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Neurodegenerative hospital admissions and long-term exposure to ambient fine particle air pollution

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Abstract

Purpose: Long-term exposure to ambient fine particle ($PM_{2.5}$) concentrations has been associated with an increased rate or risk of neurodegenerative conditions but individual PM sources have not been previously examined in relation to neurodegenerative diseases.

Methods: Using the Statewide Planning and Research Cooperative System database, we studied 63,287 hospital admissions with a primary diagnosis of either Alzheimer's disease (AD), dementia, or Parkinson's disease (PD) for New York State (NYS) residents living within 15 miles from six $PM_{2.5}$ monitoring sites. In addition to $PM_{2.5}$ concentrations, we studied seven specific $PM_{2.5}$ sources: secondary sulfate, secondary nitrate, biomass burning, diesel, spark-ignition emissions, pyrolyzed organic rich, and road dust. We estimated the rate of neurodegenerative hospital admissions associated with increased concentration of $PM_{2.5}$ and individual $PM_{2.5}$ sources average concentrations in the previous 0–29, 0–179, and 0–364 days.

Results: Increases in ambient $PM_{2.5}$ concentrations were not consistently associated with increased hospital admissions rates. Increased source-specific PM2.5 concentrations were

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associated with both increased (e.g., secondary sulfates and diesel emissions) and decreased rates (e.g., secondary nitrate and spark-ignition vehicular emissions) of neurodegenerative admissions.

Conclusions: We did not observe clear associations between overall ambient $PM_{2.5}$ concentrations or source apportioned ambient $PM_{2.5}$ contributions and rates of neurologic disease hospitalizations.

Keywords

particulate matter; air pollution; source apportionment; neurodegenerative disease; hospitalization

INTRODUCTION

Ambient air pollution, in particular exposure to particulate matter (PM), has repeatedly been associated with increased risk of cardiovascular and pulmonary morbidity and mortality. In our previous studies in New York State, we reported that increases in $PM_{2.5}$ concentrations were associated with hospital admissions due to cardiovascular diseases (Zhang et al., 2018) and respiratory conditions (Croft et al., 2019). Recent studies have reported adverse effects of air pollution on neurodegenerative outcomes, including Parkinson's disease, Alzheimer's disease and dementia, mild cognitive impairment, white matter loss, and decreased total cerebral brain volume (Bejot et al., 2018; Chen et al., 2017c). Proposed underlying mechanisms for the neurotoxic effect of air pollution include increased systemic and neuroinflammation, oxidative stress, loss of nigral dopaminergic neurons, or altered expression of micro-RNA (Allen et al., 2017; Bejot et al., 2018; Costa et al., 2017; Shou et al., 2019), and pollution effects on the cardiovascular system, could increase susceptibility to dementia, especially vascular dementia (Bejot et al., 2018).

Most epidemiologic studies of air pollution and cognitive outcomes or neurologic diseases have been either cross-sectional in nature, or utilized existing, relatively small cohorts to study these associations in secondary analyses. Nevertheless, a few studies have taken advantage of large population-based databases of diagnoses or hospitalizations that can provide a larger sample size and allow examination of associations over periods of five years or more (Kioumourtzoglou et al., 2016; Linares et al., 2017). Previous studies have consistently identified $PM_{2.5}$ associations with Alzheimer's disease, dementia, and cognitive function than with Parkinson's disease (Chen et al., 2017b; Kioumourtzoglou et al., 2016; Linares et al., 2017; Wu et al., 2015). These studies focused on either long-term (e.g. annual average) pollutant concentrations (Kioumourtzoglou et al., 2016) or short-term (e.g. average within previous few days) exposures (Guo et al., 2018; Linares et al., 2017) but have not, within an individual study, examined different exposure time windows. Furthermore, different air pollution constituents or specific sources of $PM_{2.5}$ may differentially influence neurodegenerative diseases, and but this possibility has not yet been explored.

Source apportionment analyses analyze ambient particulate chemical species and their spatial and temporal patterns of their mass concentrations to identify individual sources of ambient PM. Positive matrix factorization (PMF), a method of source apportionment, has been used to apportion the measured mass of an atmospheric pollutant at a given site to potential emission sources by solving a mass balance equation (Hopke, 2016b). Source

