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# Fine Particulate Air Pollution and All-Cause Mortality within the Harvard Six-Cities Study: Variations in Risk by Period of Exposure

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**PURPOSE:** We used Poisson regression methods to examine the relation between temporal changes in the levels of fine particulate air pollution ($PM_{2.5}$) and the risk of mortality among participants of the Harvard Six Cities longitudinal study.
**METHODS:** Our analyses were based on 1430 deaths that occurred between 1974 and 1991 in a cohort that accumulated 105,714 person-years of follow-up. For each city, indices of $PM_{2.5}$ were derived using daily samples. Individual level data were collected on several risk factors including: smoking, education, body mass index (BMI), and occupational exposure to dusts. Time-dependent indices of $PM_{2.5}$ were created across 13 calendar periods ($<$ 1979, 1979, 1980, . . . , 1989, $\geq$ 1990) to explore whether recent or chronic exposures were more important predictors of mortality.
**RESULTS:** The relative risk (RR) of mortality calculated using Poisson regression based on average city-specific exposures that remained constant during follow-up was 1.31 [95% confidence interval (CI) = 1.12–1.52] per 18.6 $\mu g/m^3$ of $PM_{2.5}$. This result was similar to the risk calculated using the Cox model (RR = 1.26, 95% CI = 1.08–1.46). The RR of mortality was attenuated when the Poisson regression model included a time-dependent estimate of exposure (RR = 1.19, 95% CI = 1.04–1.36). There was little variation in RR across time-dependent indices of $PM_{2.5}$.
**CONCLUSIONS:** The attenuated risk of mortality that was observed with a time-dependent index of $PM_{2.5}$ is due to the combined influence of city-specific variations in mortality rates and decreasing levels of air pollution that occurred during follow-up. The RR of mortality associated with $PM_{2.5}$ did not depend on when exposure occurred in relation to death, possibly because of little variation between the time-dependent city-specific exposure indices.
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KEY WORDS: Air Pollution, Mortality, Cohort Study, Fine Particulate Matter.

## INTRODUCTION

Fine particulate matter ($PM_{2.5}$), particles having an aerodynamic diameter of 2.5 μm or less, generally arise from the combustion of fossil fuels in transportation, manufacturing, and power generation. Internationally, time series studies have shown that daily numbers of deaths, hospitalisations, and emergency room visits increase when fine particulate levels are elevated (1, 2). Two large-scale prospective cohort studies provide estimates of the influence that long-term exposure to air pollution has on mortality. Dockery and colleagues (3), found a positive relation between mortality and exposure to fine particles in a study conducted in six U.S. cities. A similar result was found in the follow-up of members of the American Cancer Society's CPS II (ACS) cohort in 151 metropolitan areas (4).

Although findings from time series studies of air pollution are fairly consistent, the biological mechanisms through which exposure increases the risk of death are poorly understood and likely complex (5, 6). Fine particles have been the focus of epidemiologic studies for several reasons. First, they have higher concentrations of sulfates, nitrates, organic compounds, and transitional metals than coarse particles (7). Second, $PM_{2.5}$ exposures can account for an estimated 80–90% of the total aerosol products deposited in the alveolar region in individuals in the general population (8). Finally, fine particles appear to exhibit greater toxicity than coarse particles (9–11). It has been suggested that air pollution induces acute responses only among the segment of the population is particularly frail. Time-series studies, which assess short-term effects of air pollution, provide some support for this hypothesis. However, the increased risks reported in the Harvard Six Cities and ACS studies indicated that prolonged exposure to

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**Selected Abbreviations and Acronyms**

ACS = American Cancer Society
AIC = Akaike Information Criterion
BMI = body mass index
CPS II = Cancer Prevention Study, two
HEI = Health Effects Institute
$PM_{2.5}$ = fine particulate air pollution with a diameter of 2.5 μm or less

fine particulate matter may be an important predictor of mortality.

There are subtle differences in the design of the two aforementioned cohort studies. In the ACS study, ambient air pollution and personal covariates were available at baseline, whereas in the Harvard Six Cities study, information on individual risk factors was also collected at subsequent interviews during the follow-up period. The original analysis of the Harvard Six Cities study calculated risk estimates by using an overall city-specific summary measure of $PM_{2.5}$ derived using daily samples taken between 1979–1985, and baseline values for the risk factor data (3).

The findings from these two cohort studies have been the subject of debate regarding possible residual confounding by individual risk factors (e.g., sedentary lifestyle, passive cigarette smoke exposure) or ecologic risk factors (e.g., aspects of climate or social milieu), inadequate characterization of the relevant exposure, biases in allocating exposure to separate cities, and robustness of results to the specification of statistical models (12). These issues need to be resolved as the EPA and other regulatory agencies have relied, in part, on these studies to set standards for particulate matter in ambient air. For this reason the Health Effects Institute organized an independent re-analysis of these studies (12) to validate and replicate the original analyses and to conduct a comprehensive sensitivity analysis to test the robustness the results.

