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$PM_{2.5}$ composition and disease aggravation in amyotrophic lateral sclerosis

An analysis of long-term exposure to components of fine particulate matter in New York State

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Background: Long-term exposure to fine particulate matter ($PM_{2.5}$) has been associated with disease aggravation in amyotrophic lateral sclerosis (ALS). In this study, we characterized long-term exposure to six major $PM_{2.5}$ components and their individual association with disease aggravation in ALS.

Methods: We leveraged 15 years of data from the New York Department of Health Statewide Planning and Research Cooperative System (2000–2014) to calculate annual ALS first hospitalizations in New York State. We used the first hospital admission as a surrogate of disease aggravation and a prediction model to estimate population-weighted annual black carbon, organic matter (OM), nitrate, sulfate, sea salt, and soil concentrations at the county level. We used a multi-pollutant mixed quasi-Poisson model with county-specific random intercepts to estimate rate ratios (RR) of 1-year exposure to each $PM_{2.5}$ component and disease aggravation in ALS, adjusting for potential confounders.

Results: We observed 5,655 first ALS-related hospitalizations. The annual average hospitalization count per county was 6.08 and the average $PM_{2.5}$ total mass concentration per county was 8.1 μg/m^3—below the United States' National Ambient Air Quality Standard of 12 μg/m^3. We found a consistent positive association between ALS aggravation and OM (1.17, 95% confidence intervals [CI], 1.11, 1.24 per standard deviation [SD] increase) and a negative association with soil (RR = 0.91, 95% CI, 0.86, 0.97).

Conclusion: Our findings suggest that $PM_{2.5}$ composition may influence its effect on ALS. We found that annual increases in county-level particulate OM may be associated with disease aggravation in ALS, even at $PM_{2.5}$ levels below current standards.

Key words: $PM_{2.5}$ components; fine particulate matter composition; air pollution; amyotrophic lateral sclerosis; ALS; neurodegeneration; long-term exposures

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease characterized by progressive degeneration of spinal and cortical motor neurons that leads to paralysis and eventually death, primarily from respiratory failure.[1–3] Currently, there is no cure or effective treatment for ALS.[4] Several genetic variants have been associated with the disease, but only about 5%–10% of cases are familial with a Mendelian inheritance pattern.[3,5] 90 to 95% of ALS cases are classified as sporadic, that is, have no family history of the disease.[5] ALS has an incidence of 1.9 cases per 100,000 people that varies with geography, sex, and age.[6–11] Globally, the average age of symptoms onset ranges from 46.2 to 70 years.[6,12] Disease progression in ALS is also variable: about 10% of patients have a slow form of the disease with a post-diagnosis survival of 10 years or longer, but most cases have a shorter survival from symptoms onset to death of 24–50 months.[4] To date, several studies have assessed risk factors associated with progression and aggravation of ALS, including genetic variants, age at onset, body mass index, nutritional status, comorbidities, and to a less extent environmental factors[13–16]; however, little is still known to inform disease prognosis or treatment.

What this study adds

Assessing the specific associations of $PM_{2.5}$ components with amyotrophic lateral sclerosis (ALS) aggravation provides valuable information for understanding the potential for particulate matter chemical composition to influence $PM_{2.5}$ toxicity. This information is essential in the development of source-targeted air pollution regulations, and, importantly, identifying modifiable environmental factors that aggravate ALS may open new venues to reduce the burden of the disease.

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All code and nonpatient-related data can be obtained by e-mailing the corresponding author.

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Several experimental studies have shown that fine particulate matter ($PM_{2.5}$, particles with a diameter ≤2.5 μm) can trigger biological responses that may aggravate neurodegenerative diseases, such as oxidative stress, proteinopathies,[17–25] mitochondrial damage,[26,27] glutamatergic neurotoxicity,[28] and systemic inflammation, in turn, linked to neuroinflammation.[21,25,29–31] However, only three epidemiological studies have previously evaluated the potential $PM_{2.5}$–ALS association,[32–34] in part because the rare nature of the disease presents statistical power challenges. Two of the three previous studies focused on disease aggravation as the outcome. Myung et al[33] linked short-term exposure to $PM_{2.5}$ with disease aggravation using hospitalization data in Korea; and a previous study by our group also estimated a positive association between long-term exposure to $PM_{2.5}$ and disease aggravation in ALS.[34] Disease aggravation is an important and relevant area of study in ALS, and other neurodegenerative diseases. Identifying modifiable factors that contribute to disease aggravation could provide valuable information to improve disease prognosis and inform the development of interventions aiming to minimize disease burden. Thus, in this study, we further investigate the potential link between exposure to $PM_{2.5}$ components and disease aggravation in ALS.

