Parkinson’s disease aggravation in association with fine particle components in New York State

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ABSTRACT

Background: Long-term exposure to fine particulate matter (PM2.5) has been associated with neurodegenerative diseases, including disease aggravation in Parkinson’s disease (PD), but associations with specific PM2.5 components have not been evaluated.

Objective: To characterize the association between specific PM2.5 components and PD first hospitalization, a surrogate for disease aggravation.

Methods: We obtained data on hospitalizations from the New York Department of Health Statewide Planning and Research Cooperative System (2000–2014) to calculate annual first PD hospitalization counts in New York State per county. We used well-validated prediction models at 1 km² resolution to estimate county level population-weighted annual black carbon (BC), organic matter (OM), nitrate, sulfate, sea salt (SS), and soil particle concentrations. We then used a multi-pollutant mixed quasi-Poisson model with county-specific random intercepts to estimate rate ratios (RR) of one-year exposure to each PM2.5 component and PD disease aggravation. We evaluated potential nonlinear exposure-outcome relationships using penalized splines and accounted for potential confounders.

Results: We observed a total of 197,545 PD first hospitalizations in NYS from 2000 to 2014. The annual average count per county was 212 first hospitalizations. The RR (95% confidence interval) for PD aggravation was 1.06 (1.03, 1.10) per one standard deviation (SD) increase in nitrate concentrations and 1.06 (1.04, 1.09) for the corresponding increase in OM concentrations. We also found a nonlinear inverse association between PD aggravation and BC at concentrations above the 96th percentile. We found a marginal association with SS and no association with sulfate or soil exposure.

Conclusion: In this study, we detected associations between the PM2.5 components OM and nitrate with PD disease aggravation. Our findings support that PM2.5 adverse effects on PD may vary by particle composition.

1. Introduction

Particulate matter with a diameter ≤2.5 μm (PM2.5) is a dynamic heterogeneous mixture that changes over time and space. The main components of PM2.5 include ammonium sulfate, crustal material, black carbon (BC), ammonium nitrate, sea salt (SS), trace element oxides, and others (Snider et al., 2016; van Donkelaar et al., 2019). Exposure to PM2.5 can contribute to ischemic heart disease, cerebrovascular disease, lung cancer, chronic obstructive pulmonary disease, and lower-respiratory infections, among others (Andersen et al., 2012; Anderson et al., 2012; Naghavi et al., 2017; Yang et al., 2018; Liu et al., 2016). More recently, studies have also identified long-term PM2.5 exposure as a potential risk factor for neurodegenerative diseases (Liu et al., 2016; Palacios et al., 2014; Fu et al., 2019; Shin et al., 2018; * Corresponding author.
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Parkinson’s disease (PD) is the second most prevalent neurodegenerative disease worldwide, affecting 1–2 per 1000 of the population at any given time (Hirsch et al., 2016; Liu et al., 2016). PD neuropathology is characterized by α-synuclein-containing Lewy bodies and loss of dopaminergic neurons in the substantia nigra, but the exact pathogenesis of the disease remains unclear (Dexter and Jenner, 2013; Tysnes and Storstein, 2017). Clinical manifestations of PD include tremor, rigidity, bradykinesia (Tysnes and Storstein, 2017), and a variety of non-motor symptoms including cognitive, neuropsychiatric, sleep, autonomic and sensory disorders, as well as depression, anxiety, constipation, and erectile dysfunction (Park and Stacy, 2009). In addition to the broad spectrum of clinical symptoms, disease aggravation also varies greatly from patient to patient (Schrag et al., 2007).

