Long-term effects of PM$_{2.5}$ components on incident dementia in the northeastern United States
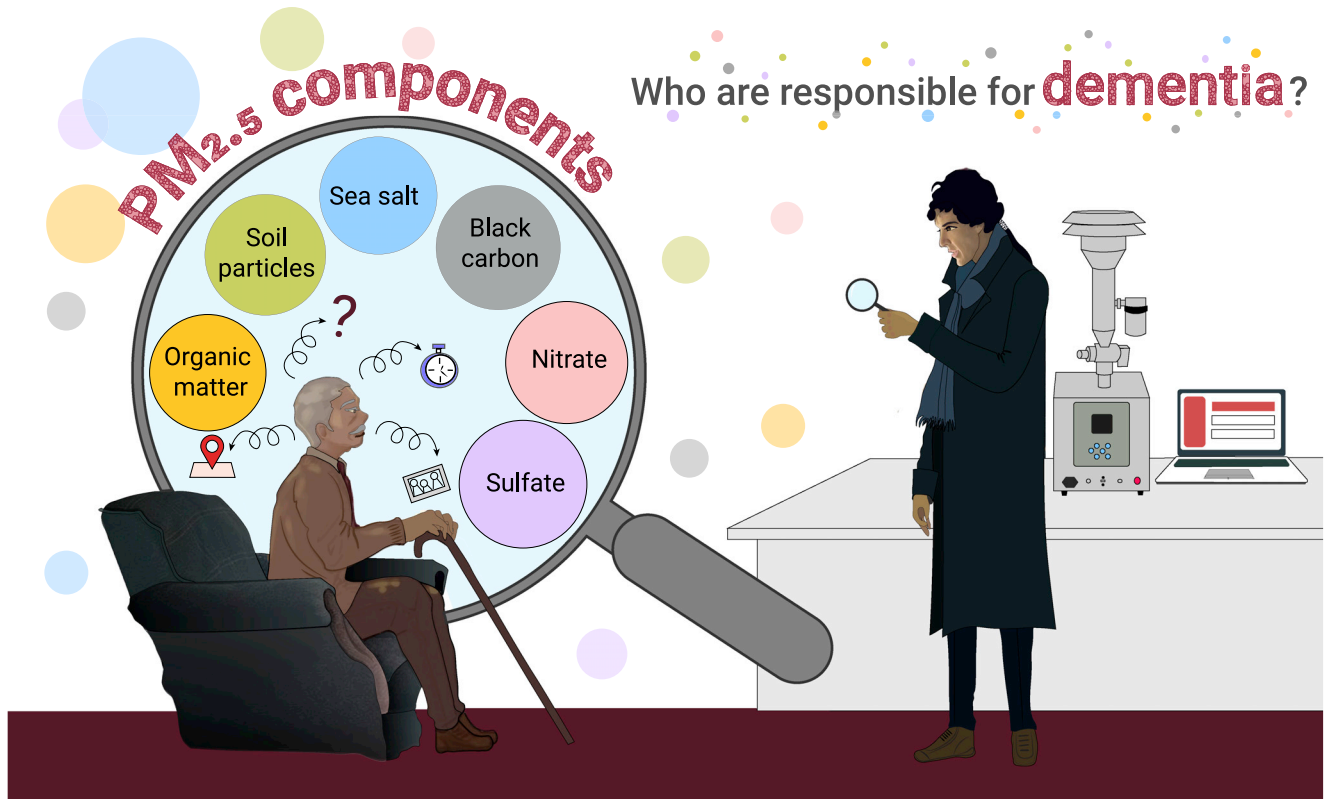
Jing Li,[1,*] Yifan Wang,[2] Kyle Steenland,[2] Pengfei Liu,[3] Aaron van Donkelaar,[4] Randall V. Martin,[4] Howard H. Chang,[5] W. Michael Caudle,[2] Joel Schwartz,[1] Petros Koutrakis,[1] and Liuhua Shi[2,*]

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GRAPHICAL ABSTRACT

PUBLIC SUMMARY

- A cohort study by resorting to the Medicare population and PM$_{2.5}$ components data

- Long-term exposure to specific PM$_{2.5}$ components can accelerate dementia progression

- Black carbon and sulfate showed the most stable associations

Long-term effects of PM$_{2.5}$ components on incident dementia in the northeastern United States

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Growing evidence has linked long-term fine particulate matter (PM$_{2.5}$) exposure to neurological disorders. Less is known about the individual effects of PM$_{2.5}$ components. A population-based cohort study investigated the association between long-term (1-year average) exposure to PM$_{2.5}$ components and dementia incidence among the elderly population (age, ≥65 years) in the United States. We used data from the Medicare Chronic Conditions Warehouse and a high-resolution PM$_{2.5}$ components dataset of the northeastern United States (2000–2017). We identified dementia diagnoses from patients' hospital and medical insurance records and carried out Cox proportional hazards regression to investigate their association with PM$_{2.5}$ components. Among ~2 million participants, 15.1% developed dementia. From the single-pollutant models, hazard ratios per interquartile range increase were 1.10 (95% confidence interval [CI]: 1.09–1.11) for black carbon, 1.08 (95% CI: 1.07, 1.10) for inorganic nitrate, 1.03 (95% CI: 1.02, 1.04) for organic matter, 1.13 (95% CI: 1.11, 1.15) for sulfate, 1.07 (95% CI: 1.06, 1.07) for soil particles, and 1.04 (95% CI: 1.03, 1.05) for sea salt. Increase in exposure to black carbon and sulfate per interquartile range had the strongest associations with dementia incidence. Penalized spline models indicated that dementia incidence increased linearly with elevated black carbon concentrations, whereas the incidence of dementia was only elevated significantly following sulfate concentrations above ~2 μg/m^3. Our study suggests that long-term exposure to PM$_{2.5}$ components is significantly associated with increased dementia incidence and that different components have different neurotoxicity. Reduction of PM$_{2.5}$ emissions, especially for main sources of black carbon and sulfate, may reduce the burden of dementia in the aging United States population.

