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 $\mu g/m^3$ 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 $\mu g/m^3$) 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 $\mu g/m^3$ as the result of a 13-mo strike at a local steel mill (12). Mortality in Dublin decreased by 8% after a 36-$\mu g/m^3$ 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-$\mu g/m^3$ 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),

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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 (7). 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 coefficient (humidity-corrected visibility data from local airports) (19), routinely collected PM_{10} 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 quarterly 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 (1,989) was chosen as the cut-off. (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 1989 (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 $\mu g/m^3$ per decade in Steubenville, 5 $\mu g/m^3$ in St. Louis, 3 $\mu g/m^3$ in Watertown, 2 $\mu g/m^3$ in Harriman, 1 $\mu g/m^3$ in Portage, and less than 1 $\mu g/m^3$ 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-$\mu g/m^3$ increase in average annual $PM_{2.5}$ pollution was comparable 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-$\mu g/m^3$ 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 1. NUMBER OF PERSON-YEARS OF FOLLOW-UP AND TOTAL DEATHS IN SIX CITIES: PERIOD 1 (1974–1989 FOLLOW-UP) AND PERIOD 2 (1990–1998 FOLLOW-UP)

Characteristics	Portage	Topeka	Watertown	Harriman	St. Louis	Steubenville
No. participants	1,630	1,238	1,332	1,258	1,292	1,346
Period 1* (1,364 deaths; 104,243 person-yr)						
Person-yr	20,224	14,967	18,640	16,991	16,572	16,849
No. deaths	212	149	238	219	267	279
Deaths/1,000 person-yr	10.5	10.0	12.8	12.9	16.1	16.6
Average $PM_{2.5}$ ($\mu g/m^3$)	11.4	12.4	15.4	20.9	19.2	29.0
Period 2 (1,368 deaths; 54,735 person-yr)						
Person-yr	11,658	9,062	8,979	8,363	8,172	8,501
No. deaths	264	184	194	229	251	246
Deaths/1,000 person-yr	22.6	20.3	21.6	27.4	30.7	28.9
Average $PM_{2.5}$, $\mu g/m^3$	10.2	13.1	12.1	18.1	13.4	22.0

* Period 1 is restricted to 1,974 through 1989, whereas the original Dockery and colleagues (7) analysis included person-years of follow-up through June 1991 for a total of 111,076 person-years and 1,430 deaths. In Period 1, average $PM_{2.5}$ ($\mu g/m^3$) is the mean concentration in 1980–1985, the years when there are monitoring data for all cities (18). In Period 2, average $PM_{2.5}$ is the mean concentrations of the estimated $PM_{2.5}$ in 1990–1998.

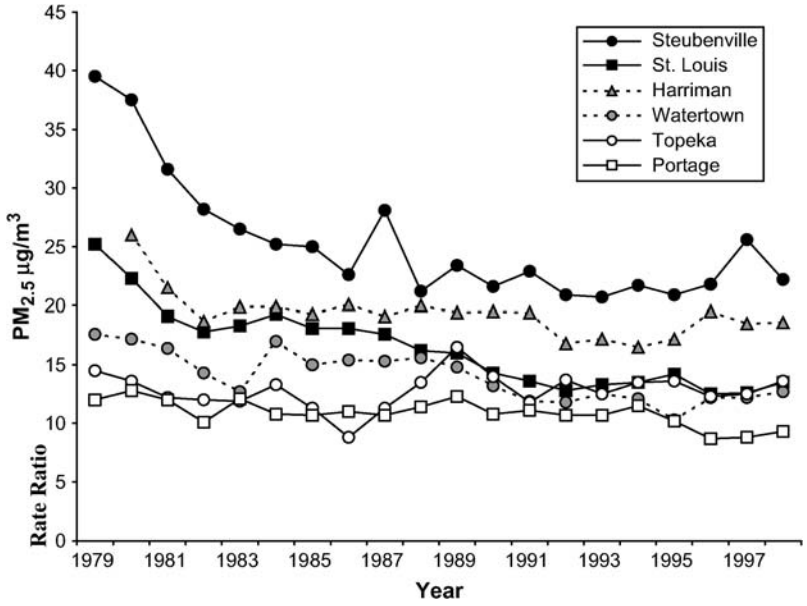

Figure 1. Annual average concentrations of $PM_{2.5}$ in the Harvard Six Cities Study. (Six Cities monitoring data for available years 1980–1988 and $PM_{2.5}$ estimated from Aerometric Information Retrieval System and extinction data for years where Six Cities data were not available.)

Table 3). We found an increased risk of total mortality associated with each 10-µg/m³ increase in average $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ over the entire follow-up ($p < 0.0001$; Table 3). We found lung cancer mortality positively associated with average $PM_{2.5}$ (p = 0.10; Table 3). Respiratory mortality also was positively associated with average $PM_{2.5}$ (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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ after controlling for such a period effect. The proportional hazards rate ratio for a 10-µg/m³ increase in $PM_{2.5}$ was comparable in both of these periods. However, we found a reduction in risk: 0.73 for each 10-µg/m³ decrease in mean $PM_{2.5}$ between periods. This reduction was observed specifically for deaths due to cardiovascular and respiratory disease and not from lung cancer, a

TABLE 2. ADJUSTED TOTAL MORTALITY RATE RATIOS AND 95% CONFIDENCE INTERVALS ESTIMATED FROM COX PROPORTIONAL HAZARDS MODEL FOR EACH FOLLOW-UP PERIOD (1974–1989 AND 1990–1998) AND THE COMPLETE FOLLOW-UP (1974–1998)

