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Original Contribution

Long-Term $PM_{2.5}$ Exposure and Respiratory, Cancer, and Cardiovascular Mortality in Older US Adults

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The impact of chronic exposure to fine particulate matter (particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$)) on respiratory disease and lung cancer mortality is poorly understood. In a cohort of 18.9 million Medicare beneficiaries (4.2 million deaths) living across the conterminous United States between 2000 and 2008, we examined the association between chronic $PM_{2.5}$ exposure and cause-specific mortality. We evaluated confounding through adjustment for neighborhood behavioral covariates and decomposition of $PM_{2.5}$ into 2 spatiotemporal scales. We found significantly positive associations of 12-month moving average $PM_{2.5}$ exposures (per 10-$\mu g/m^3$ increase) with respiratory, chronic obstructive pulmonary disease, and pneumonia mortality, with risk ratios ranging from 1.10 to 1.24. We also found significant $PM_{2.5}$-associated elevated risks for cardiovascular and lung cancer mortality. Risk ratios generally increased with longer moving averages; for example, an elevation in 60-month moving average $PM_{2.5}$ exposures was linked to 1.33 times the lung cancer mortality risk (95% confidence interval: 1.24, 1.40), as compared with 1.13 (95% confidence interval: 1.11, 1.15) for 12-month moving average exposures. Observed associations were robust in multivariable models, although evidence of unmeasured confounding remained. In this large cohort of US elderly, we provide important new evidence that long-term $PM_{2.5}$ exposure is significantly related to increased mortality from respiratory disease, lung cancer, and cardiovascular disease.

air pollution; cardiovascular disease mortality; chronic exposure; fine particles; lung cancer mortality; particulate matter; $PM_{2.5}$; respiratory disease mortality

Abbreviations: BRFSS, Behavioral Risk Factor Surveillance System; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; $PM_{2.5}$, particulate matter less than or equal to 2.5 μm in aerodynamic diameter; RR, risk ratio.

Long-term exposure to fine particulate matter (particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$)) has been associated with increased all-cause and cardiopulmonary mortality (1–13). Consistent with earlier studies such as the Harvard Six Cities and American Cancer Society cohort studies (1, 8), recent findings from the Rome Longitudinal Study (14) indicated a 4% (hazard ratio = 1.04, 95% confidence interval (CI): 1.03, 1.05) increased risk of all-cause mortality per 10-$\mu g/m^3$ increase in $PM_{2.5}$ exposure, with a higher associated risk for ischemic heart disease mortality (hazard ratio = 1.10, 95% CI: 1.06, 1.13). Investigators with the California Teachers Study and the Women's Health Initiative also reported similar findings (3, 15).

Examining the impact of long-term $PM_{2.5}$ exposure on respiratory disease mortality, however, has been more challenging. Although chronic lower respiratory diseases are the third leading cause of death in the United States, they comprise only a small fraction of overall deaths (6% in 2014) as compared with cardiac disease (23%), which comprises the largest fraction (16). The relatively small number of deaths attributed to respiratory disease probably results in insufficient statistical power to test associations between air pollution and respiratory mortality.

Additional challenges include the fact that respiratory disease in elderly persons is often accompanied by many comorbid conditions, which can result in variable cause-of-death determinations in individuals with respiratory disease. For example, the cause of death in persons with moderate chronic obstructive pulmonary disease (COPD) may be classified according to a more immediate cause of death (e.g., cardiovascular disease (CVD)), whereas the cause of death for persons with severe COPD is often listed as respiratory failure (17, 18). Since the impacts of air pollution have been shown to differ by underlying disease status (19), variable cause-of-death determinations may result in null (6, 14, 20) or inverse (21, 22) associations in studies based on small numbers of respiratory disease-related deaths. For example, while statistically significant positive associations between respiratory mortality and $PM_{2.5}$ level were found in the Canadian Community Health Survey and the Japanese Three-Prefecture cohort study (with hazard ratios ranging from 1.11 to 1.54) (22, 23), other studies have shown null associations. Positive but statistically insignificant associations, for instance, were reported in the California Teachers Study (6, 15) and the National Institutes of Health's Diet and Health Study (24). While more evidence links $PM_{2.5}$ exposure to increased risk of lung cancer mortality, this evidence is not definitive, as null associations have been reported in numerous US and European cohort studies (10, 14, 15, 25–28).

This limited and conflicting body of evidence demonstrates the need for larger studies that examine the impact of $PM_{2.5}$ on respiratory and lung cancer mortality. To do so, we examined the association between chronic $PM_{2.5}$ exposure and cause-specific mortality in a cohort of 18.9 million Medicare beneficiaries.

