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Impact of long-term temporal trends in fine particulate matter ($PM_{2.5}$) on associations of annual $PM_{2.5}$ exposure and mortality:

An analysis of over 20 million Medicare beneficiaries

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Abstract

Decreasing ambient fine particulate matter ($PM_{2.5}$) concentrations over time together with increasing life expectancy raise concerns about temporal confounding of associations between $PM_{2.5}$ and mortality. To address this issue, we examined $PM_{2.5}$-associated mortality risk ratios (MRRs) estimated for approximately 20,000,000 US Medicare beneficiaries, who lived within six miles of an Environmental Protection Agency air quality monitoring site, between December 2000 and December 2012. We assessed temporal confounding by examining whether $PM_{2.5}$-associated MRRs vary by study period length. We then evaluated three approaches to control for temporal confounding: (1) assessing exposures using the residual of $PM_{2.5}$ regressed on time; (2) adding a penalized spline term for time to the health model; and (3) including a term that describes temporal variability in $PM_{2.5}$ into the health model, with this term estimated using decomposition approaches. We found a 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure to be associated with a 1.20 times (95% confidence interval [CI] = 1.20, 1.21) higher risk of mortality across the 13-year study period, with the magnitude of the association decreasing with shorter study periods. MRRs remained statistically significant but were attenuated when models adjusted for long-term time trends in $PM_{2.5}$. The residual-based, time-adjusted MRR equaled 1.12 (95% CI = 1.11, 1.12) per 10 $\mu g/m^3$ for the 13-year study period and did not change when shorter study periods were examined. Spline- and decomposition-based approaches produced similar but less-stable MRRs. Our findings suggest that epidemiological studies of long-term $PM_{2.5}$ can be confounded by long-term time trends, and this confounding can be controlled using the residuals of $PM_{2.5}$ regressed on time.

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Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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Keywords

Medicare beneficiaries; Residual; Temporal confounding; Mortality; Fine particulate matter ($PM_{2.5}$)

Introduction

Over the last 2 decades, ambient air pollution concentrations have decreased steadily across the United States primarily as the result of emissions controls instituted as part of the Clean Air Act Amendments. In the United States, $PM_{2.5}$, annual concentrations have dropped by 24% from 2001 to 2010, with 2010 mean concentrations ranging, by location, between 3 and 18 $\mu g/m^3$.[1] These lower concentrations are projected to result in substantial health benefits. A 2011 US Environmental Protection Agency report, e.g., estimated that the Clean Air Act Amendments will prevent 230,000 early deaths in 2020, with most early deaths attributable to reductions in ambient $PM_{2.5}$.[1]

Despite these reductions, $PM_{2.5}$ concentrations continue to be linked with adverse health impacts.[2–6] Numerous multicity studies, including the American Cancer Society, Six Cities, Women's Health Initiative, Nurses' Health Study, and National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Cohort, have shown positive associations between long-term exposure and mortality.[2–7] The observed associations in these studies vary widely, with null associations in Health Professionals Follow-Up Study prospective cohort[8] and significant effect estimates ranging from a 3% increase (per 10 $\mu g/m^3$ in $PM_{2.5}$) in the NIH-AARP cohort[7] to 26% in Nurses' Health Study.[9] Variability in effect sizes has been attributed to differences in cohort characteristics, $PM_{2.5}$ composition, modeling approaches, and confounding by correlated air pollutants or unmeasured covariates.[10–13]

Another possible, but little studied, explanation for the variation in $PM_{2.5}$-associated mortality risks is confounding by long-term time trends in both $PM_{2.5}$ and mortality, where decline in ambient $PM_{2.5}$ concentrations is accompanied by increased life expectancy. Several studies provide evidence of the impact of long-term time trends on $PM_{2.5}$-associated mortality.[14] In a simulation study, Griffin et al[15] showed that the length of the study period may adversely affect the performance of the Cox proportional hazards model, increasing bias and mean and squared error (MSE) and reducing power as the strength of the linear association between exposure and time increases, as may occur with the temporal trends observed for $PM_{2.5}$. Similarly, linear models may also produce biased effect estimate, if linear trends exist between both $PM_{2.5}$ and time, and mortality and time. Consistent with this, Janes et al,[16] Greven et al,[17] and Pun et al[18] found evidence of unmeasured confounding of the association of $PM_{2.5}$ and all-cause mortality. They did so by decomposing $PM_{2.5}$ into two orthogonal components describing temporal and spatiotemporal variability, which they term "global" and "local" $PM_{2.5}$, respectively. When both terms were included in the health model, the coefficient for temporal $PM_{2.5}$ was larger and statistically significant compared with the spatiotemporal coefficient, which was null. The unequal temporal and spatiotemporal coefficients led the authors to conclude that $PM_{2.5}$

associations with mortality were confounded by unmeasured variables, such as long-term time trends.

To examine the possibility that temporal confounding is present in the mortality and $PM_{2.5}$ relationship, we analyzed data for over 20 million Medicare enrollees from 2000 to 2012 to assess the impact of long-term time trends on the association between 1-year–averaged $PM_{2.5}$ concentrations and mortality.

