-cause deaths with greater effects in subjects ≥ 75 years of age. There was suggestive evidence that women may be more susceptible to $PM_{2.5}$ effects than men, and that effects were larger in the East than in the West. Increased prevalence of central air conditioning was associated with a decreased effect of $PM_{2.5}$. Our findings describe the magnitude of the effect on all-cause and specific-cause mortality, the modifiers of this association, and suggest that $PM_{2.5}$ may pose a public health risk even at or below current ambient levels.
Journal of Exposure Science and Environmental Epidemiology (2007) **17,** 279–287. doi:10.1038/sj.jes.7500530; published online 27 September 2006

Keywords: *$PM_{2.5}$, case-crossover, particulate matter, mortality, specific-cause mortality, meta-analysis, effect modification.*

Introduction

Epidemiological and toxicological studies conducted on particles with an aerodynamic diameter of $2.5\,\mu m$ or less ($PM_{2.5}$), although limited in number, indicate that $PM_{2.5}$ has substantially greater toxicity than larger particles (Schwartz et al., 1996; Burnett et al., 2000; Cifuentes et al., 2000). One reason for the lack of studies investigating the health effects of $PM_{2.5}$ may be that it was not consistently monitored by the Environmental Protection Agency (EPA) until 1999. Additionally, studies examining the association between $PM_{2.5}$ and daily deaths have been conducted in a limited number of locations not chosen to be representative of the general population, leaving considerable uncertainty as to the population average slope of the association. Also, these studies did not look at effect modification by individual factors and community characteristics, nor did they generally have the statistical power to examine the relationship with specific-cause mortality.

Increased rates of mortality, particularly all-cause, respiratory or cardiovascular, associated with exposure to PM have been observed in epidemiologic studies (Dominici et al., 2003), and it has been suggested that inflammatory responses are involved. In a recent review, van Eeden et al. (2005) point out that the local inflammatory response in the lung associated with PM could worsen chronic obstructive pulmonary disease (COPD), and the systemic inflammatory response could worsen existing cardiovascular disease (including stroke). The local and systemic inflammatory reactions include elevation in cytokines, increase in acute phase proteins such as C-reactive protein, increase in clotting factors, destabilization of atherosclerotic plaques and cardiac arrhythmias (van Eeden et al., 2005). While the exact role of these complex inflammatory responses is not fully understood, they may contribute to the observed increase in acute mortality following exposure to PM.

In this study, we examined the association between $PM_{2.5}$ and all-cause mortality as well as respiratory, cardiovascular and stroke related causes of mortality in a large sample of more than 1.3 million deaths in 27 communities across the

1. Address all correspondence to: M Franklin, Harvard School of Public Health, Department of Environmental Health, Landmark Center West, 401 Park Drive, Room 412-E, Boston, MA 02215, USA.
Tel.: +1 617 384 8837. Fax: +1 617 384 8859.
E-mail: mfrankli@hsph.harvard.edu
Received 16 May 2006; accepted 25 August 2006; published online 27 September 2006

continental US between 1997 and 2002. The primary aims of this study were: to determine the strength of the associations; to determine whether there were differing associations between $PM_{2.5}$ exposure and mortality from different causes and at different lag periods; and to examine whether selected individual and community-specific characteristics affected these associations.

Previous studies have tended to examine the health effects of PM at various exposure time periods and have found that associations were weaker with concurrent rather than lagged exposures, but these associations can differ by cause of death (Braga et al., 2001; Zanobetti et al., 2002). To address this issue, we examined the association using same day exposure (lag 0), previous day exposure (lag 1) and the mean of 2-day exposures (lag 0–1) for each cause of death. Effect modification by age and gender were addressed in the analysis to determine whether certain subgroups of the population had differential associations with $PM_{2.5}$. We tested whether the slope of the $PM_{2.5}$-mortality association differed between communities in the East versus the West and between communities meeting versus exceeding the annual average National Ambient Air Quality Standard (NAAQS) of 15 $\mu g/m^3$. Prevalence of household central air conditioning use in each community was examined to test the hypothesis that an air-conditioned environment may reduce the effect of ambient $PM_{2.5}$ exposure. Above testing for effect modification, we also sought to explain variability between community-specific effect estimates with these community-varying characteristics.

Materials and methods

We selected 27 communities that had $PM_{2.5}$ monitoring and daily mortality data for at least 2 years of a 6-year period spanning from January 1, 1997 to December 31, 2002. The data employed in our analysis were obtained from several sources including the National Center for Health Statistics (NCHS) for the 1997–2000 mortality records, the state public health departments of California, Michigan, Minnesota, Pennsylvania, Texas and Washington for the 2000–2002 mortality records, the EPA for $PM_{2.5}$ concentrations, the Harvard School of Public Health (HSPH) for Boston area $PM_{2.5}$ concentrations, the National Climatic Data Center (NCDC) for meteorological parameters and the Department of Housing and Urban Development (HUD) for data on housing characteristics. We were interested in examining the association between $PM_{2.5}$ concentrations and mortality in metropolitan areas. However, we were restricted to conducting the analysis for the entire county surrounding each metropolitan area (which we call a ''community'') of interest because the mortality data from both the NCHS and state health departments provided location of death at a county resolution. In Washington, DC and Boston, the metropolitan area extends beyond the boundaries of one county so we aggregated air pollution and mortality data from adjacent counties. For New York city, we restricted the data to Manhattan out of concern that the canyon effects from large buildings would make the monitors less representative of the outlying boroughs.