METHODS

Study population

This study was approved by the Institutional Review Board of Northeastern University. Through the Centers for Medicare and Medicaid Services, we compiled enrollment data from 52.9 million Medicare beneficiaries aged 65–120 years residing in the conterminous United States between December 2000 and the end of 2008. For each enrollee, we obtained beneficiary-specific information on date of birth, sex, race/ethnicity, zip code of residence, and survival. Using the *International Classification of Diseases, Tenth Revision*, codes from the National Death Index, we extracted information on mortality from nonaccidental and accidental causes and 3 major causes of death (and their subcategories) that together account for over 73% of all-cause mortality: CVD, respiratory disease, and cancer (Table 1).

$PM_{2.5}$ data

We obtained data on daily $PM_{2.5}$ concentrations from the Environmental Protection Agency's Air Quality System. We considered 988 air quality monitors that had daily measurements for 4 or more calendar years, with each year having ≥9 months with ≥4 daily measurements between 2000 and 2008, and used centered $PM_{2.5}$ levels, calculated as the monthly $PM_{2.5}$ concentration at a monitor minus its monitor-specific overall mean, as our primary exposure measure (see the Web Appendix, available at https://academic.oup.com/aje, for detailed methodology). We assessed the impact of chronic $PM_{2.5}$ exposure based on 12- to 60-month moving averages for all examined outcomes.

Statistical analyses

For each month during the study period, we matched the $PM_{2.5}$ moving averages for a given monitor to eligible Medicare beneficiaries (and their data) who lived in zip codes with a geographic centroid within a 6-mile (9.6-km) radius of that monitor. The closest monitor was selected if a zip code centroid was located within the buffer zones of 2 or more valid monitors. We computed the numbers of Medicare beneficiaries and cause-specific deaths for each 5-year age interval, monitor, and study month. To avoid excessive zero counts, we collapsed ages at or above 90 years into 1 interval.

We applied log-linear regression models to examine the association between long-term $PM_{2.5}$ exposure and cause-specific mortality nationwide, as well as by 4 US Census regions (Web Appendix and Web Figure 1) (29). All results are expressed as risk ratios for dying in a given month per 10-$\mu g/m^3$ increase in moving average $PM_{2.5}$ concentration. Statistical analyses were conducted using SAS 9.4 software (SAS Institute, Inc., Cary, North Carolina) and R 3.3.1 software (R Foundation for Statistical Computing, Vienna, Austria).

For sensitivity analyses, we assessed the impact of exposure error by defining $PM_{2.5}$ exposure based on 3-mile (4.8-km) and 12-mile (19.2-km) buffer zones, as compared with the 6-mile (9.6-km) buffer zone used in our primary analysis. We also conducted multivariable regression analyses to assess the association with and without adjusting for potential confounding by behavioral covariates chosen from the Selected Metropolitan/Micropolitan Area Risk Trends of the Behavioral Risk Factor Surveillance System (BRFSS), which first became available in 2002 (30). We specifically controlled for monthly county-level prevalences of nonwhites, current smokers, persons with diabetes, heavy alcohol drinkers (i.e., >2 drinks/day), and persons with asthma, average median income, and body mass index; these variables were selected a priori based on their previous associations with either mortality or $PM_{2.5}$. Note that data on BRFSS factors were available for only a subset of our cohort, as only 534 of the 988 $PM_{2.5}$ monitors were located in a county with BRFSS data. The average $PM_{2.5}$ level from monitors included in the BRFSS analysis was 12.29 $\mu g/m^3$, whereas it was 12.04 $\mu g/m^3$ from excluded monitors. The spatial distribution of the monitors with BRFSS data was similar to that for those in our primary analysis, though with slightly fewer monitors in the Midwest (24% vs. 27% overall) and more in the Northeast (20% vs. 15% overall).

In addition, we examined the extent to which our findings remained affected by unmeasured confounding in BRFSS-adjusted models, following a method described by Greven et al. (29). We decomposed $PM_{2.5}$ data into 2 orthogonal component measures, "temporal" $PM_{2.5}$ and "spatiotemporal" $PM_{2.5}$ (previously referred to as "global" and "local" $PM_{2.5}$, respectively). We estimated their associations with cause-specific mortality simultaneously in nonadjusted and BRFSS-adjusted models using a data subset for which BRFSS data were available (Web Appendix). "Temporal" $PM_{2.5}$ represents the national temporal trends in monthly $PM_{2.5}$ concentrations centered by the average

Table 1. Characteristics of Air Pollution Monitoring Stations and $PM_{2.5}$ Exposure, Numbers of Participants, and Numbers of Deaths, Overall and by Cause, Among Medicare Enrollees Aged 65–120 Years, United States, 2000–2008