A few epidemiological studies have investigated the association of PM$_{2.5}$ exposure with increased PD risk (KIRRane et al., 2015; Liu et al., 2016; Palacios et al., 2014) and disease aggravation (Lee et al., 2017; Kioumourtzoglou et al., 2015b; Shi et al., 2020; Nunez et al., 2021). The studies that assessed PM$_{2.5}$ exposure and risk for PD in the Agricultural Health Study cohort and the Nurses’ Health Study found marginally positive and null associations, respectively (KIRRane et al., 2015; Palacios et al., 2014). In the PAGE case-control study, the association was positive only among women (Liu et al., 2016). Among US Medicare beneficiaries and in data from the New York Department of Health Statewide Planning and Research Cooperative System (SPARCS), long-term PM$_{2.5}$ exposure was positively associated with disease aggravation (Kioumourtzoglou et al., 2015b; Shi et al., 2020; Nunez et al., 2021) and in a cohort from Seoul, South Korea, short-term PM$_{2.5}$ exposure was also associated with disease aggravation (Lee et al., 2017)—these studies used PD hospitalizations as a surrogate for disease aggravation. PD–PM$_{2.5}$ studies, both for risk and disease aggravation, cover multiple geographical regions and overall present a trend for a positive association, but some differences in the magnitude of the association are observed across studies. Among other factors (e.g., windows of exposure, adjustment for confounders, exposure measurement error, and outcome definition), differences on findings could partially result from varying risk by PM$_{2.5}$ composition, which varies in space and time (Bell et al., 2007; Austin et al., 2013) and can modify PM$_{2.5}$ estimated health effects (e.g., survival (Kioumourtzoglou et al., 2015a)). Studies that evaluate exposure to specific PM$_{2.5}$ components are essential to determine whether PM$_{2.5}$ composition influences its association with neurodegenerative diseases. Furthermore, this information would be valuable in elucidating potential biological mechanisms and informative for the development of source-targeted PM$_{2.5}$ regulations.

In a previous study we found a positive association between one-year exposure to PM$_{2.5}$ and disease aggravation in PD (Nunez et al., 2021). Here we characterized one-year exposure to six specific PM$_{2.5}$ components: BC, organic matter (OM), sulfate, nitrate, SS, and soil. We used first PD hospitalization as a surrogate for disease aggravation—this decision is supported by clinical studies that show higher rates of hospitalization among PD patients relative to adults of the same age without PD (Ogub and Vidovic, 2012). We examined each PM$_{2.5}$ component’s independent association with first PD hospitalizations to identify particle components in the PM$_{2.5}$ mixture that are positively associated with aggravation of the disease. We used data on first PD hospitalizations from all of New York State (NYS) from 2000 to 2014 and air pollution estimates from previously validated models (van Donkelaar et al., 2019). Our study adds to our understanding of the potential link between long-term exposure to PM$_{2.5}$ and PD aggravation by providing information on the association with specific PM$_{2.5}$ components.

2. Methods

2.1. Study population

The New York Department of Health Statewide Planning and Research Cooperative System (SPARCS) gathers information on hospital discharges for hospitalizations and emergency department visits within NYS. SPARCS collects information on roughly 98% of the total hospitalizations in non-federal acute care facilities, regardless of insurance. SPARCS also contains data on patients’ residential address. Importantly, each patient is assigned a unique identification number at their first hospitalization, which allows for patient tracking over time. In this study, we used SPARCS data to identify first PD hospitalizations from the years 2000–2014. Data from 1995 to 1999 were used to identify patients with existing hospitalizations prior 2000. These patients were removed from our final dataset to reduce the probability of inclusion of patients with an existing PD hospitalization prior to the start of the study. We obtained approval to conduct the analysis from Columbia University Institutional Review Board. The same board waived the need for informed consent because of the public nature of the data.

2.2. Outcome definition

We extracted all first hospitalizations with International Classification of Diseases ninth revision (ICD-9) code 332.0, which specifically corresponds to PD. We used hospitalizations with a primary or secondary discharge code for PD. Hospitalizations with a primary discharge code for PD may include hospital admissions for conditions directly related to PD, such as motor complications or cognitive and psychiatric impairments. Hospitalizations with a secondary discharge code for PD may include health conditions indirectly related (e.g., falls, infections) or unrelated to PD as the primary reason of hospitalization. We restricted our study specifically to patients’ first PD hospitalization to capture the crossing point to a more clinically severe stage of disease that requires hospitalization, which we defined as disease aggravation. By focusing on patients’ first hospitalization, we evaluated whether exposure is associated with cases developing—for the first time—clinical symptoms severe enough to require hospitalization. Hospitalizations have also been used in other studies of air pollution to assess PD aggravation (Kioumourtzoglou et al., 2015b; Lee et al., 2017; Shi et al., 2020; Nunez et al., 2021).