Methods

The protocol was reviewed and approved by the Institutional Review Boards of Northeastern University.

Medicare beneficiary and mortality data

We obtained monthly mortality counts for 2000–2012 in the United States (except for Alaska and Hawaii) using data from the Centers for Medicare and Medicaid Services Medicare enrollment file, which provides demographic (age and sex), ZIP code of residence, and survival, including date of death and data for all Medicare enrollees (≥65 years).

$PM_{2.5}$ exposure

We compiled daily $PM_{2.5}$ concentrations from Environmental Protection Agency's Air Quality System from 2000 to 2012. We did so for monitoring sites ("site") with daily measurements for at least eight calendar years, with each year having 9+ months with 4+ daily measurements. For the 798 sites that met these criteria, we calculated long-term concentrations following Greven et al.[17] Briefly, we smoothed the time series at each site using a linear regression with the daily pollutant values as the response, and thin plate splines of time with four degrees of freedom per year as the predictor. For gaps longer than 90 days, we smoothed the $PM_{2.5}$ time series before and after each gap separately. We used the predicted daily values to calculate yearly moving averages for $PM_{2.5}$ each month. Yearly averages were considered valid when 350+ days were available. Sites were classified based on their geographical region: "East" of the Mississippi River, "Center" between the Mississippi River and the Sierra Nevada mountain range, and "West" of the Sierra Nevada mountain range.[17]

Data linkage

We linked data for Medicare beneficiaries (65–120 years) to $PM_{2.5}$ monitors that met the study criteria for each month of the study, which restricted our sample to those beneficiaries living in ZIP codes with centroids within six miles of a valid monitor. We then linked data for beneficiaries living in these ZIP codes to the closest corresponding site's $PM_{2.5}$ concentration for the previous 12-month period ending in that study month. We performed the ZIP code identification and linkage by year to reduce exposure error introduced by residential moves and changes in ZIP code boundaries. For each month, we calculated the total number of Medicare beneficiaries at risk and the number of deaths associated with each site.

Statistical analysis

All analyses were conducted for the entire study population living in the United States as well as separate analyses for Medicare beneficiaries living in each of three US regions (East, Central, and West). In general, we examined the variation in MRR estimates per 10 $\mu g/m^3$ increase in exposure; although for analyses comparing MRRs for base to those for time-adjusted models, we make comparisons based on an interquartile range (IQR) increase in exposure given their different variabilities. We further present graphical summaries of this variation using linear regression. SAS statistical software package (SAS Institute Inc., Cary, NC, 2003) and R-Studio, Inc., (Boston, MA) were used for all analyses.

Base models

To examine the association between $PM_{2.5}$ exposure and monthly rate of all-cause mortality, we fit an age-stratified log-linear model including offset terms for the size of the population at risk as our base model:

$$\log E(Y_{at}{}^{c}) = \log\left(h_0^c(a)\right) + \beta PM_t^c + \beta_c \mathrm{BRFSS} \quad (1)$$

where ($Y_{at}{}^{c}$) is the number of deaths at time t, in age category a, associated with site C. The exposure measure PM_t^c is the 1-year average $PM_{2.5}$ concentration at site C, preceding the month (t) of death. For each age group a and site C, mortality counts are offset by both the baseline hazard of death, $h_0^c(a)$, and the total population at risk at time t, N_{at}^c. The Poisson model was selected (over the quasi-Poisson) as overdispersion parameter values varied from 1.02 to 1.25. To reduce the computational burden of this large dataset, we assumed a constant baseline hazard of death for all age groups above 90 years of age and models were fit via the backfitting algorithm.[17–19]

To adjust for potential, measured confounders, we performed additional analyses adjusting for county-level behavioral covariates from the Selected Metropolitan/Micropolitan Area Risk Trends of the Behavioral Risk Factor Surveillance System (BRFSS), including proportions of non-whites, current smokers, diabetes, asthma, individuals possessing health care plans, and mean income and body mass index.[20] β_c is the vector of BRFSS adjustment variables. Because the BRFSS data are only available for 465 of the 798 sites with $PM_{2.5}$ monitoring data, we performed these analyses using the corresponding subset of the cohort. As appropriate, we converted results from previous studies into percent change per 10 $\mu g/m^3$ $PM_{2.5}$ increase to compare with our results.[16–18] Additionally, we assessed whether unmeasured confounding of our base models remained by decomposing $PM_{2.5}$ into two orthogonal components that capture temporal and spatiotemporal variability, following methods described by Greven et al.[17] Briefly,

- The temporal component describes national trends in exposures by centering the average exposure nationally in month t, $\overline{PM_t}$, by the average concentration for all sites over the entire study period, $\overline{PM}$:

$$\text{Temporal } PM_t = \overline{PM_t} - \overline{PM}$$

- The spatiotemporal component describes site-specific temporal trends in exposure by centering the exposure in month t at site c, PM_t^C, by the average exposure at site c, $\overline{PM_c}$, and the national trends, $(\overline{PM_t} - \overline{PM})$:

$$\text{Spation-temporal } PM_t^C = \left(\overline{PM_t^C} - \overline{PM_c}\right) - (\overline{PM_t} - \overline{PM})$$