$PM_{2.5}$ is a heterogeneous mixture of particles with various chemical components that change geographically and temporally based on local pollution sources and weather patterns.[35,36] As a result, evaluating exposure to total $PM_{2.5}$ mass does not provide information into specific pollution sources or chemical species that may be associated with ALS. Variations in $PM_{2.5}$ composition, among other factors (e.g., exposure windows, adjustment for confounders, exposure measurement error, and study design), may influence $PM_{2.5}$ effects on ALS, as shown in other health outcomes.[37–39] Thus, to further characterize the potential $PM_{2.5}$–ALS association, in this study, we assessed exposure to six major $PM_{2.5}$ components: black carbon (BC), organic matter (OM), sulfate, nitrate, sea salt (SS), and soil. We leveraged data on first ALS hospitalizations from all New York State (NYS) from 2000 to 2014 and air pollution estimates from a previously validated model[40] to evaluate $PM_{2.5}$ components' independent association with ALS disease aggravation. We focused our study on a 1-year exposure window based on existing evidence for a likely causal relationship between long-term $PM_{2.5}$ exposure and nervous system effects.[41] Our study's objective is to assess whether year-long exposures to relatively medium-to-low concentrations of $PM_{2.5}$, such as the ones observed throughout NYS, differ in their association with ALS aggravation based on $PM_{2.5}$ composition.

Methods

Study population

Hospitalization data were obtained from the New York Department of Health Statewide Planning and Research Cooperative System (SPARCS). SPARCS is a comprehensive data reporting system containing information on hospital admissions and emergency department (ED) visits for all New York State (NYS). SPARCS encompasses roughly 98% of all hospitalizations in nonfederal acute care facilities, regardless of insurance status. In addition to hospitalization diagnosis, SPARCS contains information on age, sex, and residential addresses. Patients are also assigned a unique identification number after their first hospital visit, which allows for patient tracking over time. We identified ALS patients based on hospitalizations with an ALS discharge between the years 2000 and 2014. For each patient, we only used the first hospitalization event. We used available data from 1995 to 1999 to remove some of the cases with an existing ALS hospitalization before 2000. Finally, we calculated annual first hospitalization counts per county for all NYS. We obtained approval from Columbia University Institutional Review Board to conduct the analysis. The same board waived the need for informed consent because of the public nature of the data.

Outcome definition

The International Classification of Diseases ninth revision (ICD-9) code 335.20 corresponds specifically to ALS. We used hospitalizations with a primary or secondary 335.20 discharge code to identify ALS cases. Hospitalizations with a primary discharge of ALS included patients hospitalized for a health condition directly related to ALS, such as motor complications or respiratory failure. Subjects with a secondary discharge code of ALS were hospitalized primarily for health reasons unrelated or indirectly related to ALS (e.g., infections, heart attacks). We focused our study specifically on first hospitalizations. We considered the first hospitalization as a proxy for disease aggravation. Using the incidence of the first hospitalization, we aimed to capture cases crossing to a more severe stage of the disease—cases developing for the first time clinical symptoms severe enough to require hospitalization.

Air pollution data

Annual $PM_{2.5}$ BC, nitrate, sulfate, OM, SS, and soil mass concentrations were predicted by a well-validated air pollution prediction model described in detail in van Donkelaar et al.[40] In summary, the $PM_{2.5}$ total mass was estimated from satellite retrievals, then partitioned into chemical composition based on a chemical transport model. Finally, the resulting mass estimates were statistically fused with ground-based measurements to obtain accurate continuous estimates at a 1×1 km grid despite the sparse composition of monitor density. The prediction models perform well: the cross-validated R^2 values range from 0.57 to 0.96 with the strongest agreement for sulfate ($R^2 = 0.96$) and nitrate ($R^2 = 0.86$) and the lowest for OM ($R^2 = 0.57$). We calculated annual population-weighted county averages from the grid estimates for each component and total $PM_{2.5}$ mass for our analyses. We first averaged the predicted annual concentrations over all grids within a county subdivision (minor civil county division, e.g., towns and townships), then calculated an overall county average weighting in more heavily the county subdivisions with larger populations. Finally, we scaled the air pollutant concentrations by dividing by the respective component's standard deviation (SD); scaling by SD facilitates comparability of effect estimates across components. We assigned exposures based on the patients' county of residence and year of the first hospitalization.

Potential confounders

Due to the rare nature of ALS, the unit of analysis in our study is county-year to ensure enough cases per spatial and temporal unit. By definition, in this study design, potential confounders can only be variables that vary from year to year and across counties and co-vary both with ALS first hospitalization counts (outcome) and $PM_{2.5}$ components concentration (exposure). In a county-year analysis, there can be no confounding by person-specific factors that vary within years and counties because all persons in a county during a given year are assigned the same pollutant concentration.[42]

We accounted for potential geographically varying confounding by including county-specific socioeconomic status (SES) variables. From the US Census Bureau and American Community Survey, we obtained annual median household income, percent of residents below poverty, percent of residents without a high school degree, and racial/ethnic distribution (proportion of White, Asian, Black, and Hispanic residents) data for the years 2000, 2004–2014. For years without census data (2001–2003), we interpolated available data using a generalized additive model with a penalized spline for year to allow for nonlinear time trends. To improve SES characterization, we also included annual county-level smoking prevalence and percent obesity data, which we obtained from the Behavioral Risk Factor Surveillance System

for 2000–2014. We also adjusted for urbanization level using the 2013 urban–rural classification scheme developed by the National Center for Health Statistics (NCHS).[43] This classification was explicitly developed for counties and consists of six urbanicity levels. We summarized it into four levels by combining small and medium metropolitan areas into one level and the two most rural levels into another single level. In summary, from most urban to rural, the four urbanization levels are (1) "central metro": counties that encompass the largest principal city of a metropolitan area; (2) "fringe metro": counties that do not include principal metropolitan cities (both central and fringe metro have a population ≥1 million); (3) "metro": small and medium metropolitan areas with a population of ≤999,999; and (4) "rural": micropolitan or non-metropolitan counties.[43]

We adjusted for long-term time trends by including a calendar year variable, mean winter temperature, and summer mean temperature to account for potential temporally varying confounders. We acquired data on the daily temperature at a 1/8th-degree grid from the North America Land Data Assimilation System.[44] We calculated monthly mean temperatures at the county level from the daily estimates over all grids within a county, then averaged June–August and December–February to get summer and winter mean temperatures each year, respectively.