Characteristic	ICD-10 Code	Median[a] (IQR[b])	No.	%
No. of monitoring stations			988	
$PM_{2.5}$ exposure, μg/m^3		12.5 (10.3–14.3)		
No. of Medicare enrollees		14,630 (6,777–27,142)	18,937,461	
Monthly no. and % of deaths per monitor				
All causes		2,845 (1,154–5,520)	4,190,595	100.0
Nonaccidental	A–R	2,774 (1,130–5,381)	4,097,110	98.0
Accidental	V–Y	70 (30–128)	93,467	2.2
All cardiovascular disease	I00–I99	1,069 (442–2,161)	1,683,577	40.2
Ischemic heart disease	I20–I25	508 (208–1,048)	890,806	21.3
Cerebrovascular disease	I60–I69	207 (87–396)	293,786	7.0
Congestive heart failure	I50	85 (34–170)	119,631	2.9
All respiratory disease	J00–J99	329 (138–633)	460,725	11.0
COPD	J40–J44	178 (73–337)	238,214	5.7
Pneumonia	J12–J18	78 (33–156)	126,635	3.0
All cancer	C–D	631 (256–1,230)	925,632	22.1
Lung cancer	C34	182 (73–346)	255,544	6.1

Abbreviation: COPD, chronic obstructive pulmonary disease; ICD-10, *International Classification of Diseases, Tenth Revision*; IQR, interquartile range; $PM_{2.5}$, particulate matter less than or equal to 2.5 μm in aerodynamic diameter.

[a] Median value among locations and months.

[b] 25th–75th percentiles.

concentrations for all monitors and across the study period; "spatiotemporal" $PM_{2.5}$ refers to the monitor-specific temporal trends in monthly $PM_{2.5}$ concentrations compared with the national "temporal" trends. As described in detail by Greven et al. (29), estimates of "temporal" and "spatiotemporal" $PM_{2.5}$ should be similar in the absence of confounding or model misspecification, since risks associated with the same unit change in $PM_{2.5}$ level should be the same, irrespective of whether they are estimated using "temporal" or "spatiotemporal" measures of $PM_{2.5}$.

RESULTS

Our study population included 18.9 million elderly Medicare enrollees residing in 7,788 zip codes across the United States, with an average of 10 million individuals enrolled in any given month (Table 1). This population comprised 36% of all Medicare enrollees (Web Table 1). During the study period, 4.2 million deaths were reported, with 98% and 2% of deaths being from nonaccidental causes and accidental causes (e.g., accidents, drug overdoses), respectively. CVD accounted for 40% of all mortality, followed by cancer (22%) and respiratory disease (11%). Over half of all CVD deaths were caused by ischemic heart disease, with a median of 508 deaths per month and monitor. Cerebrovascular diseases (e.g., stroke) and congestive heart failure also were significant causes of CVD mortality. Fifty-two percent of respiratory deaths were caused by COPD and 27% by pneumonia; 28% of cancer deaths were attributable to lung cancer. The annual average $PM_{2.5}$ concentration nationwide was 12.5 μg/m^3 (Web Figure 2).

Figure 1 shows the $PM_{2.5}$-associated risk ratios for total mortality and mortality from 11 causes for multiple exposure windows. We found a 10-μg/m^3 increase in 12-month moving average $PM_{2.5}$ level to be significantly associated with elevated risk of dying from all causes (risk ratio (RR) = 1.23, 95% CI: 1.22, 1.23) and nonaccidental causes (RR = 1.23, 95% CI: 1.23, 1.24) but not from accidental causes (Figure 1A). Risk ratios were greatest for CVD causes (RR = 1.56, 95% CI: 1.55, 1.57); among these, $PM_{2.5}$ exposure was linked to a 1.78-fold increase in the risk of cerebrovascular disease death (95% CI: 1.75, 1.80) and a 1.75-fold increase in the risk of ischemic heart disease death (95% CI: 1.74, 1.77) (Figure 1B). $PM_{2.5}$-associated risk of respiratory mortality (RR = 1.24, 95% CI: 1.23, 1.25) was similar to that observed for all-cause mortality (Figure 1C). An increase in $PM_{2.5}$ was significantly associated with 1.60-fold (95% CI: 1.57, 1.63) and 1.10-fold (95% CI: 1.08, 1.12) increases in the risks of pneumonia and COPD mortality, respectively. $PM_{2.5}$-associated risk ratios equaled 1.15 (95% CI: 1.14, 1.16) and 1.13 (95% CI: 1.11, 1.15) for all causes of cancer and lung cancer, respectively (Figure 1D), and were of similar magnitude as those for all-cause and respiratory mortality. $PM_{2.5}$-associated mortality risks remained significant and positive for most causes of death when longer moving averages were examined. Risk ratios increased with longer moving averages for most causes of death, except COPD mortality, for which the risk ratio associated with

60-month moving average $PM_{2.5}$ exposure was lower than the risk ratios for other moving averages. Web Table 2 shows that $PM_{2.5}$-associated mortality risks differed by region, with the highest risk ratios being found in the Northeast and the lowest in the West and South.