INTRODUCTION

Fine particulate matter (PM$_{2.5}$) is an important air pollutant worldwide and consists of a complex mixture of carbonaceous fractions, water-soluble ions, metals, crustal elements, and other constituents.[1–3] Exposure to PM$_{2.5}$ has been associated with adverse health effects, including cardiovascular disease, respiratory disease, lung cancer, and premature mortality.[4–8] Several studies also suggest that long-term PM$_{2.5}$ exposure is a risk factor for neurodegenerative diseases.[9–11]

Dementia is one of the most prevalent neurodegenerative diseases and a major public health concern. It affects more than 47 million people worldwide, resulting in substantial health and financial burdens.[12] The prevalence of dementia has increased significantly in recent years.[13] Therefore, identifying modifiable risk factors for dementia that can be addressed by interventions at the population level is a top research priority. Studies suggest that PM$_{2.5}$ has the potential to induce dementia through biological mechanisms such as systemic inflammation, oxidative stress, and neuroinflammation.[14–16] In addition, some evidence indicates that PM$_{2.5}$ can exacerbate or accelerate existing diseases via these biological pathways.[17]

A growing body of epidemiological evidence suggests that particulate air pollution contributes to dementia, including several longitudinal studies conducted in the United States and around the world.[11,18–28] The majority of these studies found positive associations between PM$_{2.5}$ and dementia. A systematic review and meta-analysis also concluded that exposure to PM$_{2.5}$ is associated with a 16% higher risk of dementia per 10 μg/m^3 increase in PM$_{2.5}$ concentration.[29] Existing studies have often relied on inpatient hospitalization records as a measure of incidence. A recent study by Shi et al.,[30] based on nationwide Medicare data in

the United States including doctor visits, also provides evidence that long-term exposure to PM$_{2.5}$ may increase the incidence of dementia.

However, previous studies have almost exclusively focused on the effects of PM$_{2.5}$ mass concentrations. As a complex mixture, the toxic effects of PM$_{2.5}$ may be determined primarily by its chemical components. PM$_{2.5}$ components, such as organic matter (OM), inorganic nitrate (NO$_3^-$), inorganic sulfate (SO$_4^{2-}$), black carbon (BC), soil particles (SOILs), and sea salt (SS), emitted from specific sources, have different physicochemical and toxicological characteristics, resulting in various health effects.[31–33] To date, the individual effects of PM$_{2.5}$ components on dementia remain unclear. There is an urgent need to evaluate the effect of exposure to various PM$_{2.5}$ components on dementia to determine which PM$_{2.5}$ components are responsible for dementia, the possible biological mechanisms, and which emission sources are the most hazardous.[32]

To fill these knowledge gaps, we build on the study by Shi et al.[30] by conducting a population-based cohort study of the Medicare dataset and a well-validated high-resolution (1 km × 1 km) PM$_{2.5}$ components dataset from 2000–2017. The latter includes data on OM, NO$_3^-$, SO$_4^{2-}$, BC, SOILs, and SS in the northeastern United States, where better exposure estimates exist. First, we identified a diagnosis of all-cause dementia using all Medicare claims including doctor visits, with the requirement of a 5-year "clean" (i.e., dementia-free) period. PM$_{2.5}$ component exposure was assigned to subjects based on resident ZIP code. The effects of long-term exposure to six major PM$_{2.5}$ components (i.e., OM, NO$_3^-$, SO$_4^{2-}$, BC, SOILs, and SS) on incident dementia were investigated using Cox proportional hazards models.

RESULTS

Study population characteristics and air pollution levels

The dementia cohort with a "clean" period of 5 years had about 2 million subjects with a median follow-up of 7 years. Regarding the demographic data, 73.2% of the people entered the cohort between ages 65 and 74, 61.6% were female, 92% were white, and more than 90% were above the poverty level. Within the population cohort, 15.1% developed dementia. The descriptive information for the dementia cohort is listed in Table 1.

Between 2000 and 2017, the northeastern United States had an average PM$_{2.5}$ mass concentration of 8.8 μg/m^3. The average concentrations of PM$_{2.5}$ components were 0.7 μg/m^3 (BC), 1.0 μg/m^3 (NO$_3^-$), 2.9 μg/m^3 (OM), 1.8 μg/m^3 (SO$_4^{2-}$), 0.3 μg/m^3 (SOILs), and 0.4 μg/m^3 (SS). The interquartile ranges (IQRs) of BC, NO$_3^-$, OM, SO$_4^{2-}$, SOILs, and SS were 0.3 μg/m^3, 0.6 μg/m^3, 1.0 μg/m^3, 1.1 μg/m^3, 0.2 μg/m^3, and 0.2 μg/m^3, respectively (Table S3). The Pearson correlations between each PM$_{2.5}$ component and PM$_{2.5}$ mass are listed in Table S4. The spatial distributions of each component at the ZIP code level over 2000–2017 are shown in Figure 1. The spatial distribution of PM$_{2.5}$ mass is shown in Figure S1. The highest PM$_{2.5}$ mass concentrations were distributed in southern areas of the northeast United States, including western and eastern Pennsylvania, New Jersey, and New York City. High BC concentrations were found in western Pennsylvania, New York City, and the border of eastern Pennsylvania and New Jersey, and the spatial distribution of OM was also similar. Compared with the other states, western Pennsylvania had higher average SO$_4^{2-}$ and SOIL levels. In contrast, high levels of NO$_3^-$ were concentrated in eastern Pennsylvania. For SS, high concentrations occurred along the eastern coastline of Massachusetts, Rhode Island, Connecticut, and New York.