Statistical analysis

We used a variation of the approach described in Wang et al[42] to estimate the association between long-term exposure to $PM_{2.5}$ components and ALS aggravation. Specifically, we ran a multivariable Poisson generalized additive mixed model with a log link and a quasi-likelihood that included all $PM_{2.5}$ components (BC, nitrate, OM, sulfate, soil, and SS), temporal and geographical confounders, population size as an offset term, and county-specific random intercepts. The quasi-likelihood allows for potential overdispersion in the outcome, the random effect accounts for within-county correlation in the exposure estimates, and the offset term for differences in population size across counties. The additive aspect of our model allowed us to test for nonlinear relationships between outcome and exposure/ (we discuss this in more detail in the following paragraph). Our model design evaluates the associations between specific $PM_{2.5}$ components and first ALS hospitalization. We included all $PM_{2.5}$ components in a single model to isolate component-specific effects and control potential co-pollutant confounding. From here on, we refer to this model as the multipollutant model.

To avoid potential misspecification and comprehensively characterize the exposure–response relationships, we evaluated nonlinearities in both confounders and $PM_{2.5}$ components. We used penalized splines (p-spline) to flexibly model the associations between the outcome and $PM_{2.5}$ components and all continuous covariates. Then, we used the generalized cross-validation (GCV) criterion to select the optimal degrees of freedom (df) in the exposure and confounding variables. Relationships with estimated df (edf) >1 were considered nonlinear and those with edf = 1 linear. When no evidence of nonlinearity was found (optimal edf = 1), we included each the $PM_{2.5}$ component or covariant as a continuous measure and modeled its linear effect. We reported the linear estimates for all $PM_{2.5}$ components and the exposure–response curve for components that deviated from linearity.

Sensitivity analysis

To assess the robustness of results from the multipollutant model, we ran six single-pollutant models, one model for each $PM_{2.5}$ component (BC, nitrate, sulfate, OM, SS, or soil). These models were constructed following the same steps as in the main analysis, with the difference that they included only one $PM_{2.5}$ component per model and were adjusted for the difference of the population-weighted $PM_{2.5}$ total mass concentration with the component (calculated as total $PM_{2.5}$ mass concentration–$PM_{2.5}$ component concentration).[45] By adjusting for the difference of $PM_{2.5}$ mass concentration with each component, we are accounting for components of $PM_{2.5}$ that may be correlated both with other components and the outcome.[46] Additionally, by including a single pollutant per model, the sensitivity analysis addressed potential issues resulting from collinearity.

We adjusted for potential confounding by long-term trends in all health models by including the calendar year. Thus, we performed a second sensitivity analysis to assess the robustness of our results to the parameterization of the variable year. For this, we compared component-specific effect estimates obtained from three multipollutant models specifying year as (a) a linear term, (b) a natural spline with 4 df, and (c) a categorical variable.

Finally, to assess whether the effects differ by age, we performed an age-stratified analysis of the multipollutant model for age groups ≥65 and <65. The stratified models were adjusted for SES and temporal and geographical confounding using the same covariates as the main analysis.

For all analyses, the linear results are presented as rate ratios (RR) per 1 SD increase in the annual concentration of a given $PM_{2.5}$ component, along with 95% confidence intervals (CI). All analyses were performed using the R Statistical Software version 4.0.3 (Foundation for Statistical Computing, Vienna, Austria).

Results

Study population characteristics

Across all 62 NYS counties, the annual mean of first ALS hospitalizations per county was 6.0 with a SD of 9.6. There were 5,655 first ALS hospitalizations (either as primary or secondary diagnosis) from 2000 to 2014. The data included 2,561 female (45.3%) and 3,093 male hospitalizations (54.7%) and one patient with anonymous sex. Across counties and years, the mean age at first hospitalization was 64.3 years (SD = 13.5). Descriptive statistics for the outcome and covariates are presented in the Table, and time trends across counties in Figure S.1; http://links.lww.com/EE/A182. Out of the total hospitalizations, a primary diagnosis for ALS was the most common primary diagnosis (41.0%), and the second most common diagnoses were for diseases of the respiratory system (16.0%). Figure 1 presents the hospitalization percent breakdown for various primary diagnosis categories.