Sensitivity analyses

We reexamined exposures using monitors located within 3 miles (4.8 km) or 12 miles (19.2 km) of the centroid of enrollee zip codes. We found that the associations between 12-month moving average $PM_{2.5}$ level and all-cause mortality were statistically significant for buffer zones of all sizes, and further were of similar magnitude as those for the 6-mile (9.6-km) buffer zone (Web Table 3). Table 2 compares the $PM_{2.5}$-associated risks for all-cause mortality and mortality from 3 major causes, estimated with and without adjustment for BRFSS covariates nationwide and by region using the smaller $PM_{2.5}$ monitor subset. We observed that most risk ratios were similar or slightly attenuated in models adjusting for BRFSS covariates, as compared with those from nonadjusted models. The largest attenuation, 3.8%, was seen for mortality from congestive heart failure (RR = 1.16 vs. RR = 1.11 in adjusted model), followed by pneumonia mortality, with a 3.1% decrease in risk ratio (RR = 1.49 vs. RR = 1.45 in adjusted model). Risk estimates for cancer and lung cancer mortality increased by 1.4% and 1.9% in the BRFSS-adjusted models, respectively. The consistently small changes in the risk ratios for adjusted models suggest little, if any, confounding of PM-mortality associations by the examined BRFSS covariates.

We further examined the ability of BRFSS-adjusted models to control for potential confounding by decomposing $PM_{2.5}$ into 2 components describing "temporal" and "spatiotemporal" variation, per the approach of Greven et al. (29) (Web Table 4). In nonadjusted models, we observed positive, statistically significant associations for an increase in "temporal" $PM_{2.5}$ levels, irrespective of the cause of death. In contrast, risk ratios associated with "spatiotemporal" $PM_{2.5}$ levels were approximately centered around 1 and were often statistically insignificant. The difference in the "temporal" and "spatiotemporal"