Table 1. Descriptive statistics for the dementia cohorts

Variables	Numbers	Percentage
Number of events	309,842	15.1
Total population	2,051,550	100
Total person-years	11,404,905	100
Median follow-up years	7	
Age at entry (years)		
65–74	1,481,574	73.2
75–115	569,976	27.8
Gender		
Male	789,610	38.9
Female	1,252,940	61.1
Race		
White	1,888,347	92.0
Black	88,327	4.3
Other	74,876	3.6
Medicaid eligibility		
Eligible	136,283	6.6
Not eligible	1,915,267	93.4
Air pollutants ($\mu g/m^3$)[a]		
$PM_{2.5}$ mass	8.8 (2.4)	
Black carbon	0.7 (0.3)	
Nitrate	1.0 (0.6)	
Organic matter	2.9 (1.0)	
Sulfate	1.8 (1.1)	
Soil particles	0.3 (0.2)	
Sea salt	0.4 (0.2)	
Area level variables[b]		
Smoking rate, %	47.6 (5.3)	
Below poverty level, %	7.9 (5.7)	
Not graduating from high school, %	20.2 (11.0)	
Population density, people/mile^2	6,326.5 (17,086.9)	
Body mass index, kg/m^2	27.2 (0.7)	
Median household income, US $1,000	69.8 (27.7)	
Owner-occupied housing units, %	70.1 (18.0)	
Black population proportion, %	6.7 (12.5)	
Number of hospitals	1.9 (4.3)	
Number of medical doctors	261.6 (1,135.1)	

[a]Presented as mean concentration (IQR).
[b]Presented as mean (SD).

Main analysis

Health effect estimates. In the single-pollutant model, long-term exposure to $PM_{2.5}$ mass and all $PM_{2.5}$ major components had a statistically significant positive association with dementia (Table 2). A per-IQR increase in concentration was associated with an increase in dementia, with a hazard ratio (HR) of 1.10 (95% confidence interval [CI]: 1.09, 1.12) for $PM_{2.5}$ mass, 1.10 (95% CI: 1.09, 1.11) for BC, 1.08 (95% CI: 1.07, 1.10) for NO_3^-, 1.03 (95% CI: 1.02, 1.04) for OM, 1.13

(95% CI: 1.11, 1.15) for SO_4^{2-}, 1.07 (95% CI: 1.06, 1.07) for SOILs, and 1.04 (95% CI: 1.03, 1.05) for SS. In multi-pollutant models, the positive associations with long-term exposure to BC (HR = 1.05; 95% CI: 1.04, 1.07), NO_3^- (HR = 1.02; 95% CI: 1.00, 1.03), SO_4^{2-} (HR = 1.05, 95% CI: 1.03, 1.07), SOILs (HR = 1.03; 95% CI: 1.02, 1.04), and SS (HR = 1.04; 95% CI: 1.03, 1.05) remained, although they were notably reduced except for SO_4^{2-}. However, OM showed a negative association with dementia (HR = 0.98; 95% CI: 0.96, 0.99). Figure 2 shows the HRs for each subgroup in single-pollutant models. We found that males had higher HRs for BC, NO_3^-, OM, SOILs, and SS, whereas females had higher HRs for SO_4^{2-}. Additionally, we observed higher HRs for BC, NO_3^-, SO_4^{2-}, SOILs, and SS among those identified as Black than for those identified as white or other races. Regarding age, those younger than 75 had stronger associations between dementia and BC, OM, SOILs, and SS than those older than 75, whereas those older than 75 had stronger associations between dementia and NO_3^- and SO_4^{2-}.

Concentration-Response (C-R) relationships. Next we evaluated the C-R relationships between each component of $PM_{2.5}$ and dementia from single-pollutant models (Figure 3). A strong near-linear relationship was observed with BC and SOILs, with no sign of threshold. Near-linear relationships were observed with NO_3^- and OM at low concentrations, and then the C-R curves leveled off at 0.5 $\mu g/m^3$ for NO_3^- and 3 $\mu g/m^3$ for OM. The C-R curves showed null associations between dementia and SO_4^{2-} at low concentrations; however, the relationship became significantly positive at high SO_4^{2-} concentrations, with a steep rise at about 2 $\mu g/m^3$. The pattern for SS was similar to SO_4^{2-}, with no significant relationship at low concentrations followed by a positive, linear relationship at high concentrations.

Sensitivity analysis. The results of the single-pollutant models adjusting for $PM_{2.5}$ mass are presented in Table S5. The patterns were similar with multi-pollutant models, with negative associations for OM and positive associations for the other components on dementia. The results of the non-mover cohort are very similar to the results of our main analysis (Table S6), suggesting little bias from residential mobility. The C-R curves from multi-pollutant models are shown in Figure S2. The C-R curves from multi-pollutant models for BC, NO_3^-, SOILs, and SS are generally consistent with those from single-pollutant models. However, for OM, a null association was observed at high concentrations after adjusting for other $PM_{2.5}$ components. We found that SO_4^{2-} exposure did not increase the risk of dementia at levels below 2 $\mu g/m^3$, followed by a monotonically increasing C-R relationship.

