Reduction in Fine Particulate Air Pollution and Mortality
Extended Follow-up of the Harvard Six Cities Study

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Rationale: A large body of epidemiologic literature has found an association of increased fine particulate air pollution (PM$_{2.5}$) with acute and chronic mortality. The effect of improvements in particle exposure is less clear.

Objectives: Earlier analysis of the Harvard Six Cities adult cohort study showed an association between long-term ambient PM$_{2.5}$ and mortality between enrollment in the mid-1970s and follow-up until 1990. We extended mortality follow-up for 8 yr in a period of reduced air pollution concentrations.

Methods: Annual city-specific PM$_{2.5}$ concentrations were measured between 1979 and 1988, and estimated for later years from publicly available data. Exposure was defined as (1) city-specific mean PM$_{2.5}$ during the two follow-up periods, (2) mean PM$_{2.5}$ in the first period and change between these periods, (3) overall mean PM$_{2.5}$ across the entire follow-up, and (4) year-specific mean PM$_{2.5}$. Mortality rate ratios were estimated with Cox proportional hazards regression controlling for individual risk factors.

Measurements and Main Results: We found an increase in overall mortality associated with each 10 µg/m$^3$ increase in PM$_{2.5}$ modeled either as the overall mean (rate ratio [RR], 1.16; 95% confidence interval [CI], 1.07–1.26) or as exposure in the year of death (RR, 1.14; 95% CI, 1.06–1.22). PM$_{2.5}$ exposure was associated with lung cancer (RR, 1.27; 95% CI, 0.96–1.69) and cardiovascular deaths (RR, 1.28; 95% CI, 1.13–1.44). Improved overall mortality was associated with decreased mean PM$_{2.5}$ (10 µg/m$^3$) between periods (RR, 0.73; 95% CI, 0.57–0.95).

Conclusion: Total, cardiovascular, and lung cancer mortality were each positively associated with ambient PM$_{2.5}$ concentrations. Reduced PM$_{2.5}$ concentrations were associated with reduced mortality risk.

Keywords: air pollution; cohort studies; follow-up studies; mortality

An extensive epidemiologic literature has documented an association of fine particulate air pollution with mortality (1, 2). Most of this research consists of time-series studies of the effects of particle exposures experienced in the few days before death. The estimated effect of particulate air pollution has been shown to increase as longer exposure periods (up to 7 wk) are considered, indicating exposures in the month(s) before death may be important (3–6). Cohort studies have associated mortality with mean particulate air pollution concentrations over much longer periods. Three follow-up cohort studies in the United States (7–10) and a recent pilot study from Europe (11) evaluated the effects of long-term average ambient concentrations of fine particles and other air pollutants over many years. These cohort studies used annual or multiyear average pollution concentrations as the exposure index, but did not examine the time periods responsible for the observed association. Cohort studies with follow-up during periods of substantial change in air pollution can address this question. The linkage between improvements in air quality and improved health outcomes is of considerable public health interest.

A small number of studies have assessed the effect of reductions in air pollution on mortality. Mortality in Utah Valley decreased by 3% when average particulate air pollution (PM$_{10}$) concentrations decreased by 15 µg/m$^3$ as the result of a 13-mo strike at a local steel mill (12). Mortality in Dublin decreased by 8% after a 36-µg/m$^3$ decrease in average particulate air pollution (black smoke) due to a ban on coal sales (13). Restrictions on the sulfur content of fuel oil in Hong Kong resulted in a 45% average reduction in SO$_2$ and the average annual trend in deaths from all causes declined 2% and from respiratory causes declined 3.9% (14). In these studies, improvements in mortality were observed in the months after well-defined improvements in ambient air quality.

Dockery and colleagues (7) evaluated the effects of long-term pollution exposure on survival of adults participating in the Harvard Six Cities Study monitored for 14 to 16 yr during the 1970s and 1980s. Exposure to particulate matter smaller than 2.5 µm in aerodynamic diameter (PM$_{2.5}$) was defined by the city-specific average during follow-up, ignoring the year-to-year fluctuations. The mortality rate ratio (RR) was 1.13 (95% confidence interval [CI], 1.04–1.73) for each 10-µg/m$^3$ increase in city-specific PM$_{2.5}$ concentrations. During follow-up, PM$_{2.5}$ concentrations dropped in all cities, although the rank ordering of cities was unchanged. Evaluation of time-varying PM$_{2.5}$ during this period showed slightly attenuated relative risk compared with estimates based on the average PM$_{2.5}$ over the entire period (15).