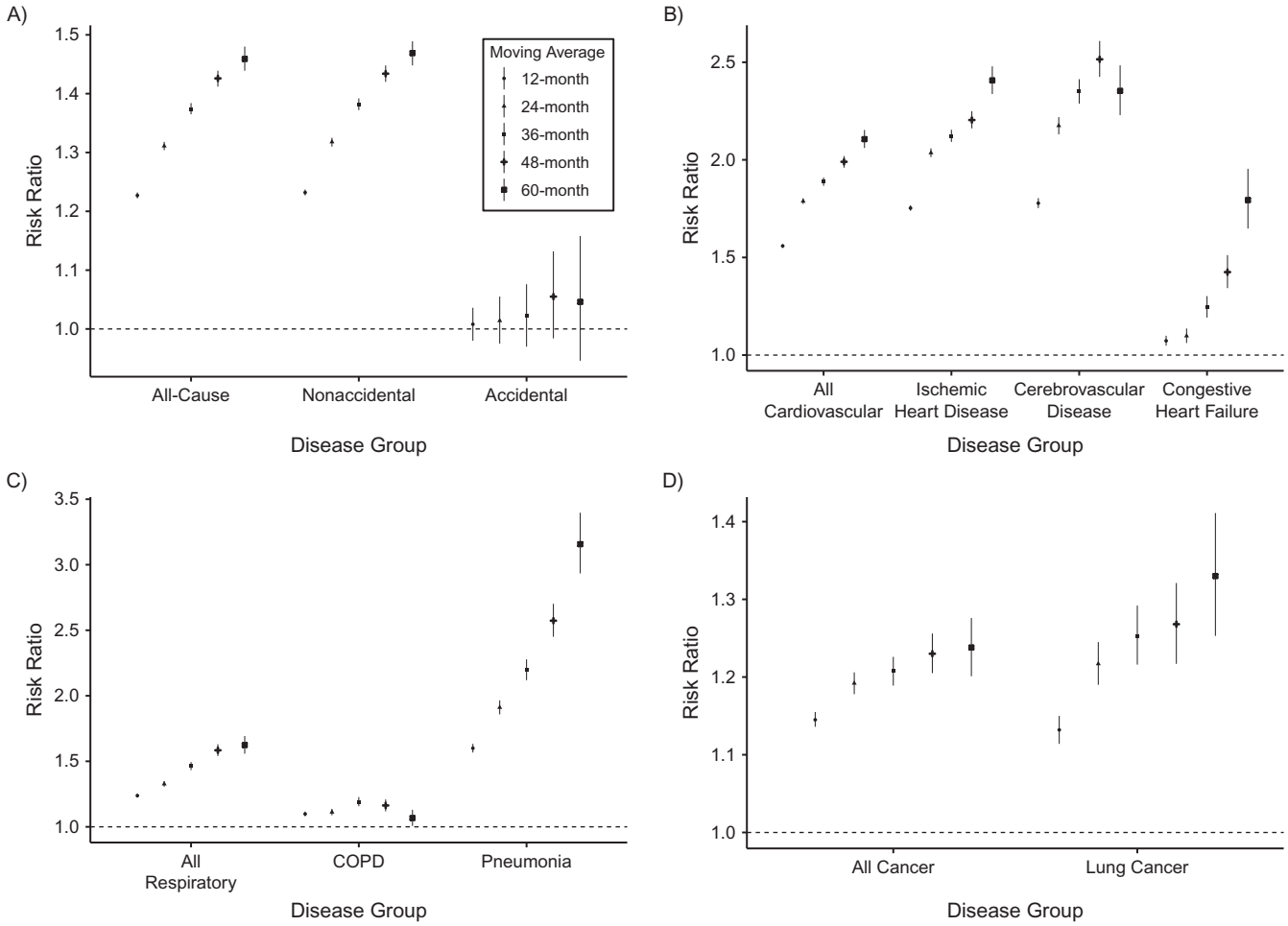

Figure 1. Risk ratios for all-cause (A), cardiovascular disease (B), respiratory disease (C), and cancer (D) mortality associated with 10-μg/m^3 increases in 12- to 60-month moving average exposure to particulate matter less than or equal to 2.5 μm in aerodynamic diameter ($PM_{2.5}$) nationwide, United States, 2000–2008. Bars, 95% confidence intervals. COPD, chronic obstructive pulmonary disease.

Table 2. Mortality Risk Associated With a 10-μg/m^3 Increase in 12-Month Moving Average $PM_{2.5}$ Concentration, Nationwide and by Region, United States, 2000–2008

Cause of Death and Region	Nonadjusted Model		BRFSS-Adjusted Model[a]	
	RR	95% CI	RR	95% CI
All causes				
United States	1.223	1.215, 1.232	1.206	1.197, 1.214
West	1.163	1.152, 1.174	1.167	1.156, 1.178
Midwest	1.210	1.193, 1.228	1.172	1.155, 1.190
South	1.215	1.193, 1.239	1.151	1.129, 1.174
Northeast	1.471	1.447, 1.496	1.397	1.372, 1.422
Accidents				
United States	1.119	1.066, 1.174	1.146	1.091, 1.205
West	1.179	1.098, 1.265	1.237	1.147, 1.335
Midwest	1.034	0.936, 1.141	1.025	0.926, 1.134
South	1.137	1.004, 1.287	1.110	0.977, 1.261
Northeast	1.064	0.942, 1.201	1.115	0.981, 1.269
All cardiovascular disease				
United States	1.502	1.487, 1.517	1.475	1.459, 1.492
West	1.388	1.368, 1.407	1.420	1.399, 1.442
Midwest	1.447	1.414, 1.481	1.344	1.313, 1.377
South	1.606	1.557, 1.656	1.457	1.411, 1.505
Northeast	1.993	1.941, 2.046	1.772	1.723, 1.822
Ischemic heart disease				
United States	1.644	1.621, 1.666	1.639	1.615, 1.663
West	1.485	1.458, 1.512	1.546	1.516, 1.577
Midwest	1.569	1.519, 1.619	1.427	1.381, 1.476
South	1.845	1.765, 1.928	1.618	1.544, 1.695
Northeast	2.338	2.259, 2.420	2.056	1.983, 2.132
Cerebrovascular disease				
United States	1.724	1.681, 1.767	1.729	1.683, 1.777
West	1.642	1.587, 1.698	1.802	1.734, 1.872
Midwest	1.622	1.533, 1.715	1.508	1.423, 1.598
South	1.828	1.700, 1.965	1.619	1.502, 1.746
Northeast	2.215	2.065, 2.377	1.927	1.787, 2.077
Congestive heart failure				
United States	1.158	1.110, 1.207	1.114	1.066, 1.163
West	0.838	0.785, 0.894	0.848	0.795, 0.904
Midwest	1.382	1.273, 1.500	1.352	1.241, 1.474
South	1.405	1.253, 1.576	1.371	1.219, 1.543
Northeast	1.665	1.507, 1.839	1.476	1.327, 1.642
All respiratory disease				
United States	1.264	1.239, 1.290	1.248	1.222, 1.274
West	1.194	1.162, 1.228	1.186	1.152, 1.220
Midwest	1.244	1.190, 1.302	1.229	1.173, 1.287
South	1.201	1.132, 1.274	1.113	1.047, 1.183
Northeast	1.648	1.565, 1.736	1.528	1.446, 1.616