2.3. Air pollution data

Annual PM$_{2.5}$, BC, nitrate, sulfate, OM, SS, and soil mass concentrations were predicted by well-validated air pollution prediction models at 1 km × 1 km grids (van Donkelaar et al., 2019). Briefly, the PM$_{2.5}$ total mass was derived from satellite retrievals, then partitioned into chemical composition using a chemical transport model. The resulting estimates, for PM$_{2.5}$ and its components, were then statistically fused with ground-based measurements to yield accurate continuous surfaces even in areas with sparse monitor density. These models perform well, with cross-validated $R^2$ values ranging from 0.67 to 0.96 with the strongest agreement for sulfate ($R^2 = 0.96$) and nitrate ($R^2 = 0.90$) and the lowest for OM ($R^2 = 0.67$). Estimates for total PM$_{2.5}$ mass have an $R^2 = 0.76$. We estimated annual population-weighted county averages for each component and total PM$_{2.5}$ as follows: first, we averaged the predicted annual concentrations over all grids within a county subdivision (minor civil county division, e.g., towns and townships), then calculated a county average where county subdivisions with larger populations held a greater weight. Lastly, we scaled concentrations by dividing by the respective component’s standard deviation (SD) to present effect estimates of linear associations per one SD increase and facilitate comparability of estimates across components. We assigned exposures based on the patients’ county of residence and year of first hospitalization.
2.4. Potential confounders

In our analysis, we used annual counts of PD first hospitalizations per county, that is, the unit of analysis is county-year. As a result, potential confounders can only be variables that vary temporally or geographically and that co-vary both with PD first hospital admission counts (outcome) and PM$_{2.5}$ component concentrations (exposure). Our study design is at the county level; thus, individual-level variables cannot act as confounders.

To account for potential confounding by factors varying across counties, in our models we included county-specific socioeconomic status (SES) variables obtained from the US Census Bureau and the American Community Survey for the years 2000, 2004–2014. For years without available data (2001–2003), we interpolated measurements using a generalized additive model with a penalized spline for year to allow for nonlinear time trends. Data included 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). 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. In addition to SES variables, we also adjusted for urbanization level. We used the 2013 six-level urban-rural classification scheme for counties developed by the National Center for Health Statistics (NCHS) (Ingram and Franco, 2014). We reduced the six levels to a four-level classification by combining small and medium metropolitan areas into one level, and the two most rural levels into a 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 (Ingram and Franco, 2014).

To account for potential temporal confounding, we adjusted our models for long-term time trends using calendar year and summer and winter mean temperatures. Data on daily mean temperature were obtained from the North American Land Data Assimilation System at a 1/8th-degree grids (Cosgrove et al., 2003). We calculated population-weighted monthly mean temperatures at the county level from daily temperatures over all grids within a county, then averaged June–August and December–February estimates to obtain the summer and winter mean temperatures, respectively, for each year.

Furthermore, in sensitivity analyses, we adjusted for total PM$_{2.5}$ mass concentration as a potential confounder. By adjusting for total PM$_{2.5}$ mass, we accounted for PM$_{2.5}$ components that correlated both with other PM$_{2.5}$ components and the outcome (Mostofsky et al., 2012).

2.5. Statistical analysis

To identify harmful PM$_{2.5}$ components, we ran a multi-pollutant model that included all PM$_{2.5}$ components simultaneously—BC, nitrate, OM, sulfate, soil, and SS. The multi-pollutant model allowed us to evaluate if annual county-wide increases in each specific component are associated with PD first hospitalization rates, while adjusting for the other PM$_{2.5}$ components.

We used a log-linear model to estimate the ratio of the rate of PD first hospitalizations across different levels of county-level PM$_{2.5}$ component concentrations. Specifically, we used a Poisson generalized additive mixed model with a log link and a quasi-likelihood to allow for potential overdispersion in the outcome. We used county-specific random intercepts to account for within-county correlated outcome observations over time and included county population size as an offset term to account for differences in population size across counties. Lastly, we allowed for nonlinear exposure-outcome relationships. After adjustment for both spatial and temporal factors (SES, urbanization, calendar year, and temperature), we assumed that variations in the PM$_{2.5}$ component concentrations were random with respect to other risk factors for PD aggravation; under this assumption, our models should provide unbiased estimates of the effects of one-year exposure to PM$_{2.5}$ components.

We followed a rigorous process to avoid potential model misspecification. We first included all terms (PM$_{2.5}$ components and potential confounders) linearly in the model. Then, we used penalized splines for all continuous covariates to allow for nonlinear confounding. After we identified the nonlinearities in confounders, we included a penalized spline for each of the PM$_{2.5}$ components to comprehensively characterize the exposure–response relationships and identify potential deviations from linearity. We used the generalized cross-validation criterion to select the optimal degrees of freedom (df) in the exposure–response curve. Relationships with estimated df (edf) > 1 are considered nonlinear and those with edf = 1 linear. We report the linear estimates for all PM$_{2.5}$ components and also the exposure–response curve for those components for which we detected nonlinearity.