Within the context of this re-analysis project, we conducted Poisson regression analyses that allowed the risk of mortality to be evaluated using data from the Harvard Six Cities according to temporal changes in $PM_{2.5}$ and individual covariates.

## SUBJECTS AND METHODS

A detailed description of the design and conduct of the Harvard Six Cities longitudinal study has been published elsewhere (3, 13). In brief, the cohort consisted of a random sample of 8111 Caucasian subjects between 25 to 74 years of age at enrollment who resided in six U.S. cities (Steubenville, OH; St. Louis, MO; Portage, WI; Topeka, KS; Watertown, MA, and Kingston/Harriman, TN). Time of enrollment varied by city, commencing in Watertown in 1974 followed by Kingston and St. Louis in 1975, Steubenville and Portage in 1976, and Topeka in 1977. Vital status was ascertained using information collected from mailings to participants (1974—1989) and by searching the National Death Index (1979—1989). Death certificates were obtained for 1410 of the 1430 subjects who had died. The underlying cause of death was coded according to the International Classification of Diseases 9th revision by a nosologist blinded to pollution levels and to study objectives.

Daily concentrations of pollutants ($PM_{2.5}$, total suspended particles, sulfur dioxide, and ozone) were estimated using a centrally located air-monitoring station within each city. Daily air samples were collected between 1979 and 1988, though data were unavailable at the beginning or end of this calendar period for some cities (Table 1). As described later in this section, log-linear regression methods were used to estimate $PM_{2.5}$ exposures during the follow-up intervals.

During follow-up, subjects were re-interviewed regarding changes in factors thought to influence mortality. Longitudinal data were available for up to four interview dates: time of enrollment, and at 3, 6, and 12 years of follow-up. The primary goal of the analysis undertaken in this report was to examine how the relative risk (RR) of mortality associated with city-specific mean levels of $PM_{2.5}$ changed when indices that incorporated annual fluctuations in concentrations of $PM_{2.5}$ and changes in individual risk factors that occurred during follow-up were modelled. The impact of these changes on risk estimates was not evaluated in the original published report (3).

### Statistical Methods

Regression methods for prospective studies frequently make use of the Cox proportional hazards model (14). The proportional hazards assumption implies that risks are estimated as a multiple of baseline disease rates. However, the effect of the explanatory variables may depend on age at risk, cumulative exposure, dose rate, or other time-related factors so proportionality in the risk estimates during follow-up may not be constant. With several time-dependent variables, parameter estimation using the Cox model may be computationally extensive and model convergence may not be obtained easily. In such situations, Poisson regression represents a suitable alternative, and when risk estimates are based on internal cohort comparisons, analyses are related to grouped Cox models and produce similar results. In this spirit, Poisson regression methods have been used extensively to assess the risk of cancer due to radiation exposure (15). The assumptions of the Poisson for longitudinal analyses are outlined by Breslow and Day (16) as follows: count variables must follow a Poisson distribution; the death rate must be constant within each strata; the observations must be independent;

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and the logarithm of the death rate is a linear function of the independent variables. For convenience, the hazard ratios from the Cox models and the rate ratios from the Poisson models are herein referred to as RRs.

The Poisson model was fit to the Harvard Six Cities data using the software EPICURE (17). First cross-classification tables were created, whereby, strata were defined according to the categories of each predictor variable. The number of deaths and person-years of follow-up were tabulated for each cell in the table. The cross-classification table was defined by sex, city, calendar period, 5-year age groupings, body mass index (BMI), educational attainment, occupational exposures and smoking behaviour. Exposure to $PM_{2.5}$ was calculated for each city and for the time-dependent indices, by calendar period. BMI was categorized into quartiles based on the frequency distribution as measured at baseline ($< 22.7$, $22.7–< 25.3$, $25.3–< 28.2$, and $\geq 28.2$ $kg/m^2$). Changes in BMI were evaluated by categorizing subjects into these same groupings using data collected during follow-up. Binary indicator variables were used to classify individuals who had completed high school, and those who were exposed to dusts and fumes in the workplace.

The effect of smoking on mortality was modeled in three ways. First, to determine whether Poisson regression produced similar results to the Cox model, analyses were conducted using the original study variables (terms for current smokers, former smokers, cigarette pack-years for current smokers, and cigarette pack-years for former smokers evaluated at baseline). Model terms representing the number of years of cigarette smoking (at baseline), and the number of cigarettes smoked weekly were also included. Finally, follow-up interview data were used to model changes over time in the number of cigarettes smoked weekly. (Inconsistencies in the reported number of smoking years and smoking status variables during follow-up interviews precluded their use as time-dependent covariates).