Table continues

Table 2. Continued

Cause of Death and Region	Nonadjusted Model		BRFSS-Adjusted Model[a]	
	RR	95% CI	RR	95% CI
COPD				
United States	1.169	1.136, 1.203	1.174	1.139, 1.209
West	1.146	1.102, 1.193	1.139	1.094, 1.186
Midwest	1.248	1.173, 1.328	1.265	1.186, 1.350
South	0.967	0.891, 1.049	0.919	0.845, 0.999
Northeast	1.357	1.254, 1.468	1.323	1.217, 1.438
Pneumonia				
United States	1.491	1.441, 1.543	1.445	1.394, 1.498
West	1.340	1.283, 1.398	1.313	1.256, 1.374
Midwest	1.554	1.419, 1.702	1.452	1.321, 1.596
South	1.816	1.611, 2.047	1.559	1.376, 1.766
Northeast	2.053	1.876, 2.247	1.829	1.661, 2.013
All cancer				
United States	1.120	1.104, 1.136	1.107	1.091, 1.124
West	1.067	1.046, 1.089	1.065	1.043, 1.088
Midwest	1.087	1.055, 1.121	1.075	1.041, 1.109
South	1.122	1.078, 1.168	1.082	1.037, 1.127
Northeast	1.342	1.295, 1.390	1.321	1.272, 1.371
Lung cancer				
United States	1.146	1.115, 1.179	1.149	1.116, 1.183
West	1.132	1.086, 1.180	1.157	1.107, 1.209
Midwest	1.037	0.979, 1.099	1.041	0.981, 1.105
South	1.205	1.118, 1.298	1.172	1.085, 1.265
Northeast	1.311	1.223, 1.405	1.329	1.235, 1.431

Abbreviations: BRFSS, Behavioral Risk Factor Surveillance System; CI, confidence interval; $PM_{2.5}$, particulate matter less than or equal to 2.5 μm in aerodynamic diameter; RR, risk ratio.

[a] Results were adjusted for county-level race (being nonwhite), smoking, diabetes, body mass index, alcohol consumption (>2 drinks/day), asthma, and median income. Data on BRFSS factors were available for only a subset of the cohort, since only 534 of the 988 $PM_{2.5}$ monitors were located in a county with BRFSS data.

coefficients suggested the presence of unmeasured confounding; this was most evident for pneumonia mortality, where the difference was the largest. In contrast, the 2 coefficients were similar for COPD mortality, suggesting little unmeasured confounding. In BRFSS-adjusted models, most risk ratios associated with "temporal" $PM_{2.5}$ levels were greatly attenuated, as compared with those for corresponding base models, especially for CVD and pneumonia deaths. Risks associated with "spatiotemporal" $PM_{2.5}$ did not change substantially upon adjustment for BRFSS covariates, and risk ratios remained centered around 1. We also found both "temporal" and "spatiotemporal" risk ratios for cancer and lung cancer mortality to be unaffected upon adjustment for BRFSS covariates. Overall, BRFSS adjustment reduced the magnitude of "temporal" risk ratios for all-cause and cardiorespiratory mortality, resulting in smaller differences between "temporal" and "spatiotemporal" risk ratios. This suggests that BRFSS covariates accounted for a portion of the unmeasured confounding but not all of it.

DISCUSSION

We assessed the impacts of long-term $PM_{2.5}$ exposure on total and cause-specific mortality in a large cohort of almost 19 million Medicare beneficiaries with 4.2 million deaths—to our knowledge, the largest cohort examined to date. By virtue of its large size, we were able to examine $PM_{2.5}$-associated impacts on multiple causes of death, most notably respiratory disease mortality, for which current evidence is sparse and conflicting. We showed that a 10-$\mu g/m^3$ elevation in 12-month moving average $PM_{2.5}$ exposure was associated with 24%, 60%, and 10% greater risks of respiratory disease, pneumonia, and COPD mortality, respectively, in an elderly population living in the United States. Elevated risk (13%) of lung cancer mortality associated with $PM_{2.5}$ was also found, as were strong and positive associations with all-cause and CVD-related mortality. Notably, the magnitudes of the associations increased as exposure windows increased from 12 months to 60 months. All associations were robust when

results were adjusted for BRFSS covariates. This adjustment controlled for some unmeasured confounding but not all, as suggested by the smaller but still persistent differences between "spatiotemporal" and "temporal" risk ratios in the BRFSS-adjusted models.