We included the temporal and spatiotemporal components jointly in our base models and compared their effect estimates, interpreting a difference in their estimates as evidence of unmeasured confounding.[17]

Evaluation of temporal confounding

We evaluated long-term time trends as a potential source of unmeasured confounding. To do so, we ran our base models using data for the entire 13-year study period (2000–2012) and for shorter study periods, ranging between 3 and 12 years in length, with each of these study periods ending in 2012 (e.g., 2001–2012, 2002–2012, 2003–2012, etc., to 2009–2012). We compared mortality risk ratios (MRRs) for the entire 13-year period with those from each of these shorter study periods, assuming that in the absence of temporal confounding, MRRs would be uniform irrespective of the study period length.

In addition to fitting our base model, we also examined three approaches to control for long-term time trends in $PM_{2.5}$. In our first approach, we adjusted for long-term time trends in $PM_{2.5}$ using a new exposure measure calculated as the residual r_t^c of the linear regression of $PM_{2.5}$ on time in 4-year intervals December 2000–2004, 2005–2008, and 2009–2012:

$$PM_t^c = \beta_0 + \beta_1 year_{2005\text{–}08} + \beta_2 year_{2009\text{–}12} + r_t^c$$

The term r_t^c was subsequently used as the exposure measure in the log-linear model:

$$\log E(Y_{at}^c) = \log(h_0^c(a)) + \beta r_t^c \quad (2)$$

Our second approach adjusted for long-term time trends in $PM_{2.5}$ by adding a penalized spline term for time, $\delta^c(t)$, modeled as two knots per study year, to our base log-linear model:

$$\log E(Y_{at}^c) = \log(N_{at}^c) + \log(h_0^c(a)) + \beta_1 PM_t^c + \beta_2 \delta(t) \quad (3)$$

For our third approach, we included the temporal component of decomposed $PM_{2.5}$ into the base model as follows:

$$\log E(Y_{at}^c) = \log(N_{at}^c) + \log(h_0^c(a)) + \beta_1 PM_{2.5} + \beta_2 \text{ Temporal } PM_t \quad (4)$$

where "temporal $PM_{2.5}$" was calculated by decomposing $PM_{2.5}$ into its orthogonal temporal and spatiotemporal components as above and in the study by Greven et al.[17]

For each of these time-adjusted approaches, we ran models using data for study periods ranging between 3 and 13 (2000–2012) years in length and examined whether MRRs varied by length of study period.

Sensitivity analyses

We ran several sensitivity analyses to examine alternate specifications of our methods to adjust for long-term time trends in $PM_{2.5}$. Specifically, for the calculation of residuals for our residual-based approach, we adjusted for time as each year rather than for each 4-year interval as in our main analysis:

$$PM_t^c = \beta_0 + \beta_1 year_{2001} + \beta_2 year_{2002} + \cdots + \beta_{12} year_{2012} + r_{t1}^c$$

as well as for years grouped into 2-, 3-, and 6-year intervals:

$$PM_t^c = \beta_0 + \beta_1 year_{2003–04} + \beta_2 year_{2005–06} + \cdots + \beta_5 year_{2011–12} + r_{t2}^c$$

$$PM_t^c = \beta_0 + \beta_1 year_{2004–06} + \beta_2 year_{2007–09} + \beta_3 year_{2010–12} + r_{t3}^c$$

$$PM_t^c = \beta_0 + \beta_1 year_{2007–12} + r_{t6}^c$$

We subsequently used the residuals from these sensitivity analyses as exposure measures in our log-linear health models and compared their ability to control for confounding by time trends. Additionally, we assessed our ability to account for long-term time trends using penalized splines for time calculated using three, four, or five knots instead of the two knots used in our main analysis.

Results

We examined 20.7 million Medicare enrollees, observing 5.5 million deaths between December 2000 and December 2012 near 798 sites across the contiguous United States (Table 1). Monthly, our analyses include on average over 9 million enrollees. $PM_{2.5}$ concentrations varied regionally, with sites located in the East having the highest mean concentrations. Yearly $PM_{2.5}$ concentrations decreased steadily during our study period (Figure 1), with larger decreases in the East and West as compared to Center. Declines in $PM_{2.5}$ concentrations were steepest between 2000 and 2009, with yearly concentrations more uniform during 2010–2012. The correlation between $PM_{2.5}$ and the residual-based exposure measure equaled 0.92, suggesting that this residual-based exposure measure explained most of the variation in $PM_{2.5}$.