Our primary goal was to assess differences in the risk of mortality according to variations in $PM_{2.5}$ level that occurred over time. Several city-specific indices of $PM_{2.5}$ were created to determine whether exposures received in the distant past were more predictive of risk. First, an overall $PM_{2.5}$ city specific mean exposure based on daily samples taken between 1979 and 1985 was modelled; this is the same index of mean annual exposure in each of the cities for the periods: $< 1979$, 1979, 1980, $\ldots$, $\geq 1990$. Because exposure data were missing for selected cities at the beginning of the follow-up interval, $PM_{2.5}$ concentrations during such time intervals were assumed to be equivalent to the earliest available annual exposure taken for that city. Similarly, unavailable $PM_{2.5}$ measures for the latter periods of follow-up where imputed from the last available city-specific annual mean exposure.

Linear regression was used to construct four additional exposure indices. These models used the log of the $PM_{2.5}$ annual mean as the dependent variable, and calendar year as the independent variable. The log-scale ensured a positive range of the dependent variable and improved the model fit relative to the standard linear model. The parameter estimates derived from these city-specific regression models were then used to predict $PM_{2.5}$ exposures for 13 calendar periods ($< 1979$, 1979, 1980, $\ldots$, 1989, $\geq 1990$). For the first period 1970–1978, $PM_{2.5}$ exposure was estimated using the city-specific exposure for 1974 as predicted by loglinear regression. Similarly, $PM_{2.5}$ levels for the most recent of the 13 calendar periods was estimated using the predicted annual exposure for 1991. The four measures of $PM_{2.5}$ estimated using loglinear regression are herein referred to as time-dependent smoothed indices and consist of the following: the mean $PM_{2.5}$ measure for each calendar period; the mean $PM_{2.5}$ exposure based on the mean annual level obtained from sampling during the current and previous year of follow-up (prior to death or censoring); the mean $PM_{2.5}$ exposure based on the mean annual level obtained from sampling performed two to four years before the current year of follow-up; the mean $PM_{2.5}$ exposure received based on the mean annual level obtained from samples performed five or more years before the current year of follow-up.

To determine which index was superior predictor of mortality, log-likelihood statistics were compared across models. The smallest log-likelihood value indicated the model with the best predictive power. The Akaike Information Criterion (AIC), which is frequently used to compare multivariate models, was not used here because our models only differed according to the index of $PM_{2.5}$ used (i.e., they had the same number of parameters), therefore the log-likelihood method was equivalent to the AIC. Models with air pollution indices were also compared tot he background model to determine whether such exposures significantly predicted mortality beyond the association explained by other risk factors. Interaction terms were also entered into the Poisson models to assess whether effect-modification was present for exposure to $PM_{2.5}$ and any of the individuals risk factors (i.e., BMI, age, sex, smoking, education, and occupational exposures). When a significant interaction was found, based on likelihood ratio test, stratified analysis was performed to characterize the modifying effect.

Although the majority of subjects (86%) did not move outside their city of residence during follow-up, the analysis was repeated excluding those who did to determine the extent to which mobility patterns biased the results.

## RESULTS

Annual mean concentrations of fine particulate matter between 1979 and 1988 within each of the six cities are provided in Table 1. Concentrations of fine particulate matter

**TABLE 1.** Average annual concentration of fine particulate matter ($PM_{2.5}$), by calendar year and city, Harvard Six-Cities Study ($\mu g/m^3$)

| Year | Portage | Topeka | Harriman | Watertown | St. Louis | Steubenville |
|---|---|---|---|---|---|---|
| 1979 | 11.4 (6.2) | 12.6 (5.8) | — | 16.7 (7.3) | 24.0 (9.6) | 40.3 (27.9) |
| 1980 | 12.8 (7.4) | 15.6 (6.7) | 26.3 (10.8) | 17.3 (9.1) | 22.7 (9.6) | 30.0 (21.5) |
| 1981 | 11.4 (6.4) | 15.1 (9.3) | 20.7 (8.3) | 16.3 (8.9) | 19.9 (9.5) | 33.5 (24.8) |
| 1982 | 10.1 (6.4) | 11.9 (8.6) | 18.7 (8.1) | 13.4 (7.0) | 17.7 (12.8) | 27.9 (18.4) |
| 1983 | 11.4 (7.0) | 11.8 (7.3) | 19.5 (11.6) | 12.3 (7.8) | 17.3 (11.5) | 25.4 (21.6) |
| 1984 | 11.1 (9.2) | 12.9 (7.4) | 19.7 (7.4) | 17.4 (9.4) | 18.4 (9.1) | 26.1 (18.6) |
| 1985 | 9.3 (7.1) | 10.5 (5.2) | 20.1 (7.9) | 14.5 (8.2) | 18.0 (10.3) | 24.7 (17.9) |
| 1986 | 10.8 (5.9) | 9.2 (6.1) | 20.5 (10.1) | — | 17.9 (10.4) | 21.7 (16.0) |
| 1987 | 10.7 (5.7) | 10.7 (6.0) | 18.6 (7.4) | — | — | 28.6 (16.9) |
| 1988 | — | 13.7 (6.9) | — | — | — | — |
| Total deaths | 232 | 156 | 222 | 248 | 281 | 291 |
| Person-years | 20700 | 15528 | 16692 | 18762 | 16964 | 17068 |
| Overall Mean[a] | 11.0 (1.0) | 12.4 (2.0) | 20.5 (2.4) | 15.2 (1.8) | 19.5 (2.5) | 28.5 (5.5) |
| Overall Mean[b] | 10.9 (7.2) | 12.1 (7.1) | 20.7 (9.4) | 14.9 (8.4) | 18.7 (10.6) | 28.6 (21.0) |