To our knowledge, this is the first study to have found positive and statistically significant associations between $PM_{2.5}$ exposures and respiratory disease-related mortality in a US population. Previously, Pinault et al. (23) and Katanoda et al. (22) reported significant and elevated $PM_{2.5}$-associated risks of respiratory disease mortality using data on adult participants in the Canadian Community Health Survey and a Japanese cohort, respectively. Our findings related to COPD and pneumonia mortality are consistent with those seen in cohorts of older Norwegian men (31) and older Japanese adults (22), respectively. Results from other studies differ, however. Pope et al. (21) reported statistically significant inverse associations of $PM_{2.5}$ with respiratory (relative risk = 0.92, 95% CI: 0.86, 0.98) and COPD (relative risk = 0.84, 95% CI: 0.77, 0.93) mortality in the American Cancer Society cohort. Gan et al. (32) found an insignificant positive association between $PM_{2.5}$ and COPD mortality after adjustment for confounders in a Canadian cohort, while investigators in other studies observed no evidence of a relationship between $PM_{2.5}$ and COPD mortality (2, 8, 22, 24). Consistent with these findings, in a meta-analysis of 17 studies, Hoek et al. (9) found an insignificant pooled excess risk (relative risk = 1.03, 95% CI: −0.94, 1.13) of respiratory disease mortality per 10-$\mu g/m^3$ increase in $PM_{2.5}$, which they attributed to possibly stronger associations between respiratory mortality and primary traffic-related indicators (i.e., nitrogen dioxide, traffic intensity) as compared with long-range transported $PM_{2.5}$ (31–33). Alternatively or in addition, our results suggest that the sample sizes of previous studies were too small to detect an association between $PM_{2.5}$ and respiratory mortality, since our findings of significant positive associations were based on 460,000 respiratory disease deaths, 240,000 COPD deaths, and 120,000 pneumonia deaths—numbers substantially larger than those in the earlier studies (e.g., 8,397 respiratory deaths in a Diet and Health Study cohort (24); 541 COPD deaths in a Canadian cohort (32)) (10). Other factors that may explain our findings could include differences in population, exposure assessment, pollution mixture, study period, outcome assessment, and confounder control (e.g., smoking status) between studies (34).

Our findings for lung cancer are consistent with conclusions of the International Agency for Research on Cancer stating that exposure to ambient air pollution and particulate matter is associated with lung cancer risk (35). This conclusion was based in large part on evidence from a meta-analysis that showed a $PM_{2.5}$-associated mortality risk for lung cancer of 1.09 (95% CI: 1.04, 1.14), reflecting results from several large-scale cohort studies carried out in North America, Europe, and Asia that showed positive relationships with lung cancer death (11, 14, 22, 36), although no association was found in other US and European cohort studies (10, 25–28). Likewise, our findings of $PM_{2.5}$-associated risks for all-cause and CVD-related deaths were consistent with, though larger in magnitude than, many of the $PM_{2.5}$-associated mortality estimates reported in previous large-scale cohort studies (2, 3, 9, 21), perhaps because of our larger sample size and longer study period.

Importantly, our findings were robust to adjustment for neighborhood behavioral characteristics, as evidenced by similar risk ratios from nonadjusted and BRFSS-adjusted models. However, when decomposing $PM_{2.5}$ into its "temporal" and "spatiotemporal" components, as in the study by Greven et al. (29), who also used a Medicare cohort and similar statistical modeling methods, we found that risk ratios associated with "temporal" $PM_{2.5}$ levels were greatly attenuated in the adjusted models as compared with nonadjusted models, while those associated with "spatiotemporal" $PM_{2.5}$ remained unchanged. Although BRFSS adjustment resulted in smaller differences between "temporal" and "spatiotemporal" risk ratios, observable differences persisted, suggesting insufficient adjustment of unmeasured confounding by BRFSS data alone (29). Other possible sources of confounding include (but are not limited to) $PM_{2.5}$ composition, correlated gaseous pollutants, and long-term time trends in both $PM_{2.5}$ concentrations and mortality. Using the same Medicare cohort for an extended study period (2000–2012), members of our research group (Eum et al., Tufts University, unpublished manuscript, 2016) observed an even smaller difference between "temporal" (RR = 1.47, 95% CI: 1.43, 1.52) and "spatiotemporal" (RR = 1.13, 95% CI: 1.12, 1.14) risk ratios upon removal of the long-term temporal trends, while both risk ratios remained statistically significant. This suggests that temporal trends may account for a substantial portion of the unmeasured confounding in the chronic $PM_{2.5}$-associated mortality risks. Notably, the "temporal" coefficients but generally not the "spatiotemporal" coefficients were statistically significant; the meaning of each coefficient, absent comparison with the other, is not clear but warrants further study.