Association of $PM_{2.5}$ and mortality

Base models—We found that a 10 μg/m^3 increase in 1-year $PM_{2.5}$ is significantly associated with a 1.20 times (95% CI = 1.20, 1.21 per 10 μg/m^3) higher rate of mortality in our Medicare cohort when data from 2000 to 2012 were analyzed (Table 2). Associations varied by geographic region, with MRRs higher in the Central (1.27; 95% CI = 1.26, 1.28) and Eastern (1.26; 95% CI = 1.25, 1.26) regions compared with the Western United States (1.12; 95% CI = 1.11, 1.12). Associations were similar when models additionally adjust for behavioral covariates (Table S1; http://links.lww.com/EE/A4), suggesting that behavioral covariates did not confound associations of $PM_{2.5}$ and mortality.

Despite this, we showed potential confounding of the association of $PM_{2.5}$ and mortality by unmeasured variables. When $PM_{2.5}$ is decomposed into its spatiotemporal and temporal components, we estimated larger MRRs for the temporal as compared to spatiotemporal component of $PM_{2.5}$ (Table S1; http://links.lww.com/EE/A4) for both base and BRFSS-adjusted models, consistent with the previous study.[17] In base models, e.g., a 10 μg/m^3 increase in temporal $PM_{2.5}$ corresponded to a 1.54 times (95% CI = 1.52, 1.56) higher rate of mortality, while spatiotemporal $PM_{2.5}$ was associated with only a 1.07 times (95% CI = 1.06, 1.09) higher rate.

Evaluation of temporal confounding

We showed $PM_{2.5}$-associated MRRs increase with the length of the study, consistent with the hypothesis of confounding by long-term time trends in $PM_{2.5}$. MRRs were lowest for the 3-year study periods (1.12; 95% CI = 1.11, 1.14) and increase steadily with longer study periods, resulting in a 0.08 higher MRR for the 13-year as compared to 3-year study period (Figure 2). Similar trends between MRRs and length of study period were observed when analyses were performed by geographic region, although these trends were less pronounced in the Central United States, consistent with the more gradual decline in $PM_{2.5}$ concentrations in the Central Unites States over the 13-year period (Figure S1; http://links.lww.com/EE/A4).

When models were adjusted for long-term time trends, MRRs remain statistically significant (Table 2) but were slightly attenuated (Table S2; http://links.lww.com/EE/A4). For the residual-based approach, we found the MRR to equal 1.04 (95% CI = 1.04, 1.04) per IQR increase in time-adjusted $PM_{2.5}$, as compared to 1.08 (95% CI = 1.08, 1.08) per IQR increase in the base model. MRRs estimated from the penalized spline- and decomposition-based approaches were also attenuated, with MRRs of 1.01 (95% CI = 1.01, 1.02) and 1.03 (95% CI = 1.02, 1.03) per IQR increase, respectively (Table S2; http://links.lww.com/EE/A4). While consistently lower, MRRs for each of the time-adjusted approaches follow the same regional patterns as with the base models, as time-adjusted MRRs were highest in the Central United States and lowest in the Western United States (Table 2; Figures S2–S4; http://links.lww.com/EE/A4).

When analyses were performed across varying study periods, we demonstrated that the residual-based approach produces MRRs that are nearly uniform (Figure 2). The residual-based MRRs for the 13- and 3-year study periods, e.g., were almost identical, with MRRs

of 1.12 (95% CI = 1.11, 1.12) and 1.12 (95% CI = 1.11, 1.14) for a 10 μg/m^3 increase in exposure, respectively. In contrast to both the base and residual-based models, MRRs for the spline- and decomposition-based approaches decrease with longer study periods. MRRs from the spline-based approach decrease from 1.09 (95% CI = 1.07, 1.10) for 3-year study period to 1.03 (95% CI = 1.02, 1.04) for 13-year study period. The decomposition-based approach shows a similar decline in MRRs, with MRRs for 3- and 13-year study periods equaling 1.11 (95% CI = 0.10, 1.12) and 1.06 (95% CI = 1.06, 1.07), respectively.

Sensitivity analyses

Sensitivity analyses demonstrated that alternate calculations of residual-based $PM_{2.5}$ exposures and of penalized splines produce similar MRRs. Residual-based exposures calculated by regressing $PM_{2.5}$ concentrations on time as 1-, 2-, or 3-year intervals result in similar MRRs as models controlling for time in 4-year intervals (Figure 3). Residual-based exposure with 6-year intervals showed slightly higher and less-consistent MRRs for longer study periods, suggesting less reliability than with the other intervals. Residual-based exposures calculated using 4-year intervals, however, were more stable, as evidenced by lowest variation in MRRs across study period length. It is also notable that residual-based exposure using 4-year time intervals requires fewer parameters than 1-, 2-, or 3-year intervals, suggesting greater statistical efficiency. For spline-based models, increasing the number of knots per year from two to three or four had little effect on the MRR, thus we selected two knots for better efficiency (results not shown).