Standard deviations in parentheses.
[a]The overall mean was calculated by taking the average of the annual summaries of $PM_{2.5}$.
[b]The overall mean was calculated by taking the average of all sample observations.

decreased over the study period in Steubenville, Harriman, and St. Louis, with less consistent downward trends in Portage, Topeka, and Watertown. The city-specific mean fine particle levels exhibited sizeable year-to-year variations.

Table 2 shows the RR of mortality observed by the original investigators for each city. After adjusting for smoking status, cigarette pack-years, education, and BMI, the RR of mortality in the most polluted city (Steubenville) was 1.26 [95% confidence interval (CI) = 1.06–1.50] relative to the least polluted city (Portage). We performed similar analyses using the multivariate Poisson regression model (Table 3). The city-specific RRs of mortality from the Poisson model were similar with those from the Cox regression analysis; for example, the above estimate of RR for Steubenville relative to Portage was 1.32 (95% CI = 1.11–1.57). However, some differences in the point estimates for these other variables were found and likely due to the categorization used in the Poisson regression model.

In Table 4 results from the Cox and Poisson models are presented. Relative risks are expressed across the range of city-specific mean estimates (18.6 $\mu g/m^3$). After adjusting for BMI, occupational exposure to dusts and fumes, age, sex, attained educational levels, and cigarette smoking, there were only modest differences in risk associated with $PM_{2.5}$ between the Poisson (RR = 1.31; 95% CI = 1.12–1.52) and the Cox (RR = 1.26; 95% CI = 1.08–1.46) models. The table also shows that the Poisson regression results were essentially unchanged when time-dependent changes in smoking and BMI were incorporated into the models.

**TABLE 2.** Relative risk of all-cause mortality in the Harvard Six-cities Study based on the Cox regression model as published by the reanalysis of these data [12]

| Variable | All subjects | Men | Women |
|---|---|---|---|
| Relative risk (95% CI)[a] | | | |
| Current smoker | 1.59 (1.31–1.92) | 1.75 (1.32–2.32) | 1.54 (1.16–2.04) |
| 25 Pack-years of smoking | 1.26 (1.16–1.38) | 1.26 (1.13–1.41) | 1.18 (0.99–1.41) |
| Former smoker | 1.20 (1.01–1.43) | 1.17 (0.93–1.48) | 1.34 (1.02–1.77) |
| 10 Pack-years of smoking | 1.16 (1.09–1.23) | 1.17 (1.10–1.25) | 1.14 (0.97–1.35) |
| Less than High School education | 1.19 (1.06–1.33) | 1.22 (1.06–1.41) | 1.13 (0.95–1.35) |
| Body Mass Index | 1.08 (1.02–1.14) | 1.03 (0.95–1.12) | 1.11 (1.03–1.20) |
| City[b] | | | |
| Portage | 1.0 | 1.0 | 1.0 — |
| Topeka | 1.01 (0.82–1.24) | 1.04 (0.79–1.36) | 0.97 (0.71–1.43) |
| Harriman | 1.17 (0.97–1.41) | 1.21 (0.96–1.54) | 1.07 (0.79–1.45) |
| Watertown | 1.07 (0.89–1.28) | 0.94 (0.73–1.20) | 1.22 (0.93–1.61) |
| St. Louis | 1.14 (0.96–1.36) | 1.15 (0.91–1.44) | 1.13 (0.86–1.50) |
| Steubenville | 1.26 (1.06–1.50) | 1.29 (1.03–1.62) | 1.23 (0.93–1.61) |

[a]Relative risks have been adjusted for age, sex and all other variables listed in the table. The relative risk for body mass index corresponds to an increases of 4.52 (1 SD).
[b]City-specific relative risks are all expressed in relation to Portage.