apportionment analyses have been conducted in numerous regions and cities around the world (Amato et al., 2016; Hopke, 2016a; Hopke, 2016b; Khare and Khanna, 2016; Zheng et al., 2016), with some examining whether individual PM sources were individually associated with the total, respiratory, and cardiovascular morbidity and mortality (Halonen et al., 2009; Thurston et al., 2005). Squizzato et al. (Squizzato et al., 2018) identified 13 possible sources of $PM_{2.5}$ at six urban sites across New York State (Bronx, Queens, Manhattan, Buffalo, Rochester, and Albany) from 2005 to 2016 with 7 sources being common to all 6 sites. Using the mass contributions of these $PM_{2.5}$ sources at each urban site, increased rates of acute cardiovascular hospitalizations were associated with increased concentrations of spark ignition vehicle emissions (GAS), diesel vehicle emissions (DIE), road dust (RD), residual oil (RO), and secondary nitrate (SN) particulate matter in the previous 1 to 7 days (Rich et al., 2019). The possibility that individual PM sources may contribute differently to neurodegenerative diseases has not been comprehensively examined previously, although some studies have reported associations with ambient black carbon (Colicino et al., 2014; Power et al., 2011), a marker of traffic pollution and toxic airborne metal concentrations (antimony, arsenic, cadmium, chromium, lead, manganese, mercury, and nickel) (Finkelstein and Jerrett, 2007; Palacios et al., 2014a).

Using ambient $PM_{2.5}$ measurements made at six monitoring sites across New York State (NYS), and the NYS Department of Health Statewide Planning and Research Cooperative System (SPARCS), a legislatively mandated database of NYS hospital discharges, we evaluated associations between increases in $PM_{2.5}$ and source specific $PM_{2.5}$ concentrations averaged over the previous 0–29, 0–179 and 0–364 days and daily hospital admissions for dementia, Alzheimer's disease, and Parkinson's disease, both individually and combined. We hypothesized that increased $PM_{2.5}$ concentrations over extended periods of up to a year were associated with increased rates of neurologic disease hospitalizations. Based on the previously cited studies, we hypothesized that increased concentrations of the source specific $PM_{2.5}$ (GAS, DIE, RD, and RO) that are likely to include oxidants or induce the formation of oxidants in the respiratory tract would also be associated with these same neurologic hospitalizations.

MATERIALS AND METHODS

Study Population and Hospital Admissions Data:

Information on hospital admissions (inpatient care) and emergency room visits (outpatient care) were obtained from the SPARCS database, which has been described previously (Jones et al., 2015; Lin et al., 2016; Zhang et al., 2018). Briefly, SPARCS is a legislatively mandated database that covers about 95% of hospitals in NYS, excluding federal (e.g. Veterans Affairs Hospitals) and psychiatric facilities. It contains billing and medical information on over 2.5 million discharges for NYS hospitals, 1.5 million ambulatory surgery center visits, and 6.5 million emergency department (ED) visits per year. SPARCS data include patient information on the principal diagnoses and up to 24 other diagnoses at the time of hospital admission, as well as demographic characteristics, event/hospital information, and the patient's residential address. We geocoded the residential address for each hospital admission using ArcGIS 10.3.1 (The NYS GIS Program Office 2017).

We retained hospital admissions from January 1, 2005 to December 31, 2016, for adult (≥18 years) residents of New York State with a "principal" diagnosis of dementia (ICD9=290 and ICD10= F03.9, F05, F01.50, F01.51), Alzheimer's disease (ICD9=331 and ICD10=G30.9, G31.01, G31.1, G91.0, G91.1, G93.7, G31.83, G31.84, G31.9), or Parkinson's disease (ICD9=332.0, 332.1, 333.0; ICD10=G20, G21.11 G21.19, G21.8, G23.0, G23.1, G23.2, G23.8). ICD-9 codes were used for the period January 2005 to September 2015, and ICD-10 for the subsequent time period. We defined overall neurodegenerative disease hospitalizations as the sum of the three individual admissions. We included only those admissions for people within 15 miles from the closest of the $PM_{2.5}$ monitoring sites in Buffalo, Rochester, Albany, Bronx, Manhattan, and Queens (identified as described below), resulting in N=63,287 hospital admissions being available for analysis.

Using these admissions, we calculated daily admission rates for each urban center in the following manner. To account for changes in population size over time, for each monitoring site we estimated the population size (denominator for the daily admission rate) within a 15 mile buffer around the monitoring station (for ≥18 age and 8 race categories for males and females separately) for each day during the study period, using population size estimates from each census tract from the 2000 and 2010 Census data and the 2011–2015 American Community Survey (ACS). For those census tracts not completely within the buffer, we scaled the population size from that census tract by the proportion of the census tract within the buffer. We then estimated the population size for each day by linear interpolation between the 2000 and 2010 Census, and between the 2010 Census and 2011–2015 ACS data; this latter trend was extrapolated until December 2016. The spatial analyses of census tracts were performed using ArcGIS 10.4.1 (ESRI), with linear interpolations computed using R 3.4.0 (R Core Team 2018). For each day at each urban site, we then divided the daily count of neurologic hospital admissions for that site by that center's daily population estimate. The study was reviewed and approved by the Institutional Review Board at the State University of New York at Albany.