Mortality Data

Until 2000, the NCHS provided researchers with national data sets of daily mortality records, which they created by aggregating state data. After 2000, the NCHS no longer provided the date of death in these data sets. We therefore had to rely on data acquired through requests to the aforementioned state public health departments for the 2001 and 2002 study years. All mortality data used in this study provide non-confidential information on individuals including state of death, county of death, age, gender, date of death and primary cause of death. For this study, we examined only those individuals who died of non-accidental causes (i.e. for 1997–1998, 9th revision International Classification of Diseases (ICD9) codes $\geq$800 and for 1999–2002, 10th revision ICD codes (ICD10) V01-Y98 were excluded). Specific causes were derived from the ICD code for the primary cause of death. The particular causes examined in this study were respiratory disease (ICD9 460–519 and ICD10 J00–J99), cardiovascular disease (ICD9 390–429 and ICD10 I01–I52) and stroke (ICD9 430–438 and ICD10 I60–J69).

Air Pollution, Meteorological and Housing Data

The majority of the air pollution data was retrieved from the EPA's Air Quality System Technology Transfer Network (AQS TTN, 2006) which provides daily and hourly $PM_{2.5}$ concentrations from the EPA's National and State Local Ambient Monitoring Stations. For the Boston area, we had access to daily $PM_{2.5}$ concentration data from the HSPH monitor located in downtown Boston which started earlier than the EPA's Boston monitor (start date of 1998 for Harvard's monitor versus 1999 for the EPA monitor). The sampling methodology for the HSPH monitor is in accordance with that used by the EPA, so there were no comparability issues in using these data.

Officially the EPA began monitoring $PM_{2.5}$ in 1997, however, most sites did not become operational until 1999. There are typically multiple monitors located within a county with some monitors providing integrated daily measurements and others providing continuous hourly measurements of $PM_{2.5}$. We focused on integrated daily measurements since the mortality data were only available at a daily time resolution, and integrated samplers do not have the problem of loss of semi-volatile elements associated with hourly samplers (Allen et al., 1997).

When more than one $PM_{2.5}$ monitor was available for a county, it was necessary to first determine which monitors represented a general population exposure over the desired

area. To do this, correlation coefficients were computed for each pair of monitors within the county. Any monitor that was not well correlated with the others ($r<0.8$ for 2 or more monitor pairs within a county) likely measured a local pollution source that would not represent the general population exposure over the entire county. Such monitors were deleted from the analysis. Once appropriate monitors were identified, it was necessary to determine a summary measure of $PM_{2.5}$ concentrations over the county. As the sampling schedule differed by monitor, with some having daily and others having measurements every 3–6 days, taking a simple average across multiple monitors would capture variation in monitor measurement patterns rather than the true variability in concentrations across the days measured in the county. To address this issue, we used an alternate averaging method based on an algorithm previously described by Schwartz (2000). After averaging we had almost daily $PM_{2.5}$ concentrations for each of the 27 communities.

Meteorological data for each community in the study were obtained from the NCDC (2006). Daily records of dry bulb and dew point temperature were retrieved from the predominant weather station closest to each of the 27 communities and were matched by date with the daily $PM_{2.5}$ concentrations. We derived daily values of apparent temperature (T_{ap}), a measure which reflects the temperature the body actually perceives, from the dry bulb (T) and dew point (T_{dp}) temperatures using the following equation: $T_{ap} = -2.653 + 0.994T + 0.0153T_{dp}^2$ (all temperatures in Celsius).

Data for community-specific prevalence of household central air conditioning were obtained from the American Housing Survey available on the HUD website (AHS, 2006). Survey data were available for all communities and for almost every year in the study period, so we averaged the data over the available years to obtain one value of central air conditioning prevalence per community.

Statistical Analysis

The statistical analysis was performed in two stages. In the first stage, a time-stratified case-crossover design was applied to examine the association between exposure to $PM_{2.5}$ and daily mortality in each community. This design is well suited to the study of air pollution exposure events on acute risk health effects such as mortality (Mittleman et al., 1995) because it inherently eliminates confounding by individual subject characteristics and longer time-varying covariates such as season (Bateson and Schwartz, 1999). As a result, the use of this design for air pollution studies is becoming widespread. Variables such as temperature and day of the week remain potential confounders because their short-term temporal fluctuations could be correlated with those of $PM_{2.5}$ concentrations. These variables were addressed by including an indicator variable for day of the week as well as a quadratic spline of apparent temperature on the day of and the day before death in the model.

For each community, cases were defined as the set of all decedents during the study period. By definition of the case-crossover design, these cases acted as their own controls on a set of predefined control days proximate to the time they became cases. A time-stratified approach was used as it has been shown to produce unbiased conditional logistic regression estimates (Janes et al., 2005). Control days for a particular subject were chosen to be every third day within the same month and year that death occurred. Every third day was chosen to reduce autocorrelation between $PM_{2.5}$ concentrations on successive days. Using a relatively short, month-long control period controls seasonal confounding and has been shown to produce unbiased estimates and coverage probabilities in simulation studies (Bateson and Schwartz, 1999). Conditional logistic regression was used to implement the case-crossover design. A lag 1 model for example, was structured such that the $PM_{2.5}$ concentration the day before a particular subject's death was compared to the concentrations the day before his or her control days. The resultant effect size estimates were expressed as a percent increase in mortality associated with a $10\,\mu g/m^3$ increase in previous day's $PM_{2.5}$ concentration. We also estimated the percent increase in mortality associated with $PM_{2.5}$ concentration the day of the event and the average of the concentrations on the same day and the day before the event (lag 0–1). As there were some randomly missing exposure data, we were unable to make meaningful use of a distributed lag model. Effect modification by age and gender was tested by separately incorporating an interaction with $PM_{2.5}$ into the conditional logistic regression model.