**TABLE 3.** Relative Risks of all-cause mortality in the Six-cities Study obtained using Poisson Regression methods

| Variable | All subjects | Men | Women |
|---|---|---|---|
| Relative risk (95% CI)[a] | | | |
| Current smoker | 1.32 (0.94–1.80) | 1.68 (0.99–2.68) | 1.14 (0.72–1.71) |
| <10 pack-years of smoking | 1.0 — | 1.0 — | 1.0 — |
| 10–<30 pack-years of smoking | 1.64 (1.18–2.33) | 1.43 (0.88–2.46) | 1.78 (1.14–2.89) |
| ≥30 pack-years of smoking | 1.87 (1.36–2.64) | 1.68 (1.07–2.83) | 1.99 (1.27–3.24) |
| Former smoker | 1.23 (0.99–1.51) | 1.20 (0.88–1.63) | 1.30 (0.95–1.74) |
| <10 pack-years of smoking | 1.0 — | 1.0 — | 1.0 — |
| 10–<25 pack-years of smoking | 0.97 (0.74–1.28) | 0.97 (0.68–1.38) | 1.13 (0.70–1.79) |
| ≥25 pack-years of smoking | 1.48 (1.18–1.88) | 1.56 (1.17–2.10) | 1.75 (1.09–2.75) |
| Less than high school | 1.26 (1.13–1.41) | 1.29 (1.12–1.49) | 1.22 (1.03–1.45) |
| education | 1.0 — | | |
| Body mass index[b] | 0.85 (0.74–0.98) | | |
| Highest quartile | 0.78 (0.67–0.90) | | |
| 3rd quartile | 0.82 (0.70–0.95) | 1.0 | 1.0 |
| 2nd quartile | | 0.91 (0.77–1.09) | 0.74 (0.59–0.93) |
| 1st quartile | 1.0 — | 0.80 (0.66–0.97) | 0.75 (0.59–0.93) |
| City[c] | 1.01 (0.82–1.24) | 0.98 (0.79–1.22) | 0.69 (0.56–0.87) |
| Portage | 1.16 (0.96–1.39) | | |
| Topeka | 1.06 (0.89–1.27) | 1.0 — | 1.0 |
| Harriman | 1.13 (0.95–1.35) | 1.04 (0.79–1.36) | 0.96 (0.69–1.31) |
| Watertown | 1.32 (1.11–1.57) | 1.20 (0.95–1.51) | 1.06 (0.78–1.43) |
| St. Louis | | 0.97 (0.76–1.24) | 1.13 (0.86–1.49) |
| Steubenville | | 1.16 (0.92–1.45) | 1.07 (0.81–1.41) |
| | | 1.39 (1.11–1.74) | 1.22 (0.93–1.61) |

[a]Relative risks have been adjusted for age, sex and all other variables listed in this table.
[b]Body mass index was categorized into quartiles based on the 8,111 subjects at baseline. The cut-points were as follows: <22.70, 25.26, 28.21, and ≥28.21 kg/m$^2$.
[c]City-specific rate ratios are all expressed in relation to Portage.

The RR of mortality due to $PM_{2.5}$ exposure decreased when time-dependent measures of air pollution were modelled (Table 5). Specifically, when the mean $PM_{2.5}$ level within each city during each period of follow-up was modelled, the RR was 1.16 (95% CI = 1.02–1.32). Similar results were observed using time-dependent indices denoting exposures received in the last two years of follow-up, and for exposures lagged 3–4 and ≥ 5 years. Effect modification was evaluated by fitting interaction terms that consisted of $PM_{2.5}$ exposure and individual risk factors (body mass index, education, smoking, age, gender, and occupational exposure to dusts). The significance of this term was formally tested by constructing a likelihood ratio test statistic. an interaction effect between $PM_{2.5}$ exposure and age was observed ($p < 0.05$), and therefore, we have also presented stratified analysis by age group (< 60, ≥ 60 years). For each

**TABLE 4.** Relative risk of all cause mortality to fine particulate matter (per 18.6 μg/m$^3$) based on Cox regression and Poisson regression with time-dependent covariates

| Model | Type | Covariates | Relative Risk (95% CI) |
|---|---|---|---|
| 1 | Cox[a] | Age (5-year groupings), sex, current smokers, pack-years for current smoker, former smokers, pack-years for former smokers, high-school education, body mass index, and occupational exposure to dust. *Note: values are based on data collected at baseline.* | 1.26 (1.08–1.46) |
| 2 | Poisson | Same as (1)[b] | 1.32 (1.13–1.53) |
| 3 | Poisson | Age, sex, number of years smoked, number of packs smoked per week, high-school education, body mass index and occupational exposure to dust. *Note: values are based on data collected at baseline.* | 1.31 (1.13–1.53) |
| 4 | Poisson | Same as (3) except deaths and person years for categories of *the number of packs smoked per week* were calculated taking into account changes as indicated by follow-up interviews. | 1.32 (1.13–1.53) |
| 5 | Poisson | Same as (4) except deaths and person years for categories of body mass index were calculated taking into account changes as indicated by follow-up interviews. | 1.31 (1.12–1.52) |

[a]As published by Krewski and colleagues [12].
[b]The use of the Poisson regression model required the categorization of body mass index as well as duration, intensity, and cumulative tobacco consumption that had been modelled as continuous variables in the Cox model.