$PM_{2.5}$ component characteristics

Average annual concentrations of $PM_{2.5}$ components are summarized in the Table. OM and sulfate had the highest mean mass concentrations constituting 35% and 31% of total $PM_{2.5}$ mass, respectively, and SS had the lowest, accounting for only 3% of total $PM_{2.5}$ mass. The concentrations of $PM_{2.5}$ components varied across counties and years. Overall, sulfate and soil concentrations have a consistent downward pattern across time; OM, nitrate, and SS also decreased over time but more gradually; BC reached a pick in 2005 and has since been decreasing (these patterns varied slightly from county to county, Figure 2). The Spearman correlation coefficient among components ranged from 0.39 to 0.9. The highest correlation was observed between soil and nitrate (0.83), followed by sulfate and nitrate (0.73). Nitrate and sulfate had the strongest correlations with $PM_{2.5}$, 0.90 and 0.86, respectively (Figure 3).

Exposure–response relationships

We found no deviations from linearity in any of the exposure-response associations. In the multi-pollutant model, we found that

Table.

Descriptive statistics per county per year (2000–2014) for the outcome, exposure variables, and covariates

	Mean (SD)	25%	Median	75%
Outcome				
ALS	6.0 (9.6)	1	2	6
Female	2.7 (4.5)	0	1	3
Male	3.3 (5.3)	0	1	3
<70 years	2.8 (5.0)	0	1	3
≥70 years	3.2 (5.1)	0	1	3.7
Exposure (μg/m^3)				
$PM_{2.5}$	8.1 (2.3)	6.4	7.6	9.2
Black carbon	0.6 (0.2)	0.5	0.6	0.7
Nitrate	0.9 (0.3)	0.7	0.9	1.1
Organic matter	2.9 (0.7)	2.4	2.7	3.3
Sulfate	2.5 (0.9)	1.8	2.4	3.1
Soil	0.3 (0.1)	0.2	0.3	0.3
Sea salt	0.2 (0.2)	0.1	0.2	0.3
Covariates				
Median income (× $1,000)	49.1 (12.6)	41.3	45.7	52.4
Percent below poverty	12.9 (4.1)	10.4	12.6	14.9
Percent without high school	18.1 (7.3)	12.8	17.3	22.2
Percent smoking prevalence	22. (3.9)	20.7	23.6	26.1
Percent obesity	25 (4.5)	22.3	25.4	27.8
Percent Hispanic	6.5 (8.6)	1.9	2.9	6.2
Percent White not Hispanic	83.6 (16.8)	80.3	90.2	94
Percent Black not Hispanic	5.7 (6.3)	1.4	3.4	7.5
Percent Asian not Hispanic	2.2 (3.4)	0.5	0.9	2.2
Summer mean temperature (°C)	20.2 (1.5)	19.2	20.2	21.1
Winter mean temperature (°C)	−3.1 (2.5)	−4.9	−3.3	−1.5

one SD increase in OM concentration is associated with a 17% (RR = 1.17, 95% CI, 1.11, 1.24) increase in the annual ALS first hospitalization rate, and 1 SD increase in SS with a 6% increase (RR = 1.06, 95% CI, 1.01, 1.11). We also found negative soil– and BC–ALS associations (RR = 0.91, 95% CI, 0.86, 0.97, and RR = 0.94, 95% CI, 0.89, 0.99, respectively). For nitrate and sulfate, we found null results (Figure 4).

Sensitivity analysis

As sensitivity analyses, we ran single-pollutant models that included only one $PM_{2.5}$ component and were adjusted for confounders and the difference of $PM_{2.5}$ mass concentration with the component. We found no deviations from linearity in any of the exposure–response associations (optimal edf = 1). Overall, the sensitivity analysis results support the main analysis except for sulfate. For OM (RR = 1.14, 95% CI, 1.07, 1.20) and soil (RR = 0.89, 95% CI, 0.83, 0.95), we found a positive and negative association respectively. We found a marginal negative association between BC and ALS first hospitalization (RR = 0.94, 95% CI, 0.87, 1.01) and a marginal positive SS–ALS association (RR = 1.05, 95% CI, 0.99, 1.11). In the case of sulfate, we found a marginal negative association with ALS (RR = 0.90, 95% CI, 0.80, 1.00), which we did not observe in the main analysis (Figure 4). We found no differences by age group (≥65 vs. <65, Figure S.2; http://links.lww.com/EE/A182).

In the main analysis, calendar year was parameterized as a linear term, based on the optimal df estimated by GCV (edf = 1). In the second sensitivity analysis, we evaluated the robustness of our results to this parameterization. The effect estimates for OM and soil remained robust regardless of whether year was specified as linear, with a natural spline, or as categorical. The results for sulfate were null across all models. The effect estimates for SS were null when year was specified as categorical (RR = 1.04, 95% CI, 0.96, 1.12) or with a natural spline (RR = 1.03, 95% CI, 0.97, 1.11) but positive if year was linear (RR = 1.06, 95% CI, 1.01, 1.11). Overall, the BC and nitrate results were the most sensitive to adjustment for time trends. The ALS–nitrate association was null when year was linear (RR = 1.02, 95% CI, 0.95, 1.10) or with a natural spline (RR = 1.02, 95% CI, 0.94, 1.11) but significantly positive when year was categorical (RR = 1.15, 95% CI, 1.03, 1.27). In the case of BC, the association was null when year was categorical (RR = 1.02, 95% CI, 0.94, 1.11) or with a natural spline (RR = 0.96, 95% CI, 0.90, 1.04), but significantly negative if year was specified as linear (RR = 0.94, 95% CI, 0.89, 0.99; Figure S.3; http://links.lww.com/EE/A182).