In doing multi-community studies, individual community estimates are often combined to generalize an overall effect across the study domain (Samoli et al., 2001). Thus, the second stage of the statistical analysis involved a meta-analysis of the community-specific effect estimates and their standard errors to obtain a pooled effect estimate. Heterogeneity in the pooled effect across the 27 communities was addressed first by using a random effects meta-analysis to obtain a 'heterogeneity' variance component (representing the true heterogeneity in response, above what would be expected by the stochastic variability in the estimates), and then by a meta-regression seeking to explain this heterogeneity. To test for significant heterogeneity, which indicated whether random effects were necessary, a Q-statistic was computed and compared to a χ^2 distribution with 26 degrees of freedom. Factors that differ between communities could be significant effect modifiers of the $PM_{2.5}$-mortality association and may explain some of the heterogeneity (Schwartz, 2000). To address this, we applied a meta-regression to examine three across-community varying characteristics: geographical region (East or West), whether the annual concentration of $PM_{2.5}$ exceeded the NAAQS of $15\,\mu g/m^3$ and the prevalence of central air conditioning.

The SAS statistical software package (SAS Institute Inc., 2003) was used to manage all data and implement the conditional logistic regression model to generate community-specific effect estimates. Meta-analysis and meta-regression were performed using the R language (R 2.2.1, 2005).

Results

The summary data for each community are presented in Table 1. In total, we examined 1,310,781 deaths between 1997 and 2002 across the 27 communities. Of these, respiratory disease accounted for 9.7%; heart disease accounted for 31.5%; and stroke accounted for 7.3% of all deaths.

The mean and s.d. for daily $PM_{2.5}$ concentration and apparent temperature, an indicator for whether a particular community had summer peaking $PM_{2.5}$ concentrations, and the percent of homes with central air conditioning over the data years for each community are also shown in Table 1. $PM_{2.5}$ concentrations ranged from 9.3 $\mu g/m^3$ in Palm Beach, FL to 28.5 $\mu g/m^3$ in Riverside, CA, while the mean concentration across all communities was 15.7 $\mu g/m^3$. On average there were 5.9% missing data for the 26 locations for which we obtained an adjusted daily $PM_{2.5}$ concentration from the EPA network, while the Boston HSPH site had 23.8% missing data due to a problem with the monitor in 2000.

The community-specific estimates of the association between all-cause deaths and exposure to $PM_{2.5}$ on the day before death are illustrated in Figure 1. We saw a statistically significant effect in large communities in the Northeast (Boston, Manhattan, Philadelphia), the Ohio River Valley (Cleveland, Columbus), the Midwest (Chicago, Memphis, Milwaukee) and the Southwest (Fresno, Phoenix, Sacramento, San Diego).

The results of pooling these estimates are presented in Table 2. We found significant heterogeneity amongst the community-specific effect estimates (Q-statistic $P \leq 0.001$) for all-cause, respiratory and cardiovascular mortality. The test for homogeneity was not rejected for the lag 1 and lag 0–1 exposure periods for stroke, indicating a fixed-effects

Table 1. Community characteristics.