**TABLE 5.** The relative risk of all cause mortality for selected indices of exposure to fine particulate matter (per 18.6 μg/m$^3$) based on multivariate Poisson regression analysis, by age group

| Model | $PM_{2.5}$ exposure city specific index | Age group (years) | | |
|---|---|---|---|---|
| | | Total | <60 | ≥60 |
| 1 | Exposure to $PM_{2.5}$ remained fixed over the entire follow-up period | 1.31 (1.12–1.52) | 1.89 (1.32–2.69) | 1.21 (1.02–1.43) |
| 2 | Exposure to $PM_{2.5}$ was defined according to 13 calendar periods (no smoothing)[a] | 1.19 (1.04–1.36) | 1.52 (1.15–2.00) | 1.11 (0.95–1.29) |
| 3 | Exposure to $PM_{2.5}$ was defined according to 13 calendar periods (smoothed)[b] | 1.16 (1.02–1.32) | 1.43 (1.10–1.85) | 1.09 (0.93–1.26) |
| 4 | Time dependent estimate of $PM_{2.5}$ received during the previous two years | 1.16 (1.02–1.31) | 1.42 (1.09–1.82) | 1.08 (0.94–1.25) |
| 5 | Time dependent estimate of $PM_{2.5}$ received 3–5 years before current year | 1.14 (1.02–1.27) | 1.35 (1.08–1.67) | 1.08 (0.95–1.22) |
| 6 | Time dependent estimate of $PM_{2.5}$ received >5 years before current year. | 1.14 (1.05–1.23) | 1.34 (1.11–1.59) | 1.09 (0.99–1.20) |

[a]Relative risks were adjusted by age, gender, body mass index, education, number of years smoked (at baseline), occupational exposures and number of cigarettes smoked weekly. These variables correspond to those included in model 5 of Table 4.

[b]For each city, exposure to $PM_{2.5}$ was estimated for 13 calendar periods using loglinear regression based on annual mean $PM_{2.5}$ levels. The calendar periods used were: 1970–1978, 1979, 1980, 1981, . . . 1989, and 1990+.

index of $PM_{2.5}$, the RR of all-cause mortality was more pronounced among subjects who were less than 60 years of age (Table 5). There was no effect modification between $PM_{2.5}$ and the other individual risk factors.

On average, subjects lived in the original city of residence for 30 years, ranging from an average of 23 years in Watertown to 44 years in St. Louis. Steubenville and St. Louis, the two cities with highest $PM_{2.5}$ levels, also had the longest average period of residency. The inclusion of the number of years of residence did not change appreciably the risk of mortality due to $PM_{2.5}$. Analysis of the mover group indicated that air pollution was not significantly related to mortality for any of the time-dependent indices considered (results not shown). Excluding movers increased the presented risk estimates modestly. For example, the RR of mortality associated with the city-specific exposure index of $PM_{2.5}$ that remained fixed over the entire follow-up period, increased from 1.31 to 1.33. Similarly, when movers were dropped from the analysis of the time dependent index of $PM_{2.5}$, the RR increased from 1.19 to 1.23.

The fit of the models that used different indices of $PM_{2.5}$ were compared using the log-likelihood statistic (Table 6). When the entire follow-up period was considered, the fixed measure of $PM_{2.5}$ improved the model fit the most. Using this index, the log likelihood statistic decreased by 12.1 when compared to the model with the same risk factors, but no $PM_{2.5}$. The number of degrees of freedom for the baseline model (Model 7) was 29167. Similar changes were observed in the log-likelihoods among subjects whose attained age was either < 60 and those who were ≥ 60 years of age and older.

## DISCUSSION

We evaluated the relationship between fixed-in-time and time-dependent measures of $PM_{2.5}$ and the risk of mortality among adult, Caucasian participants of the Harvard Six Cities cohort. The risk estimates generated by modelling fixed in time exposure indices using Poisson regression were similar to results obtained by the original investigators. RR estimates were attenuated when time-dependent indices of $PM_{2.5}$ were modelled. However, for several reasons, we were unable to discriminate between the risks of mortality across these time-dependent indices. First, although data were available at an individual level for several risk factors, the exposure of primary interest was essentially an ecologic vari-