DISCUSSION

Using a large prospective cohort study from the northeastern United States, we found that long-term exposure to BC, NO_3^-, SO_4^{2-}, SOILs, and SS elevated the risk of dementia among the elderly population (age, $\geq$65). OM has been shown to be associated with dementia only when the single-pollutant model was used, and a negative association was observed when $PM_{2.5}$ mass or other major components of $PM_{2.5}$ were adjusted. In single- and multi-pollutant models, per-IQR increases of BC and SO_4^{2-} were associated with the highest dementia risk.

BC primarily forms from incomplete combustion of fossil fuels, biofuels, and biomass.[34] It is mainly associated with incomplete combustion processes, including traffic-related pollution and biomass burning.[35] We found a positive association between BC and dementia. Despite limited studies investigating the associations between BC and neurodegenerative disorders, some researchers have observed associations between BC and quantifiable impairment of brain development in children and cognitive decline in the elderly.[36,37] A possible explanation for the neurotoxicity of BC is that BC from traffic sources can be very small ($\sim$50 nm) and may get into the bloodstream and reach the blood-brain barrier.[38] Moreover, incomplete combustion can also co-emit polycyclic aromatic hydrocarbons (PAHs), which might be coated on BC and contribute to neurotoxicity.[38]

The OM in the atmosphere is a highly complex mixture of primary and secondary organic particles made mostly of organic carbon and trace amounts of hundreds of compounds such as PAH, alkanes, esters, and fatty acids.[39] Combustion of biomass and fossil fuels is the major source of primary OM, but secondary production from oxidation of organic gases is also considered a major source of OM.[40] In particular, secondary organic aerosols are generated by reactions of terpenes with nitrogen oxides. Numerous toxicological studies have implicated OM in cancer and cardiopulmonary illness; however, the effects of OM on the nervous system are largely unknown.[41] There have been some
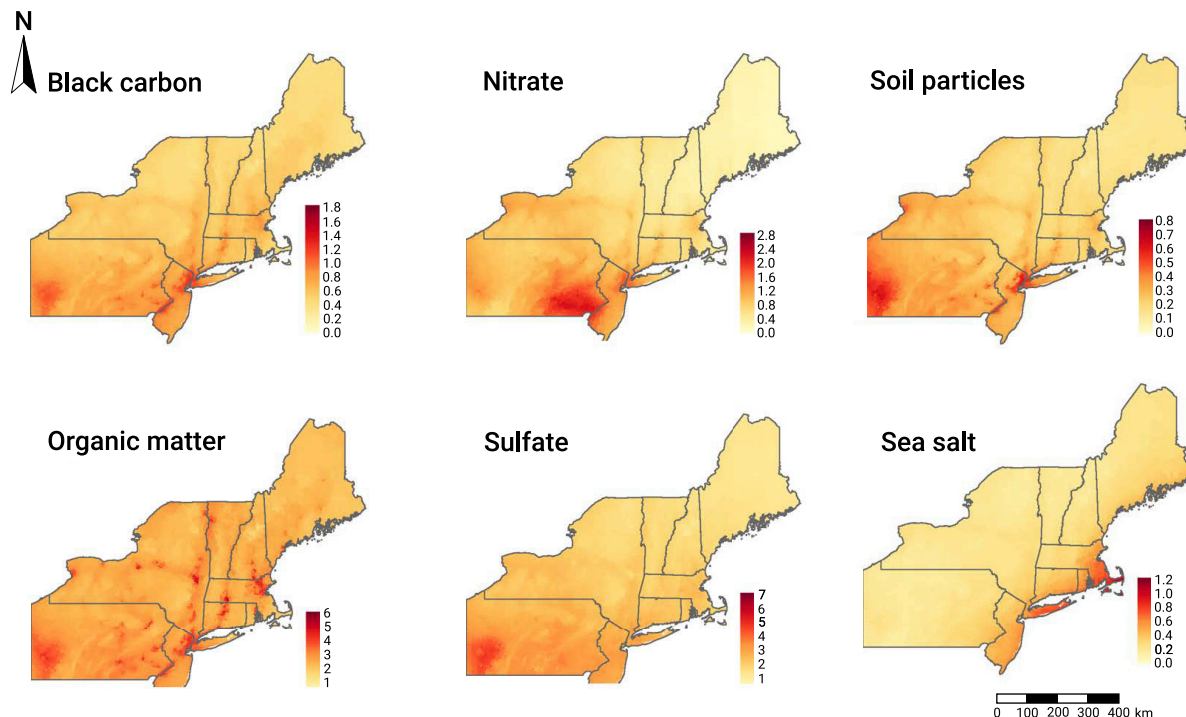
Figure 1. Average concentrations of $PM_{2.5}$ major components ($\mu g/m^3$) in the northeastern United States from 2000−2017

studies that link exposure to PAHs to neurodevelopmental disorders in children as well as neurodegenerative disease-like symptoms in zebrafish.[42,43] In our study, we observed an adverse effect of OM on dementia with the single-pollutant model, and a modest negative association was observed when $PM_{2.5}$ mass or other components of $PM_{2.5}$ were included in the model. According to the C-R relationships of the multi-pollutant model (Figure S2), for most of the OM distribution, the association was positive but became protective at high concentrations. The adjustments for other $PM_{2.5}$ components somehow reduce the associations of OM and dementia, likely because of collinearity. Moreover, the effect sizes for all components in the multi-pollutant models decreased from their levels in the single-pollutant models. Similarly, Crouse et al.[44] also observed a positive association between OM and mortality in the single-pollutant model, which reversed after adjusting for $PM_{2.5}$ mass and other components. They also attributed it to collinearity among component concentrations. The effects of OM still need to be explored.