Discussion

We showed consistent, statistically significant, and positive associations between 1-year $PM_{2.5}$ exposures and the rate of all-cause mortality among 20.7 million Medicare beneficiaries living across the United States from 2000 to 2012. In our base models, the mortality rate ratio associated with a 10 μg/m^3 increase in 1-year average $PM_{2.5}$ equaled 1.20 (95% CI = 1.20, 1.21). Consistent with our hypothesis that long-term time trends in $PM_{2.5}$ positively confound the association between $PM_{2.5}$ and mortality, we found $PM_{2.5}$-associated rates of mortality to be associated with the length of the study period, with higher MRR per 10 μg/m^3 for 13-year as compared to 3-year study periods. Of the three examined approaches, we found the residual-based approach to best control for temporal confounding, as evidenced by its statistically significant and uniform MRRs across all study period lengths, with an MRR for the 3- and 13-year study period of 1.12 (95% CI = 1.11, 1.14) and 1.12 (95% CI = 1.11, 1.12) per 10 μg/m^3 increase in exposure, respectively. Note, however, that based on our analysis alone, it is not possible to determine which approach is best suited to control for temporal confounding, indicating the need for further examination, possibly through a simulation study.

Our findings add to the body of evidence showing that long-term $PM_{2.5}$ exposures are associated with increased mortality,[2–7,9–13] lending additional support to findings from the American Cancer Society (ACS) cohort,[2] the Nurses' Health Study,[5] and the Medicare cohort.[4] Although no studies to date have explicitly examined the possible impact of temporal confounding on these associations, several studies have indirectly examined this

possibility. In a study by Lepeule et al,[6] e.g., the original[21] and initial follow-up[22] of the Six Cities Study were extended to include 11 additional years of follow-up, comprising 36 years in total (1974–2009). MRRs were estimated for the entire 36-year study period and for four, equally divided 9-year time periods. While overall $PM_{2.5}$ concentrations decreased over the 36-year study period, this decrease was uniform neither by city nor over time. $PM_{2.5}$ concentrations exhibited strong downward trends over time in only the three most polluted cities—Steubenville, Kingston-Harriman, and St. Louis, with these trends steepest and most consistent between 1979 and 1992 and to a lesser extent 2000–2009. The authors found an overall MRR for all-cause mortality of 1.14 (95% CI = 1.07, 1.22) for a 10 $\mu g/m^3$ increase in 1-year $PM_{2.5}$. When data for the four 9-year time periods were analyzed, MRRs varied widely, with values of 1.06 (95% CI = 0.96, 1.17) for 1974–1982, 1.32 (95% CI = 1.16, 1.50) for 1983–1991, 1.11 (95% CI = 0.98, 1.27) for 1992–2000, and 1.19 (95% CI = 0.91, 1.55) for 2001–2009. Notably, MRRs were highest during the period when temporal trends in $PM_{2.5}$ were strongest, providing some, albeit indirect, support for our findings of confounding by long-term temporal trends. The increased MRR for the last 9-year interval compared with the full 36-year MRR may reflect aging of the cohort.

Further support is provided by results from related studies by Janes et al,[16] Greven et al,[17] and Pun et al[18] who decomposed $PM_{2.5}$ into its temporal and spatiotemporal components and found higher and statistically significant MRRs for temporal as compared to spatiotemporal $PM_{2.5}$. The authors concluded that differences in the MRRs associated with temporal and spatiotemporal $PM_{2.5}$ reflected residual confounding by temporally varying covariates. Consistent with Greven et al,[17] additional adjustment for county-level BRFSS covariates did not reduce residual confounding, suggesting that the examined behavioral variables do not confound the $PM_{2.5}$ mortality association. This finding, however, differs from that reported by Pun et al,[18] who found that residual confounding decreased after adjustment for BRFSS covariates in models of $PM_{2.5}$ and mortality. This discrepancy likely results from the fact that the Pun et al[18] analysis assessed residual confounding by decomposing both $PM_{2.5}$ and BRFSS data into their temporal and spatiotemporal components, while we decomposed only $PM_{2.5}$ since our time-adjusted models already control indirectly for temporal trends in BRFSS data. Together, these results suggest that temporal trends in confounding variables are important to consider as well.

Our findings of increasing MRRs with longer study periods suggest that long-term temporal trends in $PM_{2.5}$ concentrations may be one source of this unmeasured confounding. We found residual-based exposures to successfully control for these time trends in $PM_{2.5}$. The ability of residual-based exposures to control for these time trends in $PM_{2.5}$ is consistent with previous studies.[23–25] For example, Mostofsky et al[25] used a residual-based approach to estimate the effect of $PM_{2.5}$ constituents while controlling for confounding by total amount of $PM_{2.5}$. To do so, they regressed each constituent of interest on the total $PM_{2.5}$ in a linear model and used the residual to estimate the effect of each individual constituent while holding $PM_{2.5}$ constant. This approach is similar to our residual-based exposure method, with the only difference being our focus on the effect of $PM_{2.5}$ while controlling for the unmeasured variables associated with long-term time trends. Because the unmeasured confounders are not perfectly correlated with time, complete control of time (through indicator functions for each month) would have likely over-adjusted for any potential

confounding, as observed when the residual model was based on time controlled in 1-, 2-, and 3-year intervals. On the other hand, using a coarser measure of time (such as 6-year intervals) may not sufficiently control for the unmeasured variables, resulting in a lack of independence between time trends and both $PM_{2.5}$ and mortality. Our results suggest that the residual model controlling for time in 4-year intervals was able to provide MRR estimates that were least affected by study period length.