City	Years of available data	Total deaths	Respiratory[a]	Cardiovascular[a]	Stroke[a]	Mean (SD) daily $PM_{2.5}$ ($\mu g/m^3$)	Summer peaking $PM_{2.5}$?	Mean (SD) daily apparent temperature (°C)	% (SD) homes with central Air conditioning
Birmingham, AL	1999–2000	17,361	10.2	27.7	8.5	20.4 (9.8)	Y	17.9 (10.6)	76.6 (1.9)
Boston, MA[b]	1998–2000	71,025	11.8	28.3	6.3	10.4 (6.5)	Y	10.3 (10.1)	16.9 (2.4)
Chicago, IL	1999–2000	87,729	9.1	33.2	6.6	17.4 (8.6)	N	9.5 (11.8)	50.0 (2.2)
Cincinnati, OH	1999–2000	18,810	10.2	28.7	7.8	18.6 (8.2)	Y	13.2 (11.2)	58.2 (4.2)
Cleveland, OH	1999–2000	31,846	7.8	36.1	6.0	18.3 (9.5)	Y	10.0 (11.3)	40.5 (3.0)
Columbus, OH	1999–2000	19,057	9.6	30.0	7.4	17.6 (9.3)	Y	11.3 (11.6)	72.1 (3.5)
Dallas, TX	1999–2002	55,575	9.0	31.1	7.2	13.1 (6.1)	Y	19.6 (11.2)	88.9 (3.0)
Detroit, MI	1999–2002	72,327	8.2	37.2	5.9	16.5 (9.3)	Y	10.3 (11.5)	53.4 (4.2)
Fresno, CA	1999–2002	21,599	10.7	32.8	8.8	22.5 (21.6)	N	16.6 (8.4)	78.2 (3.4)
Houston, TX	1999–2002	86,370	7.9	30.3	7.8	12.9 (5.9)	Y	22.2 (10.0)	83.8 (1.2)
Indianapolis, IN	1999–2000	18,162	10.3	29.0	7.2	17.0 (8.0)	Y	12.0 (11.6)	77.5 (2.0)
Las Vegas, NV	1999–2000	19,664	11.0	31.7	6.8	11.1 (6.6)	N	18.9 (9.7)	92.5 (2.6)
Los Angeles, CA	1999–2002	227,332	9.9	36.1	7.7	22.3 (12.5)	N	16.4 (4.1)	33.5 (1.9)
Manhattan, NY	1999–2000	31,101	8.7	33.3	4.0	16.3 (8.52)	Y	12.2 (10.6)	9.4 (0.5)
Memphis, TN	1999–2000	18,476	8.8	33.7	8.4	15.7 (7.1)	Y	18.3 (11.4)	75.6 (3.5)
Milwaukee, WI	1997–2000	36,637	9.9	31.8	8.0	14.1 (8.5)	N	8.9 (11.4)	50.8 (3.8)
Minneapolis, MN	1999–2002	33,501	9.8	21.9	7.6	11.4 (7.2)	N	7.9 (12.6)	62.2 (15.0)
Palm Beach, FL	1999–2000	25,233	7.9	38.0	6.8	9.3 (4.8)	N	26.6 (6.2)	87.6 (0.8)
Philadelphia, PA	1999–2002	66,074	8.5	30.3	6.7	15.3 (9.1)	Y	13.4 (11.0)	44.7 (3.2)
Phoenix, AZ	1999–2000	44,722	12.0	30.1	7.3	12.2 (6.8)	N	22.2 (9.5)	90.8 (1.0)
Pittsburgh, PA	1999–2002	68,155	9.5	32.8	7.2	15.6 (8.7)	Y	10.3 (10.9)	45.3 (3.7)
Riverside, CA	1999–2002	44,522	11.2	36.7	7.7	28.5 (17.1)	Y	21.0 (9.8)	72.0 (2.3)
Sacramento, CA	1999–2002	36,847	11.2	31.1	9.0	14.1 (13.5)	N	14.3 (6.7)	78.3 (0.6)
San Diego, CA	1999–2002	75,632	10.9	31.3	8.4	15.9 (8.3)	N	16.4 (4.1)	28.8 (5.6)
Seattle, WA	1999–2002	48,728	10.7	26.1	9.3	10.4 (6.4)	N	8.8 (5.8)	5.3 (0.3)
Tampa, FL	1999–2000	17,442	9.4	31.5	7.7	12.9 (5.7)	N	25.1 (7.8)	84.5 (3.5)
Washington, DC[c]	1999–2000	16,854	6.9	29.4	5.2	15.8 (8.7)	Y	14.7 (10.6)	80.9 (1.5)

[a]Percent of all cause mortality.
[b]Represents Boston metro area: Middlesex, Norfolk and Suffolk counties.
[c]Represents Washington and Arlington counties.

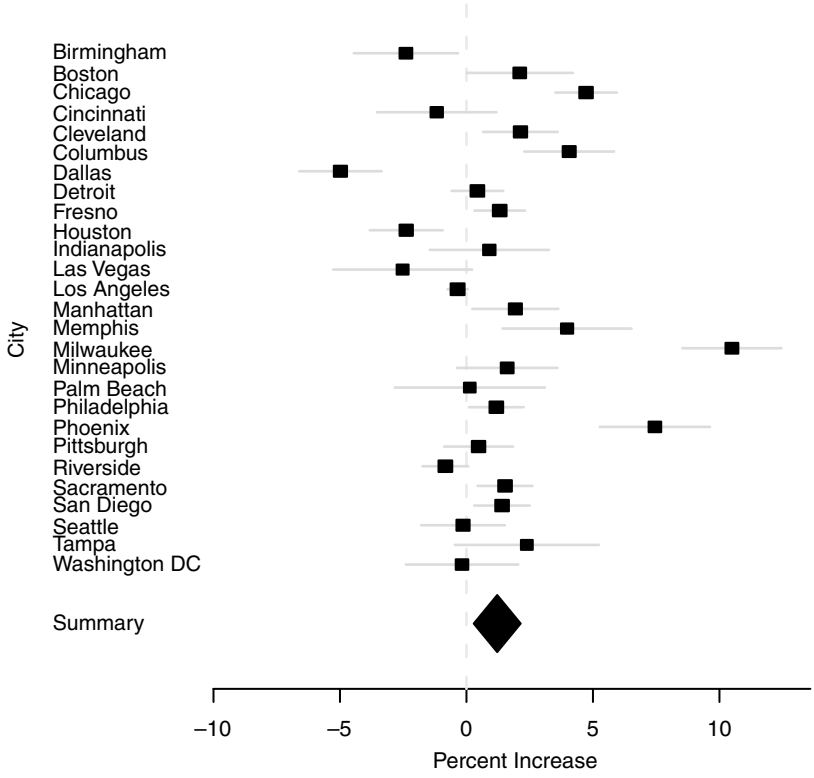

Figure 1. Community-specific estimates of the percent increase in all-cause mortality with a 10 $\mu g/m^3$ increase in previous day's concentration $PM_{2.5}$ (■ represents estimate and its size is inversely proportional to the variance; lines around ■ are 95% CI).

Table 2. Estimated percent increase in all-cause and specific-cause daily mortality with a 10 $\mu g/m^3$ increase in $PM_{2.5}$.