NO_3^- is a secondary inorganic aerosol formed in the air; its major precursor gaseous species are ammonia and nitric acid.[45] Agriculture is considered to be the major source of ammonia and nitric acid globally; however, in urban areas, traffic is considered to be the main source of nitrogen oxides.[46] We found a significant positive association between NO_3^- and dementia. A linear C-R relationship was observed in low NO_3^- concentrations, and the relationships became stable at concentrations above 0.5 $\mu g/m^3$. Although the adverse effects of NO_3^- on neurodegenerative disorders have been less explored, NO_3^- has been linked to oxidative stress, which is known to be a major pathological driver in dementia and neurodegenerative disease.[47] In addition, there is some evidence that traffic-related air pollution increases the risk of neurodegenerative disorders.[18,20,21]

SO_4^{2-} is also a secondary inorganic aerosol present in the atmosphere in the form of a mixture of ammonium sulfate, ammonium bisulfate, or sulfuric acid. Similar to our findings, van Wijngaarden et al.[48] observed a positive association between SO_4^{2-} and hospitalizations for neurodegenerative disorders with a relative risk of 1.09 (95% CI: 1.00−1.19) per IQR. In the C-R curves, we only observed a positive linear relationship between SO_4^{2-} and dementia at high SO_4^{2-} concentrations; a negative relationship was found at low SO_4^{2-} concentrations when adjusting for other major components. This effect could be explained by sulfate precipitating the toxic compound deep in the lungs by creating an acidic environment in the microcirculation that promotes absorption of metal elements of particulate matter, but only after a certain threshold of lung accumulation occurs.[49,50]

SOILs are composed of oxides and carbonates of crustal elements such as Si, Al, Fe, Ca, and Ti. They are formed through mechanical processes such as eolian erosion, transportation, and industrial processes such as mining and cement production. We found a positive association between SOILs and dementia. It has been reported that accumulation of metals in the blood and bones can damage the nervous system.[51]

SS derived from sea spray is primarily composed of sodium chloride (NaCl) but also contains other chemical ions that are common in seawater. To date, no other studies have investigated the relationship between SS and neurodegenerative disorders. It has been reported that SS is associated with cardiovascular disease, such as hypertension.[41] The effect of SS on dementia is worthy of attention based on our results.

Our study has several strengths. To the best of our knowledge, this is the first population-based, large-scale cohort study characterizing associations between $PM_{2.5}$ component exposure and incident dementia. $PM_{2.5}$ dementia effects are currently mostly studied from the total mass perspective, and only a few studies have investigated specific $PM_{2.5}$ components. Consequently, our study provides evidence for the association between $PM_{2.5}$ components and dementia, which may have implications for $PM_{2.5}$ component regulation. In addition, previous studies have almost exclusively focused on hospitalization data; in contrast, we used more comprehensive Medicare claims, including Medicare inpatient and outpatient claims, physician visits, skilled nursing facilities, and home health

Table 2. Hazard Ratio of dementia associated with per-IQR increase in $PM_{2.5}$ major components

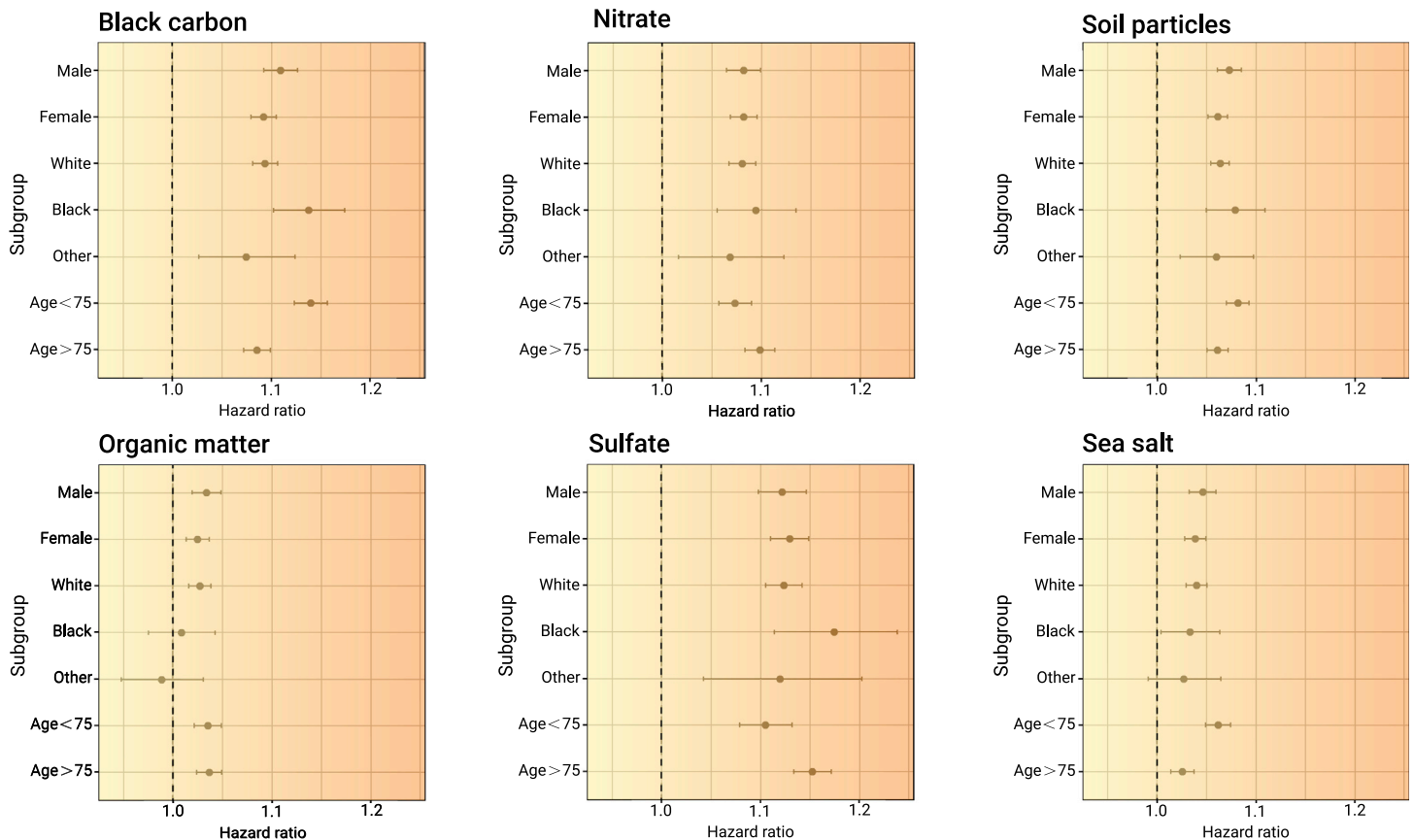| Components	Hazard Ratio (95% CI)	
	Single-pollutant model	Multi-pollutant model
Black carbon	1.10 (1.09, 1.11)	1.05 (1.04, 1.07)
Nitrate	1.08 (1.07, 1.10)	1.02 (1.00, 1.03)
Organic matter	1.03 (1.02, 1.04)	0.98 (0.96, 0.99)
Sulfate	1.13 (1.11, 1.15)	1.05 (1.03, 1.07)
Soil particles	1.07 (1.06, 1.07)	1.03 (1.02, 1.04)
Sea salt	1.04 (1.03, 1.05)	1.04 (1.03, 1.05)
$PM_{2.5}$ mass	1.10 (1.09,1.12)	–