Discussion

Exposure to $PM_{2.5}$ has been linked with disease aggravation in ALS and other neurodegenerative diseases. However, the effect of the chemical composition of $PM_{2.5}$ on those associations has been less studied. This study analyzed exposure to six major $PM_{2.5}$ components and their association with disease aggravation in ALS. We found a robust positive association between

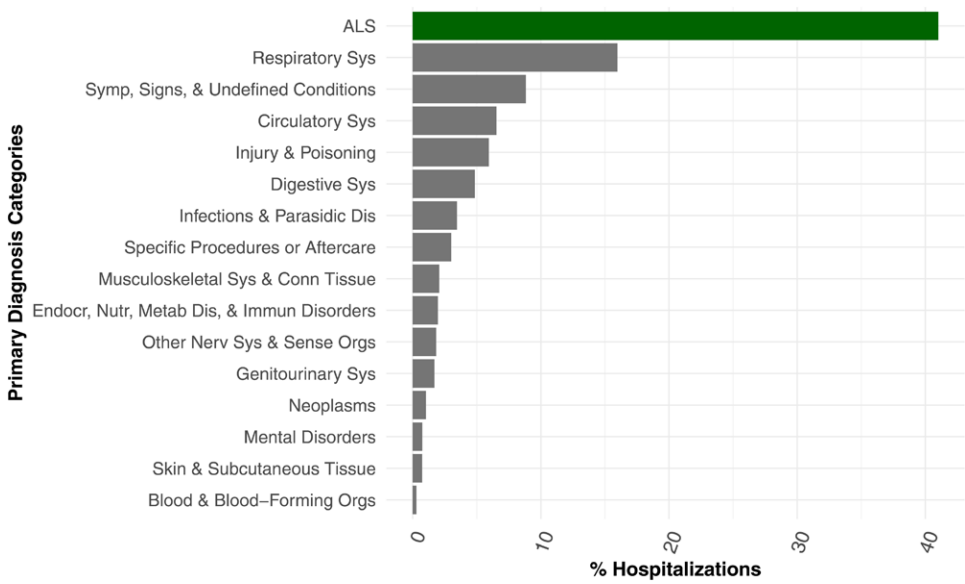

Figure 1. Primary diagnosis. Percent hospitalizations (*x* axis) out of total with a primary diagnosis within each diagnosis category (*y* axis). The percent of hospitalizations with an ALS primary diagnosis (41.0%) is highlighted in green.