Air Pollution and Weather Data:

$PM_{2.5}$ data: We retrieved $PM_{2.5}$ measurements from the USEPA Air Quality System (https://aqs.epa.gov/api) from each of six urban sites: Buffalo, Rochester, Albany, Bronx, Manhattan, and Queens (Zhang et al., 2018). At each site, hourly $PM_{2.5}$ concentrations were measured using tapered element oscillating microbalance (TEOM) monitors (DEC 2017). We computed 24-hour daily averages for each site and each day for which measurements were available for at least 18 hours (75% of a day) of that day in that site. We adjusted the TEOM $PM_{2.5}$ concentrations to the Federal Reference Method (FRM) measurements to account for seasonal bias in TEOM data (Felton, 2005; Schwab et al., 2006). Missing TEOM data were substituted with FRM concentrations if available. For each day of our 2005–2016 study period at each site, we estimated the average $PM_{2.5}$ concentration in the previous 29 days (lag days 0–29), 6 months (lag days 0–179), and 1 year (lag days 0–364). We focused on these lags because the plausible biological mechanisms are likely most relevant for longer-term exposures. Nevertheless, for exploratory analyses we also computed average $PM_{2.5}$ concentrations for the previous day (lag 0) and previous 2 weeks (lag 0–13).

$PM_{2.5}$ sources: We retrieved chemical speciation data for $PM_{2.5}$ from 2005–2016 from the EPA Chemical Speciation Network (CSN; AQS, www.epa.gov/aqs) for the six NY urban sites. Samples were collected for 24 hours every third or sixth day and analyzed for species that provide mass closure. Elemental carbon (EC) and organic carbon (OC) were determined by thermo-optical analysis, major inorganic ions by ion chromatography, and elements by energy-dispersive X-ray fluorescence. Details of the sampling methods, analytical protocols, and quality assurance/quality control are summarized in Solomon et al. (Solomon et al., 2014). Positive matrix factorization (PMF) using U.S. EPA PMF version 5, was used to identify $PM_{2.5}$ sources at each site, with complete details provided by Squizzato et al. (Squizzato et al., 2018). Seven $PM_{2.5}$ sources were resolved at all sites: secondary sulfate [AS], secondary nitrate [AN], biomass burning [BB], diesel [DIE], spark-ignition emissions [GAS], pyrolyzed organic rich [OP], and road dust [RD]. Three sources were identified only at the New York City sites (Bronx, Manhattan, Queens) (aged sea salt [AGS], fresh sea salt [FSS], and residual oil [RO]). Road salt [RS] was identified only in Buffalo, Rochester, and Albany and an industrial source [IND] was identified only in Buffalo. Details of these analyses and results were described previously (Squizzato et al., 2018). For the current analysis, we included only those $PM_{2.5}$ sources common to all sites to ensure statistically precise effect estimates: AS, AN, BB, DIE, GAS, OP and RD. For each day of the 2005–2016 study period at each site, we estimated the average source-specific $PM_{2.5}$ concentration in the previous 29 days (lag days 0–29), 6 months (lag days 0–179), and 1 year (lag days 0–364).

Weather data: Hourly temperature and relative humidity data were obtained from the National Weather Service (National Climate Data Center, https://www.ncdc.noaa.gov/cdo-web/datatools/lcd) for the nearest major airport (BUF - Buffalo, ROC - Rochester, ALB - Albany, LGA - Bronx, and JFK - Queens) or the closest weather station (Central Park for Manhattan). For each study subject living within 15 miles of our six monitoring stations, we assigned $PM_{2.5}$ source contributions, temperature, and relative humidity measurements from the nearest monitoring site. If a person lived <15 miles from more than one monitor (e.g. Bronx vs. Manhattan), we assigned concentrations/values to that person from the closest monitor.

Statistical Analyses:

We conducted descriptive analyses of hospital admission for all three primary neurologic diagnoses separately, including distributions by sex, age, race and ethnicity, year and season of admission, and length of stay. We also evaluated the distribution of $PM_{2.5}$ concentrations for different lags by study site. We examined associations for three different primary lags (previous 0–29, 0–179, and 0–364 days) and two exploratory lags (previous day and previous 0–13 days) across the entire 2005–2016 study period.