Figure 2. Hazard Ratio of dementia associated with per-IQR increase in the PM$_{2.5}$ major components by study subgroups in single-pollutant models

care. Because many dementia cases might not result in hospitalization, our study can better capture disease incidence. The requirement of a 5-year "clean" period also enables us to obtain more representative results. Last, our Cox proportional hazards models employ a generalized estimating equation (GEE) to account for potential clustering within ZIP codes and are more robust when adjusting for numerous covariates at the neighborhood and individual level, including penalized splines.

This study also has some limitations. First, for the exposure assessment, we were unable to obtain residential address information because of limitations of Medicare data. For each participant, we could only assign the annual average exposure data based on ZIP-code-level data. Therefore, exposure measurement error is likely. In addition, residential mobility could introduce some bias. Second, even with multiple covariates being controlled, we cannot fully rule out the possibility of residual confounding or unmeasured confounding bias, such as alcohol consumption, exercise frequency, and substance use, which may affect the development of dementia. Further studies taking into account the potential bias and unmeasured/residual confounding are encouraged. In addition, there were some covariates (e.g., education, income, and smoking) that were measured at the ZIP code or county level, which may not accurately reflect the differences between individuals in the cohort Third, multi-pollutant models and single-pollutant models with PM$_{2.5}$ mass adjustment have multicollinearity because of the high correlation among some PM$_{2.5}$ components. To overcome the multicollinearity limitation, advanced computationally mixture analysis methods are urgently required.[52] Fourth, the investigated six PM$_{2.5}$ components contribute to more than half of the PM$_{2.5}$ mass, whereas other trace components, such as metal elements, are not recorded because of the lack of exposure data for individual metal species.[53] Therefore, the effect of other components on dementia cannot be estimated. To provide some inspiration for further research, we display the results for these other unmeasured components as a category called "other components (equal to total PM$_{2.5}$ mass minus mass of six measured components)" in Table S7.

CONCLUSIONS

Our study provides epidemiological evidence that long-term exposure to PM$_{2.5}$ components could potentially accelerate dementia progression; the contributions

of various PM$_{2.5}$ chemical components to increased dementia incidence may vary. BC and SO$_4^{2-}$ showed the most stable associations with dementia risk, whereas OM, the largest component of PM$_{2.5}$, has the lowest effects. Reducing PM$_{2.5}$ pollution potentially has an important public health effect. We recommended that, besides PM$_{2.5}$ mass, the effect of specific PM$_{2.5}$ components on neurodegenerative disorders, especially for BC and SO$_4^{2-}$, also need to be considered for further analysis, leading to more targeted regulation of PM$_{2.5}$ components in the near future.

MATERIALS AND METHODS
Study population

This cohort study began on January 1, 2000 and ended on December 31, 2017. The Medicare denominator file and Medicare Chronic Conditions Warehouse (CCW) were used to construct this study population (age, ≥65), derived from the Centers for the Medicare and Medicaid Services (CMS). In the Medicare denominator file, Medicare beneficiaries are detailed by age, sex, race, date of death (if any), ZIP code of residence, and Medicaid eligibility status. Age, ZIP code of residence, and Medicaid eligibility were updated annually.

The outcome variable in this study was time to first diagnosis of all-cause dementia. The CCW identifies pre-defined indicators of dementia through an algorithm (https://www2.ccwdata.org/web/guest/condition-categories) that leverages Medicare claims documents (such as hospital and physician files and health insurance files), including inpatient and outpatient claims, carrier file (primarily physician visits), skilled nursing facility, and home healthcare claims. The CCW provides the date of the first occurrence with a dementia diagnosis code across these Medicare claims (ICD codes are provided in Table S1). The abovementioned Medicare algorithm for defining dementia is primarily based on previous studies.[54,55] These two Medicare databases enabled us to create a cohort of all Medicare fee-for-service (FFS) beneficiaries in nine northeastern states (Maine, New York, New Jersey, Vermont, Massachusetts, Rhode Island, Connecticut, New Hampshire, and Pennsylvania).