In this analysis, we extended the follow-up period through 1998. We evaluated the robustness of the previous findings with additional years of follow-up and examined the extent to which changes in PM$_{2.5}$ concentrations explain changes in mortality. Some of the results of this study have been previously reported in the form of an abstract (16, 17).

METHODS

Study Population and Follow-up

The study population consisted of 8,096 white participants residing in the following cities: Watertown, MA; Kingston and Harriman, TN; St. Louis, MO; Steubenville, OH; Portage, Wyocena, and Pardeeville, WI; and Topeka, KS. Participants were recruited between 1974 and 1977. The population and study design have been described previously (7),
and additional details are provided in the online supplement. Date and cause of death were determined by searching the National Death Index for calendar years 1979 to 1998. Deaths between 1974 and 1978 were identified from next-of-kin reports and Social Security records. Survival times were calculated as death date (or December 31, 1998, for surviving participants) minus enrollment date.

Air Pollution Concentrations
Each participant’s air pollution concentration was defined by city-specific mean concentrations of PM$_{2.5}$. During the original Six Cities follow-up (1979–1987), daily ambient PM$_{2.5}$ concentrations were measured at a centrally located air-monitoring station in each community (18). We estimated daily PM$_{2.5}$ concentrations after the shutdown of the Six Cities monitoring (1985–1998) using city-specific regression equations based on extinction coefficients (humidity-corrected visibility data from local airports) (19), routinely collected PM$_{2.5}$ concentrations (Environmental Protection Agency Aerometric Information Retrieval System [AIRS]) from representative monitors within 80 km, and indicators for season. (More details on the monitors selected and exposure metrics are provided in the online supplement.)

City-specific annual mean PM$_{2.5}$ was calculated as the average of the quarter-mean of the estimated seasonal values. The Pearson correlation ($r$) between the estimated and observed annual mean PM$_{2.5}$ from the Six Cities monitors during the years when both were available (1985–1987) was 0.93.

Statistical Analysis
We estimated mortality rate ratios associated with PM$_{2.5}$ by Cox proportional hazards regression models (20), controlling for baseline individual risk factors and potential confounders. Time on study was measured by calendar date. Subjects were stratified by sex and 1-yr age groups, such that each sex/age group had its own baseline hazard. We controlled for current or former smoking, number of pack-years of smoking for former and current smokers separately, education, and body mass index (linear and squared terms). We first modeled exposure using period-specific (1974–1989 vs. 1990–1998) indicators for city. The end date of the original National Death Index search (1989) was chosen as the cutoff. (Note that the Dockery and colleagues analysis [7] included several months of follow-up in 1990, which we have assigned to Period 2.)

Portage, the city with the lowest PM$_{2.5}$ levels, was the reference. To adjust for temporal trends in mortality, we included an indicator for period. We then assessed the association of mortality with average city-specific PM$_{2.5}$ for the entire period of follow-up (pollution averaged from 1980–1998) and with the period-specific average PM$_{2.5}$. We tested for a difference in association between the two periods with an interaction term (period by PM$_{2.5}$) in the model. To evaluate the effect of change in mean PM$_{2.5}$ between the two periods, we estimated the associations of period-specific mortality by including both the mean PM$_{2.5}$ in Period 1 (1980–1985) and the change in mean PM$_{2.5}$ between Period 1 and Period 2 (Period 2 [1990–1998] minus Period 1) in the model simultaneously. Finally, we treated city-specific yearly mean PM$_{2.5}$ levels as a time-varying exposure variable to evaluate the effect of particle exposures in the year of death. All analyses were performed using SAS software (version 8; SAS Institute, Cary, NC).

RESULTS

Characteristics of the Dataset
The cohort has been described in detail elsewhere (7). In brief, the average age of participants at the beginning of the study was 50 yr (range, 25–74 yr) and 55% were female. Average body mass index was 25.8 kg/m$^2$ (standard deviation, 4.5). Current smoking on enrollment ranged from 33% in Topeka to 40% in Watertown, and former smoking ranged from 21% in Harriman to 25% in both Topeka and Watertown. Education varied between cities; 12% of participants in Topeka and 45% in St. Louis had less than a high school education.

There were 104,243 person-years of follow-up and 1,364 deaths between 1974 and 1998 (Period 1) and an additional 54,735 person-years of follow-up and 1,368 deaths between 1990 and 1998 (Period 2; Table 1). The overall death rate was 13.1 deaths per 1,000 person-years in Period 1 and 25.0 in Period 2, reflecting the aging of this cohort. As in previous analyses, crude mortality rates were highest in Steubenville and St. Louis (Table 1).