2.6. Sensitivity analysis

Correlation among PM$_{2.5}$ components may result in collinearity when including them simultaneously in a regression. Thus, to assess the robustness of the multi-pollutant model and the stability of our results, we conducted a sensitivity analysis to further evaluate the exposure–response relationship of each component with the outcome. To this end, we ran separate models for each PM$_{2.5}$ component. The single-pollutant models included only 1 PM$_{2.5}$ component (BC, nitrate, sulfate, OM, SS, or soil) but, in addition to the other confounders, were adjusted for total PM$_{2.5}$ mass concentration using the population-weighted county-year PM$_{2.5}$ average. To build the single-pollutant models (total of six models), we followed the same steps as in the main analysis.

Additionally, to reduce potential PD case status misclassification, i.e., reduce the probability that the cases we included in analyses were not PD cases, we conducted a sensitivity analysis that included only patients that had at least two hospitalizations with a PD diagnosis. The year of the first hospitalization was used to assign exposure (as in the main analysis) and the second PD hospitalization only to verify the PD diagnosis, that is, hospitalization counts were obtained based on the number of patients with at least two hospitalizations. To build this model, we followed the same steps as in the main analysis to identify potential nonlinearities.

For our analyses, we present the linear associations as rate ratios (RR) per one SD increase in the annual concentration of a given PM$_{2.5}$ component. For the components with non-linear associations, we also present the entire exposure–response curve. All analyses were performed using the R Statistical Software version 3.6.1 (Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population characteristics

We included data from all 62 NYS counties. The annual average count of PD first hospitalizations per county was 212 with a SD of 354. We observed 197,545 first PD hospitalizations (either as primary or secondary diagnoses) over the 15-year period. First hospitalization counts per county and year are shown in Supplemental Fig. S.1. In summary, the most common primary diagnosis category was diseases of the circulatory system (14.1%), which includes cardiovascular diseases. Combined PD and other disease of the nervous system were the second most common category (11.7%), of which 66.2% were specifically PD primary diagnoses. Overall, first hospitalizations with a primary diagnosis of PD accounted for 7.8% of the total hospitalizations (Fig S2). Of the total cases, 46.5% were females, and 79.0% were ≥70 years old.
Across counties, the mean age (SD) at first hospitalization was 76.9 (10.6) years. Descriptive statistics for the outcome and covariates are presented in Table 1.

3.2. **PM$_{2.5}$ component characteristics**

The summary statistics and distributions for PM$_{2.5}$ components are presented in Table 1. On average, we observed the highest mass concentrations for OM and lowest for SS. OM and sulfate made up most of the annual PM$_{2.5}$ total mass (35.4% and 30.9% on average, respectively). We observed variation in the concentrations of components across counties, as well as across years—patterns varied slightly from county to county (Supplemental Fig. S.3). The Spearman correlation coefficients among components ranged from 0.36 to 0.78 (Fig. 1). We observed the highest correlation between soil and nitrate (0.78), followed by sulfate and nitrate (0.69), then sulfate and soil (0.68). Sulfate and nitrate had the strongest correlations with PM$_{2.5}$, 0.88 and 0.81 respectively.

3.3. **Exposure-response relationships**

In the multi-pollutant model, we found that a one SD increase in OM or nitrate concentration was associated with a 6% increase in annual PD first hospitalization rate (RR = 1.06, 95% CI: 1.04–1.09 and 1.06, 95% CI: 1.03–1.10, respectively). In the case of BC, we found an inverse association (RR = 0.96, 95% CI: 0.94–0.99), a marginal association for SS (RR = 1.02, 95% CI: 1.00–1.03) and no association for soil, and sulfate (Fig. 2). When we examined for potentially nonlinear relationships, we found deviations from linearity in the BC–PD and sulfate–PD associations. The nonlinear sulfate–PD association was also null and for BC negative only at high concentrations of BC (above 1.3 µg/m$^3$, i.e., the 96th percentile of the BC concentration distribution; Fig. 3).