	Lag model					
	Lag 0		Lag 1		Lag 0–1	
Mortality cause	%	95% CI	%	95% CI	%	95% CI
All-cause[a]	0.67	−0.12, 1.46	1.21	0.29, 2.14	0.82	0.02, 1.63
Respiratory[a]	1.31	−0.10, 2.73	1.78	0.20, 3.36	1.67	0.19, 3.16
Cardiovascular[a]	0.34	−0.61, 1.28	0.94	−0.14, 2.02	0.54	−0.47, 1.54
Stroke	0.62[b]	−0.69, 1.94	1.03[c]	0.02, 2.04	0.67[c]	−0.23, 1.57

[a] P-value for test of homogeneity ≤ 0.001 for all lags.
[b] P-value for test of homogeneity $= 0.03$.
[c] P-value for test of homogeneity > 0.1.

meta-analysis was appropriate for pooling these estimates. As expected, we found a stronger association between lag 1 exposure and mortality than for same day exposure. All-cause deaths increased by 1.21% (95% CI 0.29, 2.14%), respiratory related deaths increased by 1.78 % (95% CI 0.20, 3.36) and stroke related deaths increased by 1.03% (95% CI 0.02, 2.04) with a 10 $\mu g/m^3$ increase in previous day $PM_{2.5}$ concentration. Although not significant, cardiovascular related deaths showed the same pattern. Therefore, in all cases the strongest associations between $PM_{2.5}$ and mortality occurred with exposure the day before death. Compared to lag 0, the effect sizes were 1.3–2.8 times larger for the lag 1 exposure. The lag 0–1 exposure did not perform better than the lag 1 exposure.

The lag 1 exposure period was used for all examinations of effect modification. Age was an effect modifier of the association between all-cause and specific-cause mortality and $PM_{2.5}$ exposure the day before death (Table 3), although the coefficient was only significant for all cause and stroke related mortality ($P = 0.02$ and $P = 0.03$). We note that the percent increase in all-cause and every specific-cause mortality with a 10 $\mu g/m^3$ increase in lag 1 $PM_{2.5}$ was

Table 3. Effect modification of age, gender, geographic location and attainment of the $PM_{2.5}$ NAAQS on the estimated percent increase in mortality with a $10\mu g/m^3$ increase in previous day's $PM_{2.5}$ concentration.

	Mortality cause							
	All-cause		Respiratory		Cardiovascular		Stroke	
Effect modifier[a]	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Age ≥ 75	1.66[b]	0.62, 2.70	1.85	0.27, 3.44	1.29	0.15, 2.42	1.52[b]	0.37, 2.67
Age < 75	0.62	−0.30, 1.55	1.53	−0.67, 3.74	0.26	−1.04, 1.56	−0.78	−2.32, 0.76
Male	1.06	0.07, 2.06	1.90	0.14, 3.65	0.52	−0.63, 1.66	0.79	−0.42, 2.02
Female	1.34	0.40, 2.27	1.57	−0.22, 3.35	1.30	0.14, 2.46	0.79	−0.51, 2.09
East[d]	1.95[c]	0.50, 3.40	2.66	0.33, 5.00	1.52	0.06, 2.98	1.16	−0.40, 2.73
West[e]	0.05	−1.80, 1.89	0.67	−2.00, 3.34	0.11	−2.03, 2.24	0.94	−0.38, 2.26
$PM_{2.5} > 15\,\mu g/m^3$	1.10	−0.43, 2.64	1.42	−0.84, 3.68	0.88	−0.87, 2.62	0.91	−0.28, 2.10
$PM_{2.5} \leq 15\,\mu g/m^3$	1.41	−0.49, 3.30	2.46	−0.49, 5.42	1.09	−1.15, 3.32	1.36	−0.56, 3.27

[a]Effect modification of age and gender was assessed by adding an interaction term to the case-crossover model. Effect modification by geographic location and NAAQS $PM_{2.5}$ standard was assessed by using meta-regression.
[b]*P*-value ≤ 0.05 for the coefficient of effect modification.
[c]*P*-value ≤ 0.1 for the coefficient of effect modification.
[d]Includes Birmingham, Boston, Chicago, Cincinnati, Cleveland, Columbus, Detroit, Indianapolis, Manhattan, Memphis, Milwaukee, Minneapolis, Palm Beach, Philadelphia, Pittsburgh, Tampa, Washington, DC.
[e]Includes Dallas, Fresno, Houston, Las Vegas, Los Angeles, Phoenix, Riverside, Sacramento, San Diego, Seattle.

Table 4. Effect modification of central air conditioning prevalence on the estimated percent increase in mortality with a $10\mu g/m^3$ increase in previous day's $PM_{2.5}$ concentration.

		Percent increase in mortality at percentile of air conditioning prevalence			
		25th percentile[a]		75th percentile[b]	
Mortality cause	Coefficient of effect modification *P*-value	%	95% CI	%	95% CI
All-cause	0.44	1.50	0.13, 2.88	0.85	−0.64, 2.35
Respiratory	0.33	2.27	0.27, 4.27	1.04	−1.29, 3.37
Cardiovascular	0.83	1.04	−0.54, 2.63	0.81	−0.93, 2.61
Stroke	0.99	1.04	−0.44, 2.53	1.03	−0.76, 2.83

[a]Prevalence of central air conditioning at the 25th percentile = 45%.
[b]Prevalence of central air conditioning at the 75th percentile = 80%.

significant for subjects 75 years of age or older. Moreover, these estimates were almost three times larger than the effect for those younger than 75 years of age.