To better ascertain disease incidence, our cohort required that (1) all subjects were always enrolled in the Medicare FFS program and in Medicare Part A (hospital insurance) and Part B (medical insurance) from 2000–2017 and (2) there was a "clean" period of 5 years after enrollment during which there was no dementia diagnosis logged. Other authors have also used a "clean" period while studying dementia or Alzheimer's disease.[30,56] These requirements would increase the possibility that the individual did not have dementia prior
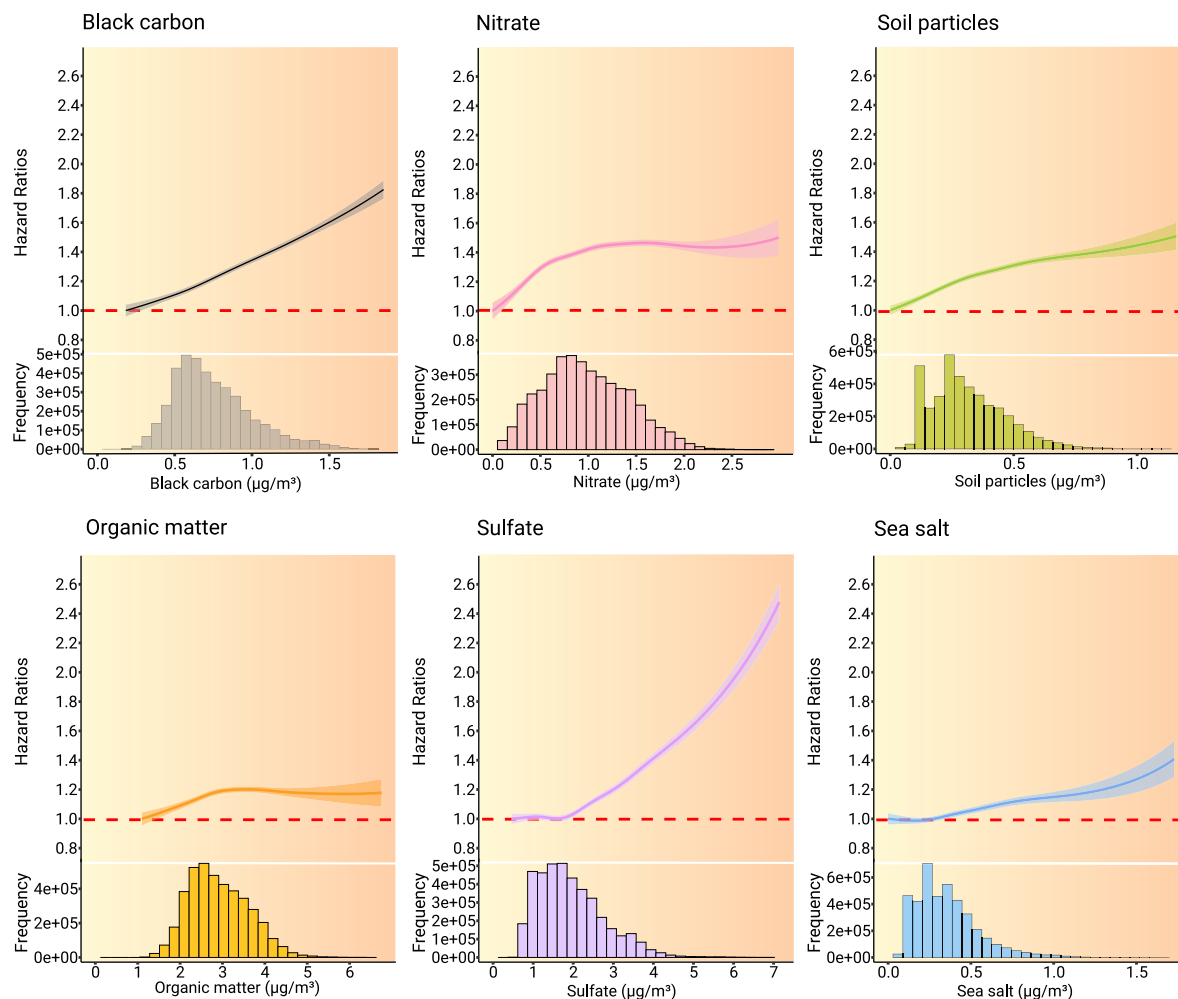
Figure 3. Concentration-Response curves from single-pollutant models for black carbon, nitrate, organic matter, sulfate, soil particles, and sea salt. The penalized spline regression models fit the concentrations of each PM$_{2.5}$ component from the 0.1th to 99.9th percentiles.

to Medicare enrollment. Subjects were entered into the cohort on the first day of the year following the period of "clean" claims, and they were followed until the first diagnosis or death of an outcome of interest across all claims in Medicare or the end of follow up. This study is approved by Emory University's Institutional Review Board (#STUDY00000316) and the CMS under the data use agreement (#RSCH-2020-55733). The Medicare dataset was stored and analyzed in the Emory Rollins School secure cluster environment (HPC) with Health Insurance Portability and Accountability Act (HIPAA) compliance.