We found this residual-based method to perform better than the spline and decomposition approaches, both of which showed declining MRRs as study periods increased, suggesting that these methods over-controlled for long-term time trends. Further, by including terms for both $PM_{2.5}$ and some adjustment for time in the model, the spline- and decomposition-based approaches may result in biased effect estimates, given collinearities of $PM_{2.5}$ and time.[26] In our data, the correlations of $PM_{2.5}$ with both the spline of $PM_{2.5}$ and decomposed $PM_{2.5}$ varied with the length of study period, with correlations for $PM_{2.5}$ and the spline of $PM_{2.5}$ equaling 0.15 for 3-year periods and increasing to 0.44 for 12-year periods. Identical correlations were observed for $PM_{2.5}$ and decomposed $PM_{2.5}$. These results suggest that the bias in MRRs derived from the spline and decomposed $PM_{2.5}$ models increases as the study length increases.

Our results are limited by several factors. First, our log-linear models aggregated data by site and limited the number of strata for computational efficiency, thus limiting our ability to control for individual-level covariates. However, when we additionally adjusted for county-level behavioral covariates, we found similar MRRs, suggesting behavioral covariates did not confound associations (Table S1; http://links.lww.com/EE/A4). Second, individual exposure measurement error is unavoidable when using the monitor level air pollution data. This exposure error is likely to be small, given results from studies that show that $PM_{2.5}$ concentrations to be moderately uniform within a given county and ambient $PM_{2.5}$ concentrations to be strong surrogates for personal $PM_{2.5}$ exposure.[27] Thus, we expect any exposure error to bias observed associations toward the null and underestimate mortality risk estimates.[28] Third, although bias may also be introduced by the “healthy worker effect” where subjects less susceptible to $PM_{2.5}$ exposures remain in our study population for longer time periods, this bias would be in the opposite direction of the observed changes. Although our study could not examine the impact of temporal variation of $PM_{2.5}$ composition on MRRs, compositional variability is unlikely to explain our findings given the strong dependence of MRRs on $PM_{2.5}$ time trends and the inconsistent time trends in $PM_{2.5}$-associated total carbon concentrations between 2000 and 2010 in the United States.[29] Finally, while we found the residual model based on 4-year intervals to best control for temporal trends, further study, such as through a simulation study, is needed to confirm our findings.

Summary

We found significant associations between 1-year $PM_{2.5}$ exposures and mortality. These associations were likely confounded by long term temporal trends in $PM_{2.5}$. We successfully controlled for this confounding by using exposure measures based on the residual of $PM_{2.5}$ regressed on time in 4-year intervals. Controlling for long term temporal $PM_{2.5}$ trends, we

found significant 11.7% increase in all-cause mortality among Medicare beneficiaries for a 10 μg/m^3 increase in $PM_{2.5}$. This MRR was reduced compared to the model without controlling for the temporal confounding. These findings demonstrate the importance and need to account for temporal trends in future air pollution health effect studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sponsorships or competing interests that may be relevant to content are disclosed at the end of the article.

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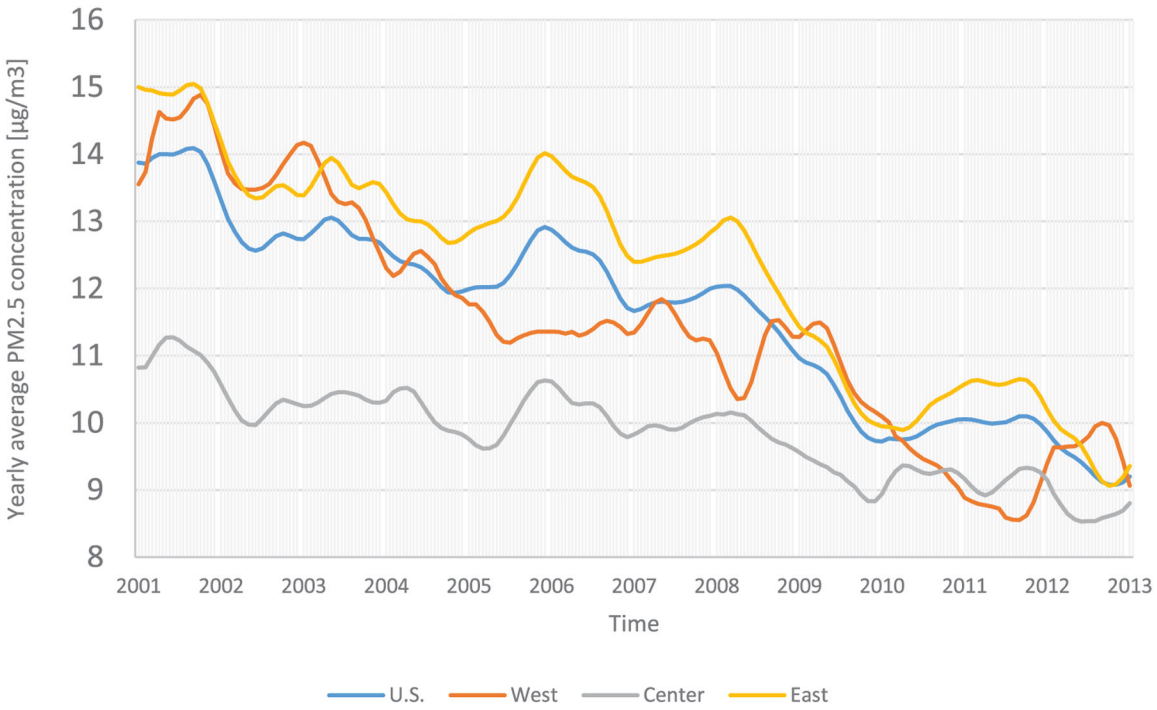