Although gender was not a statistically significant modifier of the association between mortality and $PM_{2.5}$ exposure the day before death (Table 3), a suggestive pattern was seen. Females had a somewhat larger response than males, which was more pronounced for cardiovascular deaths, but reversed for respiratory deaths.

Meta-regression results (Table 3) of the effect modification by geographic location showed that while eastern communities exhibited statistically significant effect estimates which were much larger than western communities, none of the coefficients of effect modification were statistically significant at the $\alpha = 0.05$ level. Similarly, the coefficient of effect modification for attainment of the annual NAAQS $PM_{2.5}$ standard did not significantly modify the $PM_{2.5}$-mortality association. However, the effect size in communities with annual $PM_{2.5}$ below the standard was approximately 20% higher than in the more polluted communities.

Central air conditioning prevalence had a marked impact on the $PM_{2.5}$ effect size (Table 4). We examined the percent increase in mortality with a $10\,\mu g/m^3$ increase in lag 1 $PM_{2.5}$ at the 25th and 75th percentile of the distribution of air conditioning prevalence. At the 25th percentile (45%), we found that the effect estimates for all-cause and respiratory deaths were significant. At the 75th percentile (80%), the magnitude of the $PM_{2.5}$ effect for all-cause, respiratory and cardiovascular deaths dropped substantially.

We also looked at the effect in 15 of the 27 communities that had summer peaking $PM_{2.5}$ concentrations (Table 5). These communities have their highest seasonal average $PM_{2.5}$ concentration occurring in the summer months (June, July and August), and hence should exhibit greater effect

Table 5. Effect modification of central air conditioning prevalence on the estimated percent increase in mortality with a 10 $\mu g/m^3$ increase in previous day's $PM_{2.5}$ in cities with summer peaking $PM_{2.5}$ concentrations.

		Percent increase in mortality at percentile of air conditioning prevalence			
		25th percentile[a]		75th percentile[b]	
Mortality cause	Coefficient of effect modification *P*-value	%	95% CI	%	95% CI
All-cause	0.05	1.01	−0.30, 2.32	−0.55	−1.95, 0.85
Respiratory	0.04	0.76	−1.38, 2.90	−2.08	−4.47, 0.31
Cardiovascular	0.08	0.43	−0.86, 1.72	−1.02	−2.44, 0.41
Stroke	0.49	−0.18	−2.08, 1.73	0.69	−1.19, 2.57

[a]Prevalence of central air conditioning at the 25th percentile = 45%.
[b]Prevalence of central air conditioning at the 75th percentile = 77%.

modification by a characteristic only used in the summer. We found that central air conditioning prevalence significantly modified the association between all-cause ($P = 0.05$) and respiratory ($P = 0.04$) mortality and $PM_{2.5}$. Across all outcomes, the effect of $PM_{2.5}$ disappeared in communities with high central air conditioning prevalence and summer peaking particle concentrations.

Discussion

The EPA began regulating $PM_{2.5}$ in 1997 based on a few epidemiological and toxicological studies that provided evidence that smaller particles are more harmful to health than larger particles. Almost 10 years later there continues to be a lack of $PM_{2.5}$-health effects studies in the literature, particularly multi-year and multi-community based studies of its acute effect on specific causes of mortality. In our study of 27 communities and over 1.3 million deaths we found that in comparison to similar studies of PM_{10}, the association between $PM_{2.5}$ and daily mortality was over three times larger. For instance, a 10 $\mu g/m^3$ increase in previous day's PM_{10} has been associated with a 0.27% and 0.35% increase in all-cause mortality (Dominici et al., 2005; Zeka et al., 2005); we found this increase to be 1.21% with $PM_{2.5}$. A recent study of $PM_{2.5}$ and mortality in four Australian cities reported an almost identical effect size (Simpson et al., 2005) to ours. In our study, the largest specific-cause association with $PM_{2.5}$ occurred for respiratory related deaths and its magnitude was larger than that associated with PM_{10} (Zeka et al., 2005). It is plausible that the increased respiratory mortality is effected through inflammatory responses in pulmonary cells as observed in experimental studies (van Eeden et al., 2005).

We also found a significant association with deaths from stroke that was not modified by age, gender nor did it display significant heterogeneity across communities. Associations between PM_{10} and stroke deaths have been found (Hong et al., 2002; Zeka et al., 2005), and a recent epidemiological study attributed a significant increase in ischemic stroke hospital admissions to an increase in PM_{10} concentrations (Wellenius et al., 2005). Three possible mechanisms including induced systemic inflammatory response, changes in hemostatic factors, and decreased heart rate variability were suggested for this finding.

Notably, our effect estimates are larger than those obtained by converting the PM_{10} coefficients using the average $PM_{2.5}$ to PM_{10} ratio, and assuming all of the PM_{10} effect was due to $PM_{2.5}$. This indicates that there would be an underestimate of the risk of acute effects of $PM_{2.5}$ in studies using this approach. It also suggests that the greater degree of measurement error resulting from using ambient PM_{10} as a surrogate for personal exposure instead of ambient $PM_{2.5}$ may have introduced downward bias into the effect estimates. Thus, the greater effect size we observed likely reflects both the greater toxicity of $PM_{2.5}$ and absence of measurement error inherent in using PM_{10} as a surrogate for $PM_{2.5}$.