Exposure assessment

The annual average PM$_{2.5}$ mass concentration and its six major components were estimated using well-validated PM$_{2.5}$ composition prediction models for each year. The detailed methodology can be found elsewhere.[2] Briefly, satellite-derived PM$_{2.5}$ total mass concentrations were first produced by combining satellite retrievals of aerosol optical depth, chemical transport modeling (CTM), and ground-based observations made throughout 2000–2017. These PM$_{2.5}$ values were then decomposed into individual chemical components according to CTM output and calibrated using ground-based observations from 2000–2017. Sources of compositional ground-based observations included the Clean Air Status and Trends Network, the National Core Network, the Chemical Speciation Network, and the Interagency Monitoring of Protected Visual Environments network. PM$_{2.5}$ concentrations predicted by our model were available from the Washington University Atmospheric Compositional Analysis Group (https://sites.wustl.edu/acag/) with a series of available versions. Version V4.NA.03 total PM$_{2.5}$ was used for total mass PM$_{2.5}$ concentration. V4.NA.03 modified the V4.NA.02 geographically weighted regression described by van Donkelaar et al.[2] to include new measurements of mass scattering efficiency and separate topographic and land-type-based predictor variables according to developments as part of the Mortality-Air Pollution Associations in Low-Exposure Environments (MAPLE) project. V4.NA.03 additionally utilized V4.GL.03 to provide its geophysical input.[2,57] These modifications improved performance under low PM$_{2.5}$ concentrations and enhanced consistency across the entire time series.

The proportions of each component within total PM$_{2.5}$ mass were then applied to V4.NA.03 total PM$_{2.5}$ mass according to V4.NA.02, which demonstrated good spatial agreement with average cross-validated observations over the time series with an R^2 value of 0.59 for BC, 0.86 for NO$_3^-$, 0.57 for OM, 0.96 for SO$_4^{2-}$, 0.60 for SOILs, and 0.80 for SS; cross-validation was represented using a 10-fold holdback of 10% each during the inclusion of ground-based observations using geographically weighted regression.[2] Using these data, we calculated the average PM$_{2.5}$ mass and chemical components of each 1 km^2 grid within each ZIP code in nine northeastern states and then averaged them annually between 2000 and 2017 as indicators of long-term exposure. Our exposure estimates were assigned depending on the ZIP code of the individual's residential address and the calendar year. We used annual average PM$_{2.5}$ mass and components during the same year window because we had observed previously that PM$_{2.5}$ in the current year could have higher estimate effects on dementia than alternative exposure windows, implying an acceleration of an existing dementia progression by PM$_{2.5}$.[30]

Covariates

Several individual-level and neighborhood-level covariates were collected to account for possible confounding. The individual-level covariates, including age at entry, race, sex, and Medicaid eligibility, were obtained from the Medicare denominator file. Neighborhood-level covariates included ZIP-code-level SES variables, county-level behavioral risk factors, and health care capacity variables. The ZIP-code-level variables (percentage of population above 65 years of age living below the poverty line, population density, Black population proportion, percentage of people older than 65 not graduated from high school, median household income, and percentage of owner-occupied housing units) were derived from the US Census and American Community Survey (ACS). County-level behavioral risk factors (smoking rate and body mass index) and health care capacity variables (number of hospitals and active medical doctors) were obtained from the Behavioral Risk Factor Surveillance System (BRFSS) and the Area Health Resources Files, respectively.

Statistical analysis

Single-pollutant and multi-pollutant (where we entered all six components) Cox proportional hazards models with GEE were used to quantify the association between annual mean exposure to PM$_{2.5}$ components and incident dementia among the elderly. The models were adjusted for the abovementioned neighborhood-level status, behavioral risk factors, and health care capacity variables (Table S2). With GEE, all models were adjusted for residual autocorrelation within the ZIP code, allowing us to obtain statistically more robust confidence intervals for effect estimates.[58] This resulted in our estimates being less likely to be affected by within-ZIP-code dependence of observations.

The results from models were presented as HRs with 95% CIs per IQR increase in the annual average concentration of each PM$_{2.5}$ component. To identify subpopulations that might be particularly susceptible, we performed subgroup analyses for the single-pollutant models based on race (white versus Blacks versus others), gender (men versus women), and age (>75 years versus ≤75 years). To account for possible nonlinearity between PM$_{2.5}$ components and dementia, we fit penalized spline models[59] by including a penalized thin spline term for each component in the computationally scalable stratified Cox-equivalent Poisson regressions.[11] The spline term was included in the models one at a time; i.e., we fit single-pollutant models to assess the potential nonlinearity in the C-R relationships for each component. The models adjusted for the same covariates as our main model.[11]

Sensitivity analysis

To assess the robustness of our main results, we conducted several sensitivity analyses. First, we additionally adjusted for the total PM$_{2.5}$ mass concentration in single-pollutant models. Second, we conducted a non-mover cohort analysis for subjects who did not move during the follow-up period to account for a potential bias related to change in residential address. Third, we fit multi-pollutant penalized spline models and investigated whether the C-R relationships were consistent.

All computations for the analysis were conducted on the Rollins HPC Cluster at Emory University, with the statistical analysis done with R software, version 4.0.2. Statistical significance was determined by two-sided p < 0.05.

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AUTHOR CONTRIBUTIONS

L.S. designed the research and directed its implementation. J.L. and L.S. analyzed data. J.L. and Y.W. made the figures and tables. L.S. prepared the health dataset. A.v.D. and R.V.M. prepared the exposure dataset. J.L., H.H.C., K.S., P.L., W.M.C., J.S., P.K., and L.S. interpreted the results. J.L. wrote the manuscript with input from all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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SUPPLEMENTAL INFORMATION

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