The positive associations of $PM_{2.5}$ with cardiorespiratory and lung cancer mortality are consistent with biological pathways through which $PM_{2.5}$ may influence health. $PM_{2.5}$ has been shown to deposit in the alveolar region of the lung and to move into interstitial spaces between cells and towards other organs (e.g., the heart and brain). Particulate matter is hypothesized to induce pulmonary and systemic inflammation, the release of potentially harmful cytokines (e.g., interleukin-6), hypercoagulability, and enhanced thrombosis and to alter cardiac autonomic function, thereby causing or accelerating the development of atherosclerosis and CVD-related diseases (21, 37, 38). The mechanisms through which chronic $PM_{2.5}$ exposure may increase risk of respiratory disease mortality are poorly defined but may involve systemic inflammation and oxidative stress in the lung epithelial cells (39–41). Other pathways may include decrements in lung function and airway hyperreactivity, thereby causing respiratory symptoms/disease (e.g., COPD exacerbation) and even death (21, 42). Furthermore, it has been suggested that in target cells, particulate matter induces reactive oxygen and nitrogen species, acting as both DNA-damaging species and inflammation-signaling moieties involved in pathways such as genotoxicity and cell and tissue proliferation, ultimately promoting lung cancer (43).

Our study had several limitations. First, we did not have information on beneficiaries' activity and mobility patterns, which may have contributed to exposure misclassification. While we used ambient, nearest-monitor $PM_{2.5}$ concentrations, which are imperfect proxies of personal $PM_{2.5}$ exposure, previous studies have shown chronic health risks to be underestimated using

nearest-monitor exposures, which lends support to our finding of significant positive associations (44). We linked $PM_{2.5}$ exposure to beneficiary information by year in order to account for residential moves and zip code boundary changes, and we used exposure values that were geographically close to residences, capturing exposures that resulted from nearby $PM_{2.5}$ emission sources, and thus reducing the potential for exposure misclassification. This is supported by results from our sensitivity analyses, which showed similar risk ratios associated with $PM_{2.5}$ exposures based on 3-mile (4.8-km) buffer zones as compared with 6-mile (9.6-km) buffer zones. Second, the number of associations between $PM_{2.5}$ exposure and cause-specific mortality that were examined raises concerns regarding multiple comparisons; however, given the consistency of our findings across outcomes and their high level of significance, we believe that our findings are nevertheless robust. Third, although we did not have data on personal-level characteristics, we adjusted for county-level BRFSS variables, including those related to smoking and comorbidity. We found that adjustment for BRFSS variables did not eliminate the observed significant, positive $PM_{2.5}$-mortality associations. Confounding by personal-level characteristics is unlikely to explain our findings, since, in a reanalysis of the American Cancer Society and Six Cities studies, Krewski et al. (45) reported little change in the risk estimates with adjustment for individual-level characteristics. Nonetheless, residual confounding by unmeasured covariates, such as long-term temporal trends, remains. Lastly, our findings may not be generalizable to younger age groups or to beneficiaries living away from air pollution monitors.

These limitations are balanced by the substantial strengths of our study. With nearly 19 million Medicare beneficiaries and 4.2 million deaths over the study period, our study was well-powered to detect meaningful associations, allowing us to provide valuable new information on the relationship between $PM_{2.5}$ exposures and specific CVD, respiratory, and cancer-related deaths, in addition to all-cause mortality. Our findings imply that a decrease of 1 $\mu g/m^3$ in population-averaged $PM_{2.5}$ exposure would result in 38,403 fewer all-cause deaths, 21,503 fewer CVD deaths, and 1,150 fewer COPD deaths per year nationwide, respectively, given the mean $PM_{2.5}$ concentration of 12.5 $\mu g/m^3$ and the 1,858,081 all-cause, 477,840 CVD, and 122,375 COPD deaths that occurred in the elderly (ages ≥65 years) US population in 2012, respectively (46).

In conclusion, we found new evidence of positive associations between chronic $PM_{2.5}$ exposure and respiratory and pneumonia mortality in a large US elderly cohort. We also found adverse associations of $PM_{2.5}$ with lung cancer and CVD-related mortality. Findings were statistically robust upon adjustment for neighborhood behavioral covariates, though unmeasured confounding remained.

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