We examined subgroups of the population to determine whether the $PM_{2.5}$-mortality association differed from that of the overall population. Our observation of a statistically significant difference in the effect estimates for subjects 75 years and older suggests that the elderly are more susceptible to increases in $PM_{2.5}$. The elderly have been examined in several prior studies of health effects associated with particulate matter air pollution and are frequently linked to having increased susceptibility in comparison to younger individuals (Zeka et al., 2006). There have been fewer studies of gender in air pollution studies and we found suggestive evidence that women were more susceptible to the effects of $PM_{2.5}$, particularly with respect to cardiovascular related mortality. In the Atherosclerosis Risk in Communities Study (Schroeder et al., 2003) a significant association between lung function and 10-year incidence of coronary, heart disease (CHD) in both genders was found; however, lung function had a greater proportional effect on the hazard of developing CHD in women than in men. Suggested biological plausibility for this finding included gender differences in the

anatomy and physiology of the respiratory system, and differences in particle deposition in the lung (Bennett et al., 1996; Kim and Hu, 1998). An epidemiological study by Zanobetti and Schwartz (2000) found that the effect of PM_{10} on mortality was higher in women than in men, and Ito and Thurston (1996) found a similar effect in African American women.

Examination of community-specific characteristics as effect modifiers of the $PM_{2.5}$-mortality relationship led to interesting results. The magnitude of all effect estimates was consistently greater in eastern communities than in western communities, indicating that there is a regional difference in the effect of $PM_{2.5}$ exposure. The lack of statistical significance the may be explained by the fact that far fewer of the communities we examined were located in the West, and that we classified two south-centrally located communities (Dallas and Houston, TX) as ''western'' in order to increase the sample size for the West. The regional differences we observed are corroborated by a recent study by Dominici et al. (2006) who found that the association between a $10\,\mu g/m^3$ increase in $PM_{2.5}$ and hospital admissions for cardiovascular outcomes was significantly higher in the East than in the West.

Even though the change in the relationship was not statistically significant, a larger effect was observed for communities with annual concentrations below $15\,\mu g/m^3$ than above $15\,\mu g/m^3$. This pattern occurred for all-cause and each specific-cause of death, suggesting that health effects may still be seen below the NAAQS standard.

We found a marked decrease in the effect of $PM_{2.5}$ with an increase in central air conditioning prevalence. As it had been found that the association between PM_{10} and hospital admissions for cardiovascular and cardiopulmonary disease was significantly decreased in cities where central air conditioning use was higher (Janssen et al., 2002), we were interested in seeing whether we would see an effect of central air conditioning across our 27 communities. Overall, we found that central air conditioning resulted in a large, although not statistically significant, reduction in mortality associated with $PM_{2.5}$. As air conditioning is mostly used in the summer months, it was of interest to see how the $PM_{2.5}$-mortality association changed for a subset of communities having summer peaking $PM_{2.5}$ concentrations. For this subset, we found a substantial and statistically significant reduction in all-cause and respiratory mortality associated with $PM_{2.5}$ indicating that central air conditioning may provide a ''protective'' effect. This observed effect modification was likely due to a reduction in exposure to ambient $PM_{2.5}$ because of filters in air conditioners and low air exchange rates typical in air-conditioned homes. The latter is supported by the work of Sarnat et al. (2000) who showed that the slope of the association between personal exposure to $PM_{2.5}$ and ambient $PM_{2.5}$ was smaller in low ventilation environments.

Some of the variance in the estimated coefficients across all of the communities in our study represents true variation in the concentration-response relation, but much of it is stochastic variability. Geography accounts for 17% of the estimated true variation of all-cause deaths between communities but only 3% for stroke-related deaths. Whether or not a community meets the annual NAAQS standard contributes $<1\%$ of the estimated true variation. On the other hand, central air conditioning was able to explain 60% of the estimated true variation of respiratory deaths and 35% of all-cause deaths. While this is a substantial portion of the variation, particularly for respiratory deaths, unexplained variability remains. Likely candidates include variations in other factors that affect exposure such as time spent outdoors, other housing characteristics and variations in the composition of the particles. Toxicity of the particle may not solely be related to its size, but also to its composition (Laden et al., 2000). Unfortunately, information on composition was not available for us to explore its effect in these communities.

To investigate co-pollutants, Dominici et al. (2005) adjusted for ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide and found no change in the magnitude of the effect between PM_{10} and mortality, suggesting that the univariate association between particulate matter and mortality is not confounded by other pollutants. Similarly, Schwartz (2004) used a case-crossover approach to examine the PM_{10}-mortality association and found that when control days were matched on concentrations of gaseous air pollutants, the PM_{10} effect was not significantly changed from when no matching was done. Given this literature and the fact that inclusion of gases would reduce the power in our study, we chose not to investigate co-pollutants as there is no reason to believe they would behave any differently with the $PM_{2.5}$-mortality relationship.

Although we have taken an adjusted average of $PM_{2.5}$ concentrations from a few monitors to characterize a population exposure in each of the 27 communities, $PM_{2.5}$ is more spatially homogeneous than PM_{10}, for which this practice is widespread. Studies of personal exposure have shown that temporal fluctuations in outdoor $PM_{2.5}$ are a good surrogate for temporal fluctuations in personal exposure to $PM_{2.5}$ (Sarnat et al., 2000, 2005). Remaining exposure error would be expected to bias the estimated effect of $PM_{2.5}$ downward (Zeger et al., 2000).

In summary, our findings suggest that even at current and relatively low ambient concentrations, particulate matter air pollution continues to pose a public health risk.

Acknowledgements

This work was supported by the Harvard School of Public Health Environmental Protection Agency PM Center Grant R827353.