### Table 1

Mean, standard deviation, and inter-quartile range for Parkinson’s disease first hospitalization counts, PM$_{2.5}$ components’ concentration, and covariates. Summary statistics are based on annual per county (New York State) averages from 2000 to 2014.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean (St Dev)</th>
<th>Min/ Max</th>
<th>25%</th>
<th>Median</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>212.8 (354.0)</td>
<td>34.0</td>
<td>61.5</td>
<td>194.7</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>99.3 (167.3)</td>
<td>15.0</td>
<td>28.0</td>
<td>92.0</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>114.2 (188.3)</td>
<td>19.0</td>
<td>34.0</td>
<td>103.0</td>
<td></td>
</tr>
<tr>
<td>&lt;70 years</td>
<td>45.4 (81.7)</td>
<td>6.0</td>
<td>14.0</td>
<td>38.0</td>
<td></td>
</tr>
<tr>
<td>≥70 years</td>
<td>168.3 (279.6)</td>
<td>27.7</td>
<td>48.0</td>
<td>153.2</td>
<td></td>
</tr>
<tr>
<td>Exposure (µg/m$^3$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>8.16 (2.30)</td>
<td>4.16/ 17.4</td>
<td>6.92</td>
<td>8.28</td>
<td>9.76</td>
</tr>
<tr>
<td>Black Carbon</td>
<td>0.66 (0.24)</td>
<td>0.28/ 1.72</td>
<td>0.51</td>
<td>0.59</td>
<td>0.71</td>
</tr>
<tr>
<td>Nitrate</td>
<td>0.96 (0.33)</td>
<td>0.32/ 2.17</td>
<td>0.73</td>
<td>0.91</td>
<td>1.14</td>
</tr>
<tr>
<td>Organic Matter</td>
<td>2.87 (0.67)</td>
<td>1.56/ 5.97</td>
<td>2.36</td>
<td>2.74</td>
<td>3.30</td>
</tr>
<tr>
<td>Sulfate</td>
<td>2.51 (0.87)</td>
<td>1.05/ 5.27</td>
<td>1.79</td>
<td>2.41</td>
<td>3.09</td>
</tr>
<tr>
<td>Soil</td>
<td>0.29 (0.10)</td>
<td>0.09/ 0.75</td>
<td>0.22</td>
<td>0.28</td>
<td>0.33</td>
</tr>
<tr>
<td>Sea Salt</td>
<td>0.26 (0.16)</td>
<td>0.07/ 1.26</td>
<td>0.15</td>
<td>0.21</td>
<td>0.32</td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median income ( × $1000)</td>
<td>49.1 (12.60)</td>
<td>41.3</td>
<td>45.7</td>
<td>52.4</td>
<td></td>
</tr>
<tr>
<td>Percent below poverty</td>
<td>12.9 (4.10)</td>
<td>10.4</td>
<td>12.6</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>Percent w/o high school</td>
<td>18.1 (7.3)</td>
<td>12.8</td>
<td>17.3</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>Percent smoking prevalence</td>
<td>22. (3.9)</td>
<td>20.7</td>
<td>23.6</td>
<td>26.1</td>
<td></td>
</tr>
<tr>
<td>Percent obesity</td>
<td>25 (4.5)</td>
<td>22.3</td>
<td>25.4</td>
<td>27.8</td>
<td></td>
</tr>
<tr>
<td>Percent Hispanic</td>
<td>6.5 (8.6)</td>
<td>1.9</td>
<td>2.9</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Percent White not Hispanic</td>
<td>83.6 (16.8)</td>
<td>80.3</td>
<td>90.2</td>
<td>94.0</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>5.7 (6.3)</td>
<td>1.4</td>
<td>3.4</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Percent Black not Hispanic</td>
<td>2.2 (3.4)</td>
<td>0.5</td>
<td>0.9</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>20.2 (1.5)</td>
<td>19.2</td>
<td>20.2</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>Summer mean temp. (°C)</td>
<td>–3.1 (2.5)</td>
<td>–4.9</td>
<td>–3.3</td>
<td>–1.5</td>
<td></td>
</tr>
<tr>
<td>Winter mean temp. (°C)</td>
<td>–0.88 (0.7)</td>
<td>0.62</td>
<td>0.63</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

### 4. Discussion

In this study we aimed to identify specific PM$_{2.5}$ components that are associated with clinical disease aggravation in PD, using a patient’s first hospitalization as a surrogate. We characterized the exposure–response curves for six PM$_{2.5}$ components (OM, BC, nitrate, sulfate, SS and soil) that constitute a large proportion of the total annual PM$_{2.5}$ mass concentration in NYS. In summary, we found that an increase in county-level annual OM and nitrate concentrations were independently associated with increased first PD hospitalization rates. For BC, we unexpectedly found a nonlinear negative association above the 96th concentration percentile, while for sulfate and soil the results were null. The SS–PD association was only marginally positive in the main analysis but null in all sensitivity analyses. Our results for BC, nitrate, and OM...
were robust to the sensitivity analyses.