Trends in PM$_{2.5}$ Concentrations
Annual mean PM$_{2.5}$ concentrations decreased during the study period in all cities (Figure 1) but most dramatically in the dirtiest cities. Fitting a straight line to the annual means, PM$_{2.5}$ declined on average 7 μg/m$^3$ per decade in Steubenville, 5 μg/m$^3$ in St. Louis, 3 μg/m$^3$ in Watertown, 2 μg/m$^3$ in Harriman, 1 μg/m$^3$ in Portage, and less than 1 μg/m$^3$ in Topeka.

Association of PM$_{2.5}$ with Mortality
We calculated city-specific adjusted all-cause mortality rate ratios for Period 1, Period 2, and the complete period of follow-up compared with Portage (Table 2). City-specific rate ratios decreased with decreasing PM$_{2.5}$ (Figure 2). Similar results were found for cardiovascular mortality (see online supplement).

The effect of each 10-μg/m$^3$ increase in average annual PM$_{2.5}$ concentration was compared in Period 1 (RR, 1.17; 95% CI, 1.08–1.26; p = 0.0001) and Period 2 (RR, 1.13; 95% CI, 1.01–1.27; p = 0.03, interaction p = 0.82). Controlling for exposure in Period 1, each 10-μg/m$^3$ reduction in Period 2 mean PM$_{2.5}$ was associated with a reduction in risk (RR, 0.73; 95% CI, 0.57–0.95; p = 0.019; 0.82). Controlling for exposure in Period 1, each 10-μg/m$^3$ reduction in Period 2 mean PM$_{2.5}$ was associated with a reduction in risk (RR, 0.73; 95% CI, 0.57–0.95; p = 0.019;...
Table 3). We found an increased risk of total mortality associated with each 10-μg/m³ increase in average PM₂.₅ over the entire follow-up period (RR, 1.16; 95% CI, 1.07–1.26; p = 0.0004; Table 3). We found essentially the same association of total mortality with the annual mean PM₂.₅ level in the year of death (RR, 1.14; 95% CI, 1.06–1.22; p = 0.0003). These results were not substantially changed in sensitivity analyses, removing one city at a time from the analysis (data not shown).

Cardiovascular mortality was positively associated with average PM₂.₅ over the entire follow-up (p < 0.0001; Table 3). We found lung cancer mortality positively associated with average PM₂.₅ (Table 3), but the association was not statistically significant (p = 0.63). There was no association (p = 0.71) with other causes of death (Table 3). There were stronger reductions in cardiovascular and respiratory mortality risk with each 10-μg/m³ improvement in city-specific mean PM₂.₅ in Period 2 compared with Period 1 (Table 3), but little evidence of reductions in lung cancer risk (Table 3).

**DISCUSSION**

With approximately 50% more person-years of follow-up and twice the number of deaths compared with the original Six Cities chronic mortality air pollution analysis (7), we observed significant associations of fine particulate air pollution with mortality. More importantly, we were able to evaluate the effect of changing average ambient PM₂.₅ concentrations since the original follow-up. Covariate adjusted mortality rates declined between 1974 and 1989 (Period 1) and 1990 and 1998 (Period 2), consistent with the general increase in adult life expectancy in the United States. However, the drop in the adjusted mortality rate was largest in the cities with the largest reductions in PM₂.₅ after controlling for such a period effect. The proportional hazards rate ratio for a 10-μg/m³ increase in PM₂.₅ was comparable in both of these periods. However, we found a reduction in risk: 0.73 for each 10-μg/m³ decrease in mean PM₂.₅ between periods. This reduction was observed specifically for deaths due to cardiovascular and respiratory disease and not from lung cancer, a
disease with a longer latency period and less reversibility. These findings suggest that the mortality effects of long-term air pollution may be at least partially reversible over periods of a decade.

We found equivalent, statistically significant increased risk in overall mortality associated with each 10-μg/m³ increase in PM2.5 modeled either as average over the entire follow-up (RR, 1.16; 95% CI, 1.07–1.26) or as average in the year of death (RR, 1.14; 95% CI, 1.06–1.22). These findings also suggest that mortality effects may be partially reversible, but over time periods possibly as short as a year.

Exposure to PM2.5 was statistically significantly associated with deaths due to cardiovascular disease, and the association with lung cancer mortality was of borderline significance. The number of nonmalignant respiratory deaths was small (although comparable to numbers for lung cancer), but the PM2.5-associated risk was positive, although weak.