References

AHS. *Department of Housing and Urban Development, American Housing Survey*, Available from: www.huduser.org/datasets/ahs.html, accessed March, 2006.

Allen G., Sioutas C., Koutrakis P., Reiss R., Lurmann F., and Roberts P. Evaluation of the TEOM method for measurement of ambient particulate mass in urban areas. *JAWMA* 1997: 47(6): 682–689.

AQS TTN. *US Environmental Protection Agency, Air Quality System Technology Transfer Network*. Available from http://www.epa.gov/ttn/airs/airsaqs/, accessed March, 2006.

Bateson T., and Schwartz J. Control for seasonal variation time trend in case-crossover studies of acute effects of environmental exposures. *Epidemiology* 1999: 10(4): 539–544.

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

Braga A., Zanobetti A., and Schwartz J. The lag structure between particulate air pollution and respiratory and cardiovascular deaths in 10 US cities. *J Occup Environ Med* 2001: 43(11): 927–933.

Burnett R., et al. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. *Inhal Toxicol* 2000: 12(Suppl 4): 15–39.

Cifuentes L., Vega J., Köpfer K., and Lave L. Effect of the fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago, Chile. *JAWMA* 2000: 50: 1287–1298.

Dominici F., McDermott A., Daniels M., Zeger S., and Samet J. Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: mortality among residents of 90 cities. *J Toxicol Environ Health A* 2005: 68: 1071–1092.

Dominici F., McDermott A., Zeger S., and Samet J. National maps of the effects of particulate matter on mortality: exploring geographical variation. *Environ Health Perspect* 2003: 111(1): 39–44.

Dominici F., et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006: 295(10): 1127–1134.

Hong Y., Lee J., Ho K., Ha E., Schwartz J., and Christiani D. Effects of air pollutants on acute stroke mortality. *Environ Health Perspect* 2002: 110(2): 187–192.

Ito K., and Thurston G. Daily PM10-mortality associations: an investigation of at-risk subpopulations. *J Expo Anal Environ Epidemiol* 1996: 6(1): 79–95.

Janes H., Sheppard L., and Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implication for bias. *Epidemiology* 2005: 16(6): 717–725.

Janssen N., Schwartz J., Zanobetti A., and Suh H. Air conditioning and source-specific particles as modifiers of the effect of PM10 on hospital admissions for heart and lung disease. *Environ Health Perspect* 2002: 110(1): 43–49.

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

Laden F., Neas L., Dockery D., and Schwartz J. Association of fine particulate matter from different sources with daily mortality in six US cities. *Environ Health Perspect* 2000: 108(10): 941–947.

Mittleman M., Maclure M., and Robins J. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am J Epidemiol* 1995: 142(1): 91–98.

NCDC. *National Oceanic and Atmospheric Association, National Climactic Data Center*, Available from http://www.ncdc.noaa.gov/oa/ncdc.html, accessed January, 2006.

R 2.2.1. *A Language and Environment*, The R Development Core Team, Copyright © 2005.

Samoli E., et al. Investigating regional differences in short-term effects of air pollution on daily mortality in the APHEA project: a sensitivity analysis for controlling long-term trends and seasonality. *Environ Health Perspect* 2001: 109(4): 349–353.

Sarnat J., Brown K., Schwartz J., Coull B., and Koutrakis P. Ambient gas concentrations and personal particulate matter exposures: implications for studying the health effects of particles. *Epidemiology* 2005: 16(3): 385–395.

Sarnat J., Koutrakis P., and Suh H. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. *JAWMA* 2000: 50(7): 1184–1198.

SAS Institute Inc. *Version 9.1 of the SAS System for Windows*. Copyright © 2002-2003 Cary, NC, USA.

Schroeder E., et al. Lung function and incident coronary heart disease: the atherosclerosis risk in communities study. *Am J Epidemiol* 2003: 158(12): 1171–1181.

Schwartz J. Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. *Environ Health Perspect* 2000: 108: 563–568.

Schwartz J. Is the association of airborne particles with daily deaths confounded by gaseous air pollutants? An approach to control by matching. *Environ Health Perspect* 2004: 112(5): 557–561.

Schwartz J., Dockery D., and Neas L. Is daily mortality associated specifically with fine particles? *JAWMA* 1996: 46: 927–939.

Simpson R., et al. The short-term effects of air pollution on daily mortality in four Australian cities. *Aust NZ J Public Health* 2005: 29(3): 205–212.

van Eeden S., Yeung A., Quinlam K., and Hogg J. Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005: 2(1): 61–67.

Wellenius G., Schwartz J., and Mittleman M. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke* 2005: 36(12): 2545–2549.

Zanobetti A., and Schwartz J. Race, gender, and social status as modifiers of the effects of PM10 on mortality. *J Occup Environ Med* 2000: 42(5): 469–474.

Zanobetti A., et al. The temporal pattern of mortality responses to air pollution: a multi-city assessment of mortality displacement. *Epidemiology* 2002: 13(1): 87–93.

Zeger S., et al. Exposure Measurement Error in Time-Series Studies of Air Pollution: Concepts and Consequences. *Environ Health Perspect* 2000: 108(5): 419–426.

Zeka A., Zanobetti A., and Schwartz J. Short term effects of particulate matter on cause specific mortality: effects of lags and modification by city characteristics. *J Occup Environ Med* 2005: 62: 718–725.

Zeka A., Zanobetti A., and Schwartz J. Individual modifiers of the effects of particulate matter on daily mortality. *Am J Epidemiol* 2006: 163(9): 849–859.