Figure 1.
One-year average $PM_{2.5}$ concentrations: December 2000 to December 2012.

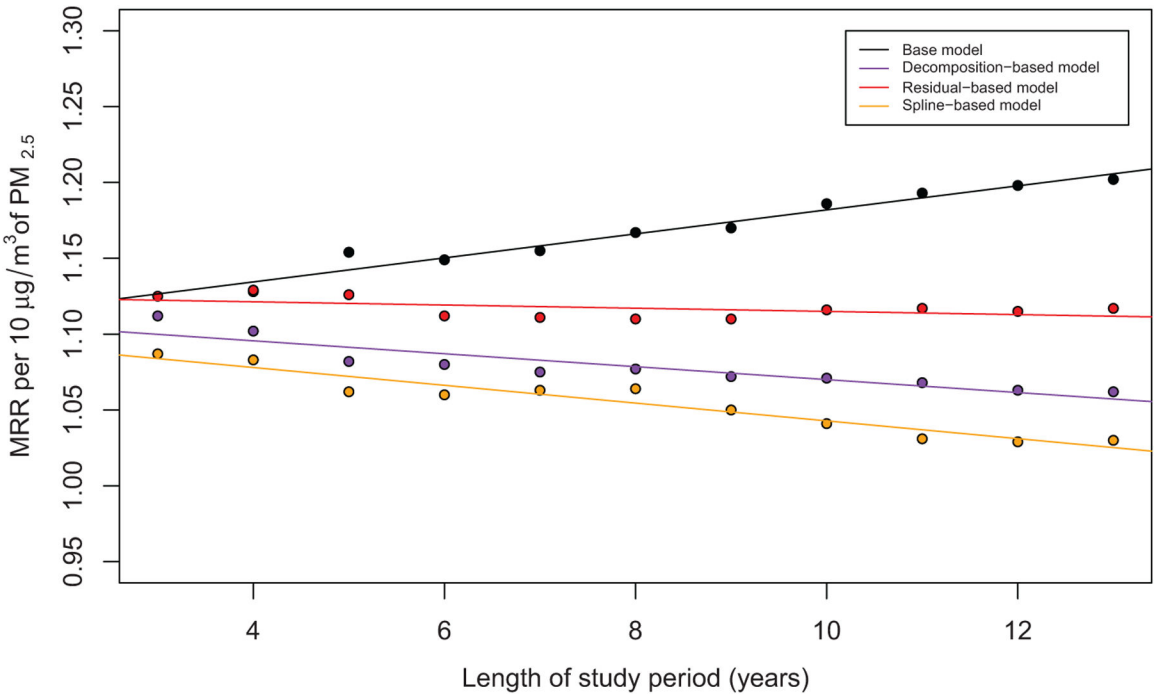

Figure 2.

MRRs per 10 µg/m^3 increase in $PM_{2.5}$ by length of study period: for base and time-adjusted models.