	Period 1	Period 2	Complete
Person-Yr of Follow-up	104,243	54,735	158,978
Deaths	1,364	1,368	2,732
	RR (*95% CI*)	RR (*95% CI*)	RR (*95% CI*)
City-specific model*			
Portage	1.00		1.00
Topeka	1.06 (0.86–1.31)	1.01 (0.83–1.22)	1.03 (0.89–1.19)
Watertown	1.06 (0.87–1.28)	0.82 (0.67–1.00)	0.95 (0.83–1.08)
Harriman	1.19 (0.98–1.44)	1.10 (0.91–1.33)	1.15 (1.01–1.32)
St. Louis	1.15 (0.96–1.38)	0.96 (0.80–1.15)	1.05 (0.93–1.20)
Steubenville	1.31 (1.10–1.57)	1.06 (0.89–1.27)	1.18 (1.04–1.34)
Period	1.00	0.97 (0.70–1.35)	

Definition of abbreviations: CI = confidence interval; RR = rate ratio.

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.

* City-specific rate ratios are all expressed in relation to Portage.

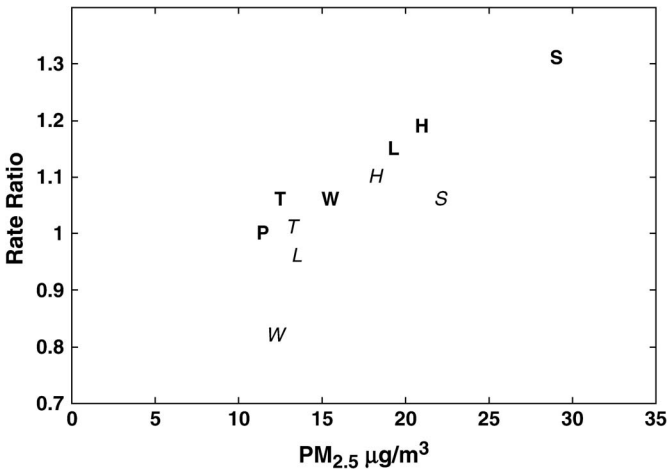

Figure 2. Estimated adjusted rate ratios for total mortality and $PM_{2.5}$ levels in the Six Cities Study by period. P denotes Portage, WI (reference for both periods); T = Topeka, KS; W = Watertown, MA; L = St. Louis, MO; H = Harriman, TN; S = Steubenville, OH. A term for Period 1 (1 if Period 2, 0 if Period 1) was included in the model. *Bold letters* represent Period 1 (1974–1989) and *italicized letters* represent Period 2 (1990–1998). In Period 1, $PM_{2.5}$ ($\mu g/m^3$) is defined as the mean concentration during 1980–1985, the years where there are monitoring data for all cities (18). In Period 2, $PM_{2.5}$ is defined as the mean concentrations of the estimated $PM_{2.5}$ in 1990–1998.

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-$\mu g/m^3$ increase in $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$-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 $PM_{2.5}$ were observed for all-cause, lung cancer, and cardiopulmonary mortality (10). In analyses of cause-specific mortality, each 10-$\mu g/m^3$ increase in $PM_{2.5}$ 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 PM_{10} 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

TABLE 3. ADJUSTED PROPORTIONAL HAZARD MORTALITY RATE RATIOS AND 95% CONFIDENCE INTERVALS FOR A 10-$\mu g/m^3$ INCREASE IN AVERAGE AMBIENT $PM_{2.5}$ OVER THE ENTIRE FOLLOW-UP (1974–1998) AND THE RATE RATIOS FOR AVERAGE $PM_{2.5}$ IN PERIOD 1 AND THE DECREASE IN LEVELS BETWEEN THE TWO PERIODS

		RR (*95% CI*)		
		Model 1	Model 2	
	Cases	Entire Follow-Up Average $PM_{2.5}$[†]	Period 1 Average $PM_{2.5}$[‡]	Decrease in Average $PM_{2.5}$[‡]
Total mortality	2,732	1.16 (1.07–1.26)	1.18 (1.09–1.27)	0.73 (0.57–0.95)
Cardiovascular*	1,196	1.28 (1.13–1.44)	1.28 (1.14–1.43)	0.69 (0.46–1.01)
Respiratory*	195	1.08 (0.79–1.49)	1.21 (0.89–1.66)	0.43 (0.16–1.13)
Lung cancer*	226	1.27 (0.96–1.69)	1.20 (0.91–1.58)	1.06 (0.43–2.62)
Other	1,115	1.02 (0.90–1.17)	1.05 (0.93–1.19)	0.85 (0.56–1.27)

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.

* Cardiovascular disease (International Classification of Disease, 9th edition [ICD-9] codes 400–440); nonmalignant respiratory disease (ICD-9 codes 485–496); lung cancer (ICD-9 code 162).

† Average $PM_{2.5}$ calculated as the average of Six Cities monitoring data for available years 1980–1988 and $PM_{2.5}$ estimated from Aerometric Information Retrieval System and extinction data for years where Six Cities data were not available.

‡ Average $PM_{2.5}$ in Period 1 calculated as the average from 1980–1985, the years where there are monitoring data for all cities, decrease in average $PM_{2.5}$ (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 improvement 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_{10} 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. Therefore, 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} measurements 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 locations preclude comparisons with current observations. Estimating 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.

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