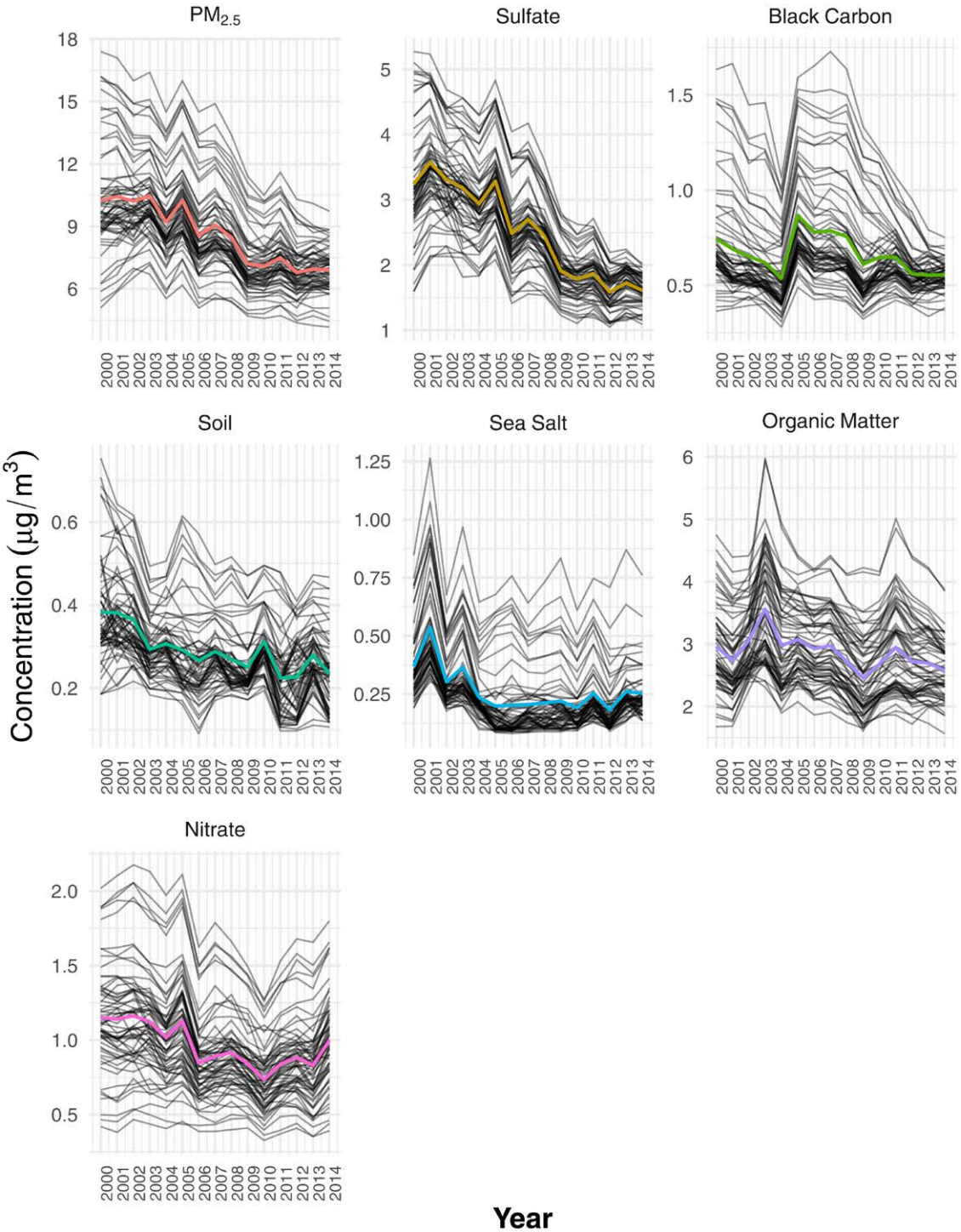

Figure 2. $PM_{2.5}$ components concentrations. The spaghetti plots show the annual mean concentrations per county (gray lines) and across NYS (colored lines) from 2000 to 2014 for each $PM_{2.5}$ component and total $PM_{2.5}$ mass.

ALS aggravation and OM and a negative association with soil. The results from the multipollutant model were stable as indicated by the similarity in CIs compared to single-pollutant models, indicating that there is enough information in the model to handle any correlations among components adequately.

Only a small number of epidemiological studies have evaluated the association between exposure to specific air pollution sources or chemical compounds and ALS. Seelen et al. found a positive association between exposure to nitrogen dioxide and traffic-related $PM_{2.5}$ with ALS diagnosis but Filippini et al.[47] found limited evidence for an association between traffic-related particles with a diameter ≤10 µm (PM_{10}) and ALS diagnosis, indicating that fine particle components may be of more relevance. Furthermore, an occupational study found a higher risk for ALS among workers exposed to diesel . Myung et al.[33] and Dickerson et al.[48] found a positive association between exposure to carbon monoxide (a combustion product) and sulfur dioxide (associated with coal power plants and oil industry[49,50]) with ALS aggravation. Another study evaluated exposure to various hazardous air pollutants including metals, aromatic solvents, chlorinated solvents, and pesticides and reported a positive association between exposure to aromatic solvents—a

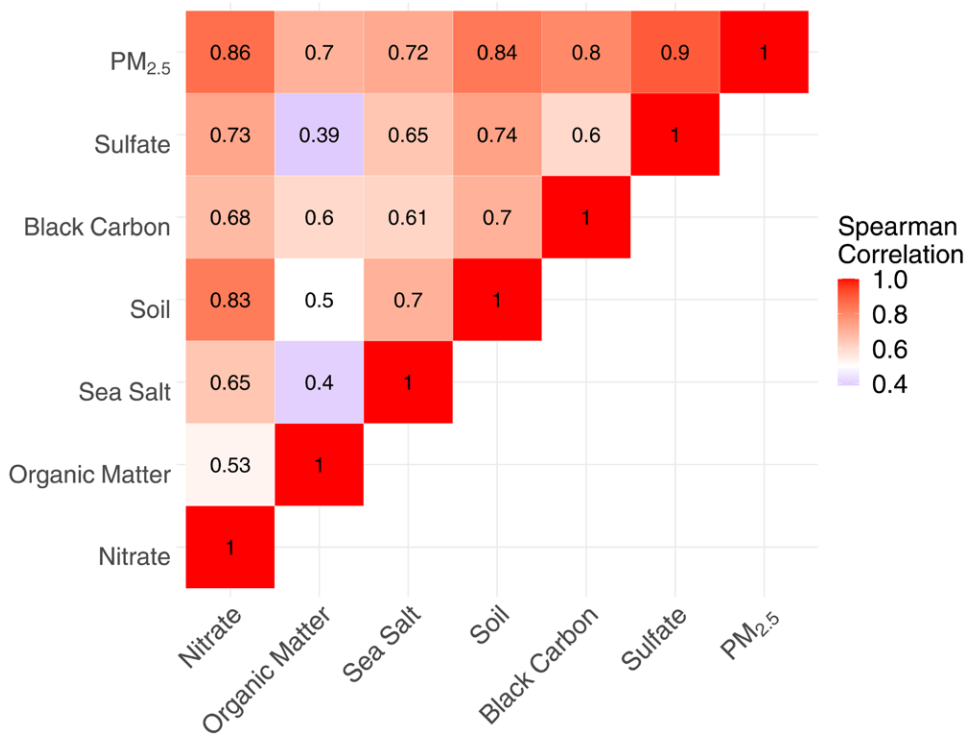

Figure 3. $PM_{2.5}$ component correlations. Spearman correlation coefficients were estimated from annual population-weighted county mean concentrations in NYS from 2000 to 2014.