**TABLE 6.** The log-likelihood goodness of fit for models that include selected indices of exposure to fine particulate matter (per 18.6 μg/m$^3$) based on multivariate Poisson regression analysis, by age group

| Model | $PM_{2.5}$ exposure city specific index | Age group (years) | | |
|---|---|---|---|---|
| | | Total | <60 | ≥60 |
| 1 | Exposure to $PM_{2.5}$ remained fixed over the entire follow-up period | 9964.6 | 2325.4 | 7606.2 |
| 2 | Exposure to $PM_{2.5}$ was defined according to 13 calendar periods (not smoothed) | 9970.3 | 2328.1 | 7609.6 |
| 3 | Exposure to $PM_{2.5}$ was defined according to 13 calendar periods (smoothed)[b] | 9971.5 | 2330.6 | 7609.9 |
| 4 | Time dependent estimate of $PM_{2.5}$ received during the previous two years | 9971.5 | 2330.5 | 7609.9 |
| 5 | Time dependent estimate of $PM_{2.5}$ received 3–5 years before current year | 9971.2 | 2330.4 | 7609.7 |
| 6 | Time dependent estimate of $PM_{2.5}$ received >5 years before current year | 9967.3 | 2327.8 | 7607.7 |
| 7 | Model with no index of air pollution | 9976.7 | 2337.4 | 7611.1 |

[a]Relative risks were adjusted by age, gender, body mass index, education, number of years smoked (at baseline), occupational exposures and number of cigarettes smoked weekly.

[b]For each city, exposure to $PM_{2.5}$ was estimated for 13 calendar periods using loglinear regression based on annual mean $PM_{2.5}$ levels. The calendar periods used were: 1970–1978, 1979, 1980, 1981, . . . 1989, and 1990+.

able derived for each of the six cities. For each city, strong Person correlations coefficients ($r > 0.90$) were observed between the various time-dependent indices of $PM_{2.5}$ considered, moreover, the rank ordering of $PM_{2.5}$ levels across cities during follow-up changes little. Given these points, it is not surprising that for most time-dependent indices, the risk of mortality associated with $PM_{2.5}$ were similar.

Our finding of an attenuated risk estimate when city specific $PM_{2.5}$ exposures were modelled as time varying rather than constant over follow-up requires comment. A plot of the city-specific mortality rates, adjusted for age and sex, indicated that there were considerable fluctuations in the mortality rates across the calendar periods that were modelled (Figure 1). This result is not surprisingly in light of the size of the cohort (8111), and the number of cities ($n = 6$) and calendar periods that defined the strata that contained the person-years and deaths. The magnitude of these annual variations in mortality rates may have dampened any real $PM_{2.5}$ effect on mortality. Similar analyses of larger sized cohorts, such as the ACS CPS II could provide valuable insights on the extent of this bias.

A limitation of this study was the absence of sampling data to characterize $PM_{2.5}$ exposures before 1979, thereby preventing us from constructing lifetime indices to test the hypothesis that cumulative exposure increases the risk of mortality. However, if the relative ranking of $PM_{2.5}$ levels across cities observed after 1979 were similar to that preceding enrollment, then a summary measure derived using several years of sampling data may yield a more accurate representation of the relevant exposure than one based on a year of data. For this reason, our finding of an attenuated risk estimate with time-dependent exposure indices may be viewed as being consistent with the hypothesis that cumulative or lifelong exposures to $PM_{2.5}$ is an important predictor of mortality.

Flexible risk modelling to test the Cox proportional hazards assumption within these data (12) recently showed that the hazard ratio was not constant over follow-up, thereby suggesting that time-dependent $PM_{2.5}$ exposures should be used to characterize the risk of mortality. Our analysis presents a summary measure of the RR of mortality averaged over time-dependent exposures to $PM_{2.5}$. The summary measure's utility is diminished if this risk estimate varies across calendar periods. Indeed, stratified analysis produced more pronounced RR estimates for the period before and after 1985, roughly the midpoint of the period for which exposure data were available (data not shown). However, this period effect was not statistically significant based on the likelihood ratio test for the associated interaction term, and it is possible the difference may be due to unmeasured confounding variables or chance.

The stronger association between exposure to $PM_{2.5}$ and mortality among younger subjects ($< 60$) is consistent with the recent re-analysis performed on this cohort (12). Based on a Cox proportional hazards model, for each $PM_{2.5}$ increment of 18.6 $\mu g/m^3$, Krewski and colleagues observed a RR of 2.42 (95% CI = 0.88–6.61) among subjects less than 40