The BC component of PM$_{2.5}$ consists of soot, charcoal, char, and other light absorbing refractory matter. BC is mainly associated with traffic-related pollution in urban settings and is concentrated next to busy roads and highways (Tomasi et al., 2017). Although the health impacts of BC on cognition have been extensively studied (Power et al., 2011; Suglia et al., 2008; Colicino et al., 2016; Clifford et al., 2016), its association with neurodegenerative disorders, such as PD, is not as well characterized. A study by Toro et al. (2019) is the only other epidemiological study that has evaluated the association between long-term BC exposure and PD. This study was a case-control analysis in the Netherlands based on residence-level exposure and the authors reported no association. Chen et al. (2017) examined the association between residential proximity to road and clinical diagnosis of PD in an Ontario population cohort and also found no association. However, two studies in Denmark and Taiwan have linked other traffic-related pollutants (nitrogen oxides and carbon monoxide) to risk of PD (Ritz et al., 2016; Lee et al., 2016). In NYS, we found an unexpected association between annual BC exposure and PD first hospitalizations; for most of the BC distribution the association was null but became protective at high concentrations, i.e., above the 96th percentile of the BC distribution (~1.3 μg/m$^3$). This finding is unexpected and we are unable to explain it after assessing potential sources of bias and plausible biological pathways.

In the case of the PM$_{2.5}$ component nitrate, we estimated a consistently positive nitrate-PD association. Nitrate is mainly a secondary particle found in the atmosphere in the form of ammonium nitrate (Tomasi et al., 2017). Although globally agricultural activities are considered major source of ammonium nitrate, in urban sites, traffic is suggested as the primary source (Zhou et al., 2019). In urban New York, up to 99% of airborne nitrate has been traced back to traffic emissions (Zhou et al., 2019; Sun et al., 2014; Shon et al., 2012). Compared to BC, the adverse health effects resulting from nitrate exposure have been less explored. Three studies have linked nitrate exposure to all-cause mortality (Ostro et al., 2007; Cao et al., 2012; Hoek et al., 2000) and one to cardiovascular- and respiratory-related mortality (Cao et al., 2012). van Wijngaarden et al., 2021 evaluated nitrate’s association with PD hospitalizations in six NYS urban centers but found no association. In our study, we found a consistent increase in annual PD first hospitalization rates related to increases in annual nitrate concentrations at the county level. Although there is no previous evidence indicating an association between nitrate exposure and disease aggravation in PD, Ritz et al. (2016) and Lee et al. (2016) linked nitrogen oxides and carbon monoxide, both traffic-related pollutants, to risk for PD.

The OM component of PM$_{2.5}$ is itself a highly complex mixture of primary and secondary organic particles that includes hundreds of compounds such as organic carbon, polycyclic aromatic hydrocarbons (PAH), alkanes, and fatty acids (Jacobson et al., 2000)—composition may differ from region to region as well. Some OM compounds have known toxicity, for example PAHs are known carcinogens and immunosuppressants (Abdel-Shafy and Mansour, 2016), but the health effects of the wide variety of organic compounds present in PM$_{2.5}$ remain largely uncharacterized (Jacobson et al., 2000). OM constitutes a large percentage of PM$_{2.5}$ in some regions, including NYS; however, the contribution of OM to the adverse effects of PM$_{2.5}$ on the nervous system is still largely unknown. Some studies have linked prenatal and postnatal exposure to PAHs with neurodevelopmental disturbances, impaired learning and memory deficits in children (Peterson et al., 2015), inflammatory responses in vitro and in vivo (Den Hartigh et al., 2010), and degenerative disease-like syndromes in zebrafish (Gao et al., 2015). In our study, we found a consistently positive association between OM exposure and disease aggravation in PD. Given its high neurotoxic potential, more studies evaluating its association with neurodegenerative diseases, such as PD, are warranted.