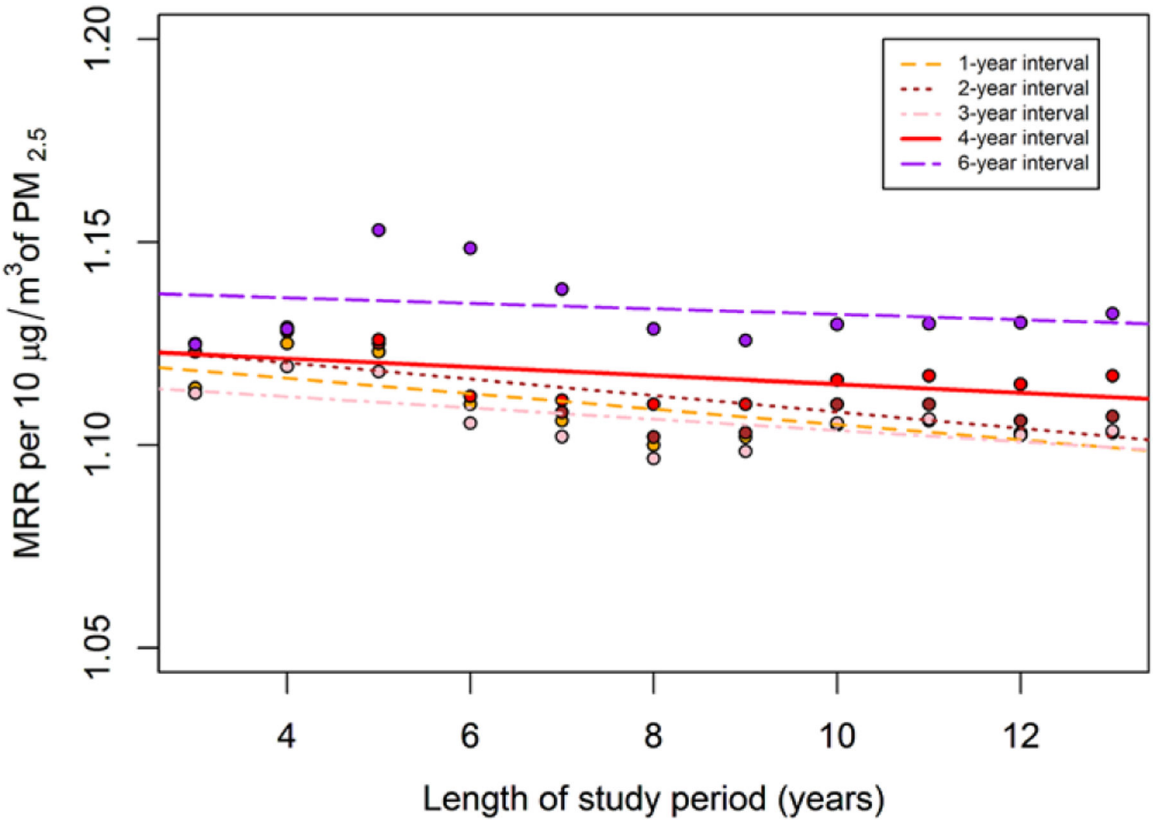

Figure 3.

MRRs per 10 μg/m^3 increase in $PM_{2.5}$ by length of study period: residual-based model using different time intervals to control for temporal trends.

Table 1

Descriptive statistics of all-cause mortality for the period of December 2000 to December 2012.[a]

Variable	West	Center	East	United States
No. monitors[a]	93	195	510	798
1-year $PM_{2.5}$ ($\mu g/m^3$)[b]	11.46 (4.57)	9.87 (2.37)	12.33 (2.68)	11.65 (3.09)
No. Medicare enrollees[a]				
Total	3,931,203	3,112,854	13,832,532	20,744,214
By month[b]	1,739,901 (140,871)	1,254,360 (123,762)	6,062,825 (378,173)	9,057,086 (609,378)
No. deaths				
Total	976,007	769,092	3,739,848	5,484,947
By month[b]	6,731 (703)	5,304 (705)	25,792 (2,409)	37,827 (3,711)

[a]Monitors include those with 8+ calendar years of data, each having 10+ months with 4+ valid measurements. All beneficiaries living in ZIP codes with centroids within 6 miles of a monitor were included in the analysis.

[b]Values are means (SD).

Table 2

MRRs (95% confidence intervals) per 10 μg/m^3 increase in 1-year moving average $PM_{2.5}$ [a] for base and time-adjusted models: 2000–2012.

Region	Monitors	Base model [b]	Time-adjusted models		
			Residual [c]	Penalized spline [d]	Decomposition [e]
United States	798	1.20 (1.20, 1.21)	1.12 (1.11, 1.12)	1.03 (1.02, 1.04)	1.06 (1.06, 1.07)
West	93	1.12 (1.11, 1.12)	1.04 (1.04, 1.05)	0.91 (0.90, 0.92)	1.00 (1.00, 1.01)
Center	195	1.27 (1.26, 1.28)	1.20 (1.18, 1.21)	1.15 (1.13, 1.17)	1.18 (1.17, 1.19)
East	510	1.26 (1.25, 1.26)	1.16 (1.15, 1.16)	1.14 (1.13, 1.15)	1.11 (1.10, 1.11)

[a] Exposures estimated as the 1-year moving average $PM_{2.5}$ exposures for all models except for the residual-based time-adjusted model; exposures for the residual-based model estimated as the 1-year moving average of the residuals of $PM_{2.5}$ regressed on year in 4-year intervals.

[b] Log-linear models adjusted for age and regions; all $P < 0.001$.

[c] Model adjusted for long-term time trends in $PM_{2.5}$ using a new exposure measure based on the residuals of $PM_{2.5}$ regressed on year in 4-year intervals.

[d] Model adjusted for long-term time trends in $PM_{2.5}$ by adding a penalized spline term for time to the base model.

[e] Model adjusted for long-term time trends in $PM_{2.5}$ by adding a term that describes only temporal variation in $PM_{2.5}$, which was calculated by decomposing $PM_{2.5}$ into its temporal and spatiotemporal components following Greven et al.[17]