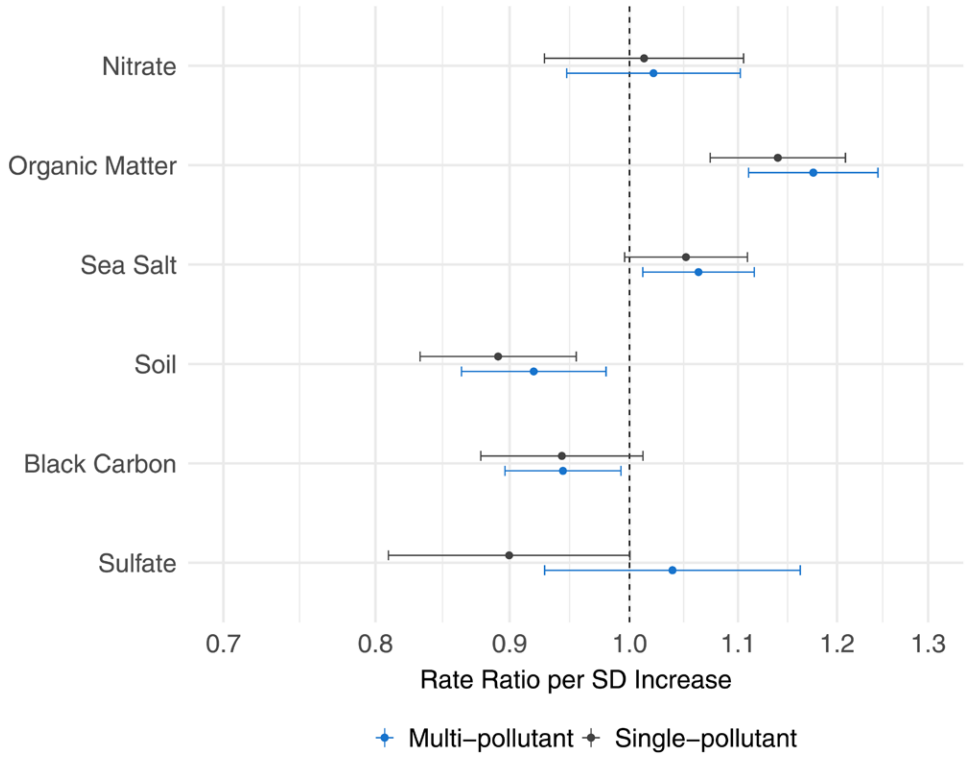

Figure 4. $PM_{2.5}$ component associations. Linear associations between 1-year exposure to each $PM_{2.5}$ component and first ALS hospitalization in New York State (2000–2014). The multipollutant model (blue) included all $PM_{2.5}$ components and the single-pollutant models (black) included each $PM_{2.5}$ component in separate models, adjusted for total $PM_{2.5}$ mass. All models were adjusted for potential temporal and geographical confounders. The effect estimates correspond to the rate ratios of first ALS hospitalization per one standard deviation increase in annual $PM_{2.5}$ component concentrations. Bars represent 95% confidence intervals.

constituent of OM—and ALS.[51] Finally, a recent cohort study found an association between ALS clinical diagnosis and various metals from road traffic non-tailpipe emissions.[52] Overall, previous findings suggest that some traffic-related pollutants may be relevant to ALS diagnosis and aggravation. Our work complements previous studies by providing effect estimates for major $PM_{2.5}$ components, some of which were not evaluated previously. The findings in our research bring particular attention to the OM $PM_{2.5}$ component. Interestingly, in a previous study, we also found an association between OM and disease aggravation in Parkinson's disease[38]—further highlighting the potential relevance of OM in neurodegenerative disease.

OM is frequently the major fraction of ambient $PM_{2.5}$ in urban areas[53,54]—where much of the $PM_{2.5}$ exposure occurs due to the high density of population and emission sources. In our exposure data, OM contributes the largest fraction to $PM_{2.5}$ total mass (on average 35%). Over the past decades, regulatory actions resulted in significant reductions of sulfate and nitrate particle components in NYS but the improvements in OM were smaller.[55] OM is a complex mixture of thousands of individual compounds directly emitted (primary) or generated by atmospheric chemical processes (secondary).[55,56] Several OM compounds are well-known toxins (e.g., polycyclic aromatic hydrocarbons); however, the majority of OM mass remains unspeciated.[53,54,56] A large fraction of OM is organic carbon (OC).[57] In NYS, an important source of OC emissions is motor vehicles. Primary $PM_{2.5}$ emissions from automobiles are composed mainly of elemental and organic carbon (>80%).[55] Motor vehicle exhaust is also a source of volatile organic compounds that contribute to the formation of secondary OM particles.[55] Residential wood combustion is another significant source of primary OC in NYS. In 2014, residential wood combustion accounted for 10% of primary $PM_{2.5}$ emissions in NYC and NYS exceeded emissions from all other heating fuels.[55] Furthermore, similar to vehicle exhaust, residential wood combustion is also a source of chemical compounds that contribute to the formation of secondary OM.[55] Although motor vehicles and residential wood combustion are the major sources of OM in NYS, OM may not serve as a tracer to the same sources at a different location or even time period.[58] Thus, up-to-date source apportionment studies specific to geographical regions are essential to identifying relevant sources of air pollutants potentially associated with ALS or other neurodegenerative diseases.