Sulfate is mainly a secondary particle found in the atmosphere in the form of ammonium sulfate. Sulfate is mostly regionally transported in some regions, including NYS; however, the adverse health effects resulting from sulfate exposure have been less explored with adverse respiratory and cardiovascular effects, as well as mortality (Pope III et al., 2007; Lepeule et al., 2012; Schwartz et al., 1996; Chen et al., 2018; Jones et al., 2015; Brook et al., 2007; Ito et al., 2011; Gwynn et al., 2000; Atkinson et al., 2015). Only one study estimated sulfate effects on hospitalizations for neurodegenerative disorders and found a positive association, however, the association was observed when Alzheimer’s disease, PD, and dementia were combined into a single outcome; in PD-specific models the estimated association was null (van Wijngaarden et al., 2021). In our study, we found no association between sulfate exposure and PD disease aggravation in the main analysis and a marginally negative association in the single-pollutant model, which is likely to result from the high correlation between sulfate and PM$_{2.5}$, since this model was adjusted for PM$_{2.5}$.

4.1. Strengths and limitations

Disease aggravation in PD varies among patients, but the drivers of such variation are still largely unknown (Schrag et al., 2007)—our study address this knowledge gap. Furthermore, PM$_{2.5}$ exposure has been
identified as a potential risk factor for PD and other health outcomes, but little is actually known about whether this association is influenced by PM$_{2.5}$ composition. Here, we evaluated one-year exposure to six PM$_{2.5}$ components to estimate single-pollutant associations with disease aggravation in PD. Our study also covers a geographical area that encompasses both urban and rural locations, as well as a diverse population (SPARCS includes information on hospitalizations of all ages and independently of health insurance). Finally, we used flexible models that allowed us to test both linear and nonlinear associations to better characterize the exposure–response relationships.

Our study also has a number of limitations. Primarily, we did not have data on non-cases to perform an individual-level time-to-event analysis. Instead, our analysis is at the county level. Although we have a smaller number of data points than a traditional daily time series study, we also have many more events per unit of analysis. The fact that we were able to detect statistically significant associations indicates that any impact on statistical power due to the limited number of county-years in our analysis is likely small. Another limitation is that the variability of county-wide averages for some of the examined PM$_{2.5}$ components is quite low; this could also have impacted our statistical power and hindered our ability to detect associations. We used predicted PM$_{2.5}$ component concentrations to assign county-level exposures based on county of residence, which is expected to result in some exposure measurement error; however, this prediction models have good predictive accuracy (van Donkelaar et al., 2019) and are spatially resolved to capture county-level population-wide exposures. The cross-validated R$^2$ varied by PM$_{2.5}$ component; we would thus expect more error for OM as it is the component with the lowest R$^2$. In the case of components with high spatial heterogeneity, such as BC, a county-wide average may inadequately reflect individual exposures. Previous studies indicate this bias is likely towards the null (Kioumourtzoglou et al., 2014; Hart et al., 2015; Wu et al., 2019). Although the PM$_{2.5}$ components in this study account for a large portion of the total PM$_{2.5}$ mass, they do not capture all PM$_{2.5}$ components. For instance, metals—which account for a small percent of total PM$_{2.5}$ mass—were not evaluated in this study but have been previously linked to PD (Finkelstein and Jerrett, 2007; Willis et al., 2010). Lastly, first hospitalizations data is likely to miss a number of the total cases of PD aggravation and potentially misclassify some non-PD related hospitalizations as aggravation episodes. However, although first hospitalization is not a specific marker of disease aggravation, it captures a significant number of cases entering a severe stage of the disease as indicated in clinical studies of PD hospitalizations (Oguh and Videnovic, 2012). To our knowledge there is paucity on data on clinical disease aggravation for PD, with specific measurements or scores of aggravation, from large cohorts that live over large geographical areas to allow for proper exposure contrasts.

5. Conclusion

We characterized the independent associations between exposure to specific PM$_{2.5}$ components and PD aggravation. We found positive associations for some—but not all—PM$_{2.5}$ components, which may explain some of the variability in total PM$_{2.5}$ estimates reported across previous studies from different geographical regions. Specifically, we identified nitrate and OM as PM$_{2.5}$ components positive associated with PD. Overall, our findings support that PM$_{2.5}$ compositional profile may play a role in its association with PD disease aggravation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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