Chronic exposure studies have observed increased mortality rates associated with PM. However, the evidence is limited mainly to the Harvard Six Cities Study and three other studies. The American Cancer Society Study, a cohort of 552,138 adults with 7 yr of follow-up, assessed risk for 151 U.S. metropolitan statistical areas (8). With an additional 9 yr of follow-up, statistically significant elevations in risk associated with PM2.5 were observed for all-cause, lung cancer, and cardiopulmonary mortality (10). In analyses of cause-specific mortality, each 10-μg/m³ increase in PM2.5 was associated with 8 to 18% increases in cardiovascular mortality, but only weak associations were found with nonmalignant respiratory deaths (21). In the Adventist Health Study of Smog, a 15-yr follow-up of 6,338 nonsmoking Californians, Abbey and coworkers found mean PM2.5 associated with increased lung cancer mortality in men and women, and nonsignificantly increased all-cause and cardiopulmonary mortality in men (9). A pilot prospective study of 4,466 participants monitored for 8 yr in the Netherlands concluded that long-term exposure to traffic-related particulate air pollution measured by black smoke was associated with increased all-cause mortality (11).

Although a large body of literature has shown associations between particulate air pollution and mortality, the relative contributions of acute and chronic exposures are not known. Effect estimates from prospective studies are substantially greater than those indicated by daily time-series studies (22). The majority of this difference may be explained by expanding the exposure period from days to months. Two independent studies have assessed the mortality effects over 40 d rather than 1 or 2 d after particle exposure. In both studies, the extended PM effects for periods of up to 6 wk were at least twice the short-term effects (3, 5). Schwartz showed in a time-series study in Boston that moving the time scale from days to months (i.e., 60 d) increased the estimated PM effect and captured approximately half the difference between the time-series and long-term cohort studies (4). He concluded that decades of exposure are not required to develop most of the risk increase seen in cohort studies. Our

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**TABLE 3. ADJUSTED PROPORTIONAL HAZARD MORTALITY RATE RATIOS AND 95% CONFIDENCE INTERVALS FOR A 10-μg/m³ INCREASE IN AVERAGE AMBIENT PM2.5 OVER THE ENTIRE FOLLOW-UP (1974–1998) AND THE RATE RATIOS FOR AVERAGE PM2.5 IN PERIOD 1 AND THE DECREASE IN LEVELS BETWEEN THE TWO PERIODS**

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Entire Follow-Up</td>
<td>Period 1</td>
</tr>
<tr>
<td></td>
<td>Average PM2.5</td>
<td>Average PM2.5</td>
<td>Average PM2.5</td>
</tr>
<tr>
<td>Total mortality</td>
<td>2,732</td>
<td>1.16 (1.07–1.26)</td>
<td>1.18 (1.09–1.27)</td>
</tr>
<tr>
<td>Cardiovascular*</td>
<td>1,196</td>
<td>1.28 (1.13–1.44)</td>
<td>1.28 (1.14–1.43)</td>
</tr>
<tr>
<td>Respiratory*</td>
<td>195</td>
<td>1.08 (0.79–1.49)</td>
<td>1.21 (0.89–1.66)</td>
</tr>
<tr>
<td>Lung cancer*</td>
<td>226</td>
<td>1.27 (0.96–1.69)</td>
<td>1.20 (0.91–1.58)</td>
</tr>
<tr>
<td>Other</td>
<td>1,115</td>
<td>1.02 (0.90–1.17)</td>
<td>1.05 (0.93–1.19)</td>
</tr>
</tbody>
</table>

For definition of abbreviations, see Table 2.
Rate ratios have been adjusted for age in 1-yr categories, sex, current smoker, current pack-years of smoking, former smoker, former pack-years of smoking, less than high school education, and linear and quadratic terms for body mass index.

† Average PM2.5 calculated as the average of Six Cities monitoring data for available years 1980–1988 and PM2.5 estimated from Aereometric Information Retrieval System and extinction data for years where Six Cities data were not available.
‡ Average PM2.5 in Period 1 calculated as the average from 1980–1985, the years where there are monitoring data for all cities, decrease in average PM2.5 (average Period 2 (1990–1998) — average Period 1).
results show that PM-associated mortality decreased in the
decade of the 1990s compared with the mid-1970s and 1980s,
consistent with the decrease in ambient PM$_{2.5}$ concentrations.
Furthermore, the similarity of effect for the annual air pollution
metric compared with the mean over the study period (1980–
1998) suggests that air pollution during the last year may be
important. At least part of the PM$_{2.5}$-associated mortality may
be reversible, suggesting ambient PM$_{2.5}$ is likely associated with
exacerbation of existing disease. However, there also appears
to be a second independent effect that could be described as
development of chronic disease.