Our results also suggest a marginally positive association between SS exposure and ALS and a negative association with soil and BC. In NYS, SS and soil contribute little to the net $PM_{2.5}$ mass (3.2% and 3.5%, respectively; see the Table). SS is mainly composed of chloride ions, and studies characterizing $PM_{2.5}$ composition in the United States indicate that the contribution of SS to $PM_{2.5}$ is substantial only in non-urban coastal areas.[57] Soil particle mass in the northeastern United States tends to be low and patterns could reflect the impact of long-range transport from North Africa.[57] The protective association between soil and ALS could result from decreases of toxic components in the net $PM_{2.5}$ mass as soil concentration increases. Our analysis does not evaluate this explicitly, but we observed a stronger negative association in the soil single-pollutant model relative to the multipollutant model, which would support this hypothesis. However, future studies are needed to determine if the negative soil–ALS association is real, but currently, anthropogenic activities are not significant contributors to this component. We also found a marginal negative BC–ALS association that did not hold to our sensitivity analyses, indicating this effect estimate is not robust and may be due to residual confounding.

Strengths and limitations

To our knowledge, our study is the first to assess exposure to specific fine particle components in association with ALS disease aggravation. Disease prognosis in ALS patients is variable and little is known about environmental factors that contribute to patient deterioration. Our study is one of the most extensive studies to date of environmental risk factors of ALS and one of the few epidemiological studies that assessed exposure to air pollution in ALS. $PM_{2.5}$ exposure has been identified as a risk factor for several adverse health outcomes, but more studies are needed to determine if chemical composition influences $PM_{2.5}$ toxicity and identify potential toxic components and relevant sources. Thus, we evaluated long-term exposure to specific $PM_{2.5}$ components and estimated component-specific associations with disease aggravation in ALS. Our study brings insight into the role that $PM_{2.5}$ chemical composition may play in its adverse effects and highlights potentially relevant pollution sources. Importantly, our study covers a geographical area that includes urban and rural locations and a diverse population. Other studies using hospitalization data to examine the $PM_{2.5}$ association with neurodegenerative disease in the United States have leveraged information from the Medicare population, which only includes enrollees ≥65 years old.[59,60] SPARCS includes information on hospitalizations of all ages and independently of health insurance.

However, our findings should be interpreted in light of our limitations. Since SPARCS only includes information on hospitalizations, we did not have data on noncases to perform an individual-level time-to-event analysis. In our study design, the unit of observation is county-year; the number of events per unit of analysis is important for statistical power in this design, and—due to the rare nature of the disease—we were limited to a county-level analysis. To assess exposure, we used population-weighted averages for each $PM_{2.5}$ component to reduce exposure measurement error. Although aggregation is expected to induce some exposure measurement error, the error component specific to the aggregation is expected to be Berkson[61–63] and should not bias the estimated effects, albeit classical error contributions cannot be excluded. Exposure measurement error can also be induced by patient mobility if a patient relocates to a different county in the year of hospitalization. A second limitation is that we used predicted $PM_{2.5}$ component concentrations to assign exposures rather than actual measurements. The prediction models have good predictive accuracy[40] and are highly spatially resolved to capture county-level population-wide exposures, but some exposure measurement error is still expected. The cross-validated R^2 varied by $PM_{2.5}$ component and we would, thus, expect more error for OM.[40] It is also important to note that a county-wide average may inadequately reflect population exposures for components with high spatial heterogeneity, such as BC. However, the resulting bias is likely toward the null, as suggested by previous studies.[63–65] The $PM_{2.5}$ components analyzed in our study account for a significant fraction of total $PM_{2.5}$ mass; however, they do not encompass all $PM_{2.5}$ components. For example, metals account for a small percentage of total $PM_{2.5}$ mass and were not evaluated in this study but were previously linked to neurodegenerative diseases.[52,66,67] Additionally, we analyzed OM's total particulate mass but OM is itself a mixture and includes multiple chemical compounds. We also did not evaluate potential interactions or additive effects among the components, which could play a role in the overall $PM_{2.5}$ neurotoxicity. It should be noted that there are other routes of exposure to some of these components, other than through ambient $PM_{2.5}$, such as occupational exposures. However, given the exposure window (year of hospitalization) and the county-level analysis, we do not expect other contributions to the total personal component exposures to induce bias. Finally, first hospitalization data are likely to miss some aggravation cases, as patients may not be hospitalized even as disease symptoms worsen. However, although the first hospitalization is not specific to disease aggravation, it captures a significant number of cases entering a severe stage of the disease.[68]

Conclusion

Our study provides valuable information into particulate characteristics that may contribute to the adverse association between $PM_{2.5}$ and ALS. We found positive associations for some—but not all—$PM_{2.5}$ chemical components, providing further evidence that $PM_{2.5}$ compositional characteristics may play a role in its adverse neurotoxic effects. Specifically, we found a robust association between the OM $PM_{2.5}$ component and disease aggravation in ALS. This information can be useful in identifying relevant pollution sources for targeted regulations and in studies of $PM_{2.5}$ toxicity and ALS pathology.

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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