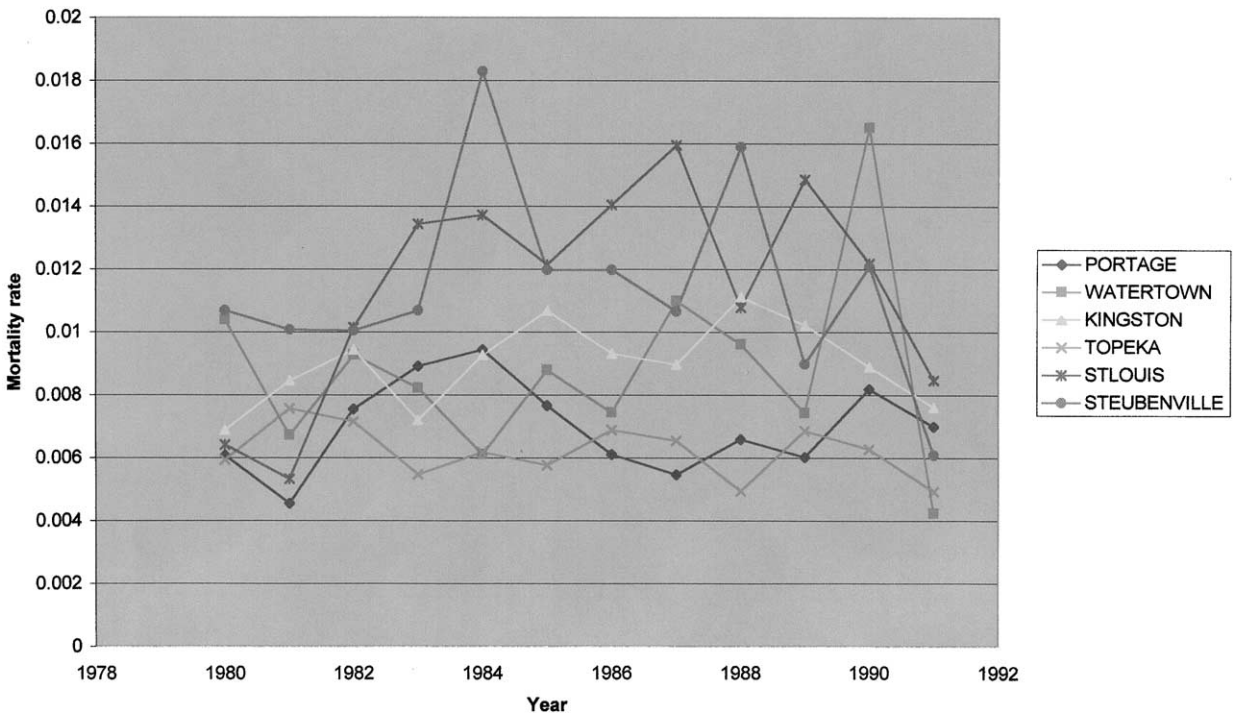


**FIGURE 1.** All-cause mortality rates standardized by age-group and gender, by calendar period, Harvard Six-Cities Study.

years of age, 1.70 (1.10–2.62) for those aged 41–55 years, and 1.32 (1.08–1.62) for those aged > 55 years. This finding is inconsistent with the "harvesting" hypothesis that purports that air pollution exerts an influence on mortality by advancing the date of death among those of poor health, such as the elderly. If increased mortality is the result chronic exposure to $PM_{2.5}$, the availability of only recently measured levels of air pollution may have lead to increased exposure misclassification among older members of this cohort. The net effect of this misclassification would be consistent with the attenuated risk estimates that were found among younger segment of this cohort. An important limitation of the Harvard Six Cities cohort is the unavailability of data needed to identify individuals with underlying preexisting comorbid conditions. Recent analyses in Montreal have shown that this is an important consideration, and that several underlying conditions render individuals more susceptible to the effects of ambient air pollution (18).

Ideally, a study designed to evaluate risk of mortality from $PM_{2.5}$ exposure would have complete lifetime exposure data for individuals. During follow-up, several individuals moved outside their original city of residence, therefore potentially introducing bias when using baseline city-specific exposure estimates. To investigate this potential bias, we re-calculated mortality risks after excluding subjects who moved and found only a modest increase. Unfortunately, the number of movers was small, limiting the statistical inferences that could be drawn from this population.

Various approaches to estimating lifetime risk associated with intermittent or time-dependent exposures have been considered elsewhere (19–21). Exposure to air pollution varies considerably over an individual's lifetime due to intrinsic fluctuations in ambient pollutants, changes in residence, occupation and lifestyle. Characterizing health risks associated with such exposures is difficult as the biological effectiveness of $PM_{2.5}$ likely varies with age (22–24), and our understanding of these age-specific mechanisms is limited. Indeed, applying lifetime average exposure estimates can lead to overestimates of risk by several orders of magnitude when the actual exposure occurs at a time of relative effectiveness (25). Conversely, applying an average lifetime dose may underestimate the risk when exposure occurs at times of low relative effectiveness. With sufficient understanding of the age-specific biological effectiveness of $PM_{2.5}$ exposure, a lifetime equivalent dose could be derived (25). However, this understanding can only be achieved by assembling a study population of individuals whose exposure profiles are heterogeneous and vary over time. Such an approach has provided insights regarding mechanisms of radon-induced lung cancer in mining cohorts (15). Regrettably, high correlations between indices of $PM_{2.5}$ preclude such analyses within the Harvard Six Cities cohort.

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