Our ability to assess the appropriate time scale is limited
because, although PM$_{2.5}$ levels declined, the ranking of cities did
not change substantially over most of the study period. However,
the largest improvements in PM$_{2.5}$ concentrations were in cities
with the highest initial concentrations. There was also some
variation in city-specific annual mean PM$_{2.5}$ concentrations. We
did not examine time periods shorter than 1 yr in this analysis.

The original Six Cities Study mortality analysis has undergone
an extensive reanalysis performed by an independent group of
researchers (23). The original data were validated, the original
findings reproduced, and these estimates were found to be robust
to alternative models and to inclusion of other posited city-
specific confounders. Alternative metrics of PM$_{2.5}$ were not found
to alter risk of all-cause mortality during the original period of
follow-up (15).

Cardiovascular mortality rates have decreased in the United
States over the course of this study (24). However, this improve-
ment in cardiovascular mortality should affect all cities, and
should not be larger in cities with the greatest improvement in
PM$_{2.5}$ concentrations. Moreover, PM$_{2.5}$ concentrations fluctuated
year to year, including increases as well as decreases from the
preceding year. Yet, using PM$_{2.5}$ as a time-varying covariate did
not noticeably change the association. Thus, long-term secular
trends are unlikely to explain our results.

This analysis lacked continuous monitoring of PM$_{2.5}$ levels
during the extended follow-up period. Six Cities monitoring of
air pollutants ended in 1987 in most cities. The AIRS monitoring
network began collecting PM$_{2.5}$ data in 1985. PM$_{2.5}$ measurements
did not start until 1999, and even then did not include monitoring
in all of the Six Cities or in the original monitoring sites. There-
fore, Period 2 is completely dependent on estimated PM$_{2.5}$ levels.
We estimated the levels and patterns of PM$_{2.5}$ during the missing
years using city-specific regression of the original Six Cities PM$_{2.5}$
measurements against the relative humidity–adjusted extinction
coefficients from nearby airports and routine PM$_{10}$ measure-
ments from multiple nearby monitors. We assumed that the
local change in PM$_{2.5}$ would follow the local PM$_{10}$ and extinction
coefficient measurements, and that differences due to siting of
the monitors and methodologies would have remained constant.
Differences in measurement techniques and measurement loca-
tions preclude comparisons with current observations. Estimat-
ing the pattern of PM$_{2.5}$ over time using the actual measured
PM$_{10}$ and extinction data has its limitations, but it is likely to be
closer to reality than extrapolating levels beyond the available
sampling data, as has been done previously (15).

Follow-up information on individual risk factors was available
during the course of the first 12 yr of follow-up. Three follow-up
questionnaires were administered to the participants. There was
no updated information available on individual risk factors or
residence during the extended period of follow-up. In the
original study, baseline characteristics were used to control for
confounding factors (7). Although these factors were significantly
associated with mortality, they did not substantially confound
the relationship with air pollution. In the reanalysis, Krewski
and colleagues (23) evaluated the effect of updating smoking
status and body mass index during the course of the original
study. They restricted the study population to the 81.5% of
the people who did not move from their original cities at any
time during the study period. These alternative analyses did
not change the conclusions about the association of air pollution
and mortality. Therefore, we elected to use baseline characteristics
in this analysis. We acknowledge that this modeling choice may
lead to misclassification of confounders such as smoking status
and body mass index, and that the associations of these factors
and air pollution may have changed. For example, trends in
smoking cessation are different in different parts of the country
(25). Although these factors were significantly associated with
mortality, they did not substantially confound the relationship
with air pollution. In addition, censoring movers as defined in
Krewski and colleagues’ analysis (23) at the start of the continued
follow-up or excluding all movers from the analysis did not
change our results (data not presented). A limitation of this
analysis is that individual level covariates were not available for
this population in the second period of follow-up.

In this extended follow-up during a time of air pollution
reductions, we had a unique opportunity to assess the effect of
recent versus past exposures. City-specific average PM$_{2.5}$ levels
were lower in the extended follow-up during the 1990s than in
the first follow-up (1974–1989) and mortality risk ratios in this
period also were lower. This suggests that the PM$_{2.5}$-associated
mortality in this 25-yr follow-up was at least in part reversible.

Conflict of Interest Statement: None of the authors have a financial relationship
with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors thank William Cormack Ramsey, Elizabeth
Solomon, and Martha Fay for their work in tracking participants and Jaime Hart
and Allan Heff for their help with manuscript preparation.

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