We used generalized additive quasi-Poisson models to estimate the rate of neurologic hospital admissions (total and cause-specific) associated with interquartile range increases in $PM_{2.5}$ concentration and source specific $PM_{2.5}$ contribution. The quasi-Poisson model extends the Poisson model to allow the variance of the outcome to be larger than its mean. Models adjusted for long-term non-cyclical (secular) time trends that also account for

seasonality, day of the week (as 6 dummy variables), public holidays (yes/no), temperature, and relative humidity. Smoothing natural splines used 4 degrees of freedom per year for time trend, 3 degrees of freedom for temperature, and 3 degrees of freedom for relative humidity. Degrees of freedom (df) were selected for the overall study area after examining QAIC statistics to determine model fit for a range of degrees of freedom and considering model parsimony. We used the estimated population size within each 15 km buffer around the monitoring site, as described above, as an offset. Missing pollutant data were handled by excluding the hospitalization, and only hospitalizations with complete data were included.

To evaluate whether $PM_{2.5}$ associations with hospitalizations across all sites were robust, we first ran separate models for each site to obtain site-specific relative rate estimates and their standard errors. We then pooled the 6 site-specific estimates of association into an overall estimate using fixed-effect meta-analyses with an inverse-variance weighting method. Results from random effects models were similar and so are not reported here. We evaluated heterogeneity of $PM_{2.5}$ associations with hospitalizations across study sites. Because statistical heterogeneity ($p<0.05$) across sites was observed for only a few associations, in the main text we reported overall estimates only, but indicated where heterogeneity was observed. Site-specific estimates are presented in Supplemental materials.

We selected the lag-specific interquartile ranges (IQR) for the Albany site to scale our estimates of association across all analyses, as used in our previous studies (Croft et al., 2019; Hopke et al., 2019; Zhang et al., 2018). Associations with $P<0.05$ were considered statistically significant. All data management and statistical analyses were done using R version 3.4.1 (https://www.r-project.org/).

RESULTS

Characteristics of hospital admissions are shown in Table 1. Of the 63,287 hospital admissions during the study period, 35,706 (56.4%) were due to Alzheimer's disease, 16,366 (25.9%) were due to dementia, and 11,215 (17.7%) due to Parkinson's disease. Of all neurological hospital admissions, over 86% were in NYC (Bronx, Manhattan, and Queens). The average age at admission was 77 years, with the Parkinson's disease patients being slightly younger. The majority of patients were white, although less so in NYC sites (39.8% −61.1%) as compared to the other three sites (~85%). Hospitalizations were similarly distributed across years and seasons, although dementia hospital admissions were substantially greater in 2016 compared to previous years. Length of stay was longest for dementia hospitalizations (13 days) and shortest for Parkinson's disease hospitalizations (6 days). Across the study period, the incidence rate/year decreased for all neurologic disease hospital admissions combined, with 4.9 admissions/1000 people per year from 2005–2007 to 4.2 admissions/1000 people per year from 2014–2016. This trend was primarily due to a reduction in Alzheimer's disease hospital admissions (from 2.8 to 2.0 admissions/1000 people, respectively). Trends for dementia (about 1.3/1000 people per year) and Parkinson's disease (about 0.8/1000 people per year) remained relatively stable. The most common co-morbidities were essential hypertension (49.8%−52.5% across sites), persistent mental disorders due to conditions classified elsewhere (42.8%−55.6%), and disorders of lipoid metabolism (23.3%−32.8%) (Supplemental Table S1).

Table 2 displays trends in daily $PM_{2.5}$ concentrations across sites and lag times (previous 29, 159, and 364 days). Generally, $PM_{2.5}$ levels were lower in Rochester and Albany compared to other sites. $PM_{2.5}$ concentrations decreased by as much as 4–5 $\mu g/m^3$ over the study period, depending on the site (Figure S1). Descriptive statistics for source specific $PM_{2.5}$ contributions for the different lags are shown in Table 3. The majority of total $PM_{2.5}$ mass (~67%) was comprised of secondary sulfate, secondary nitrate, and spark-ignition emissions sources. For each source specific $PM_{2.5}$, concentrations were similar for the three lag periods. Correlations between $PM_{2.5}$ and source specific $PM_{2.5}$ concentrations are shown in Supplemental Table S2. Generally, correlations were weak to moderate, ranging from almost null (e.g. for several AS correlations) to about 0.7 (e.g. correlation between PM2.5 and AS).

Rate ratios (RR) and 95% confidence interval (CI) of total and cause-specific neurological disease hospital admissions visits associated with each IQR increase in $PM_{2.5}$ concentration, by lag time and outcome, are shown in Table 4. Most RR estimates were small and indicative of no association with $PM_{2.5}$ concentrations. Nevertheless, each IQR increase in $PM_{2.5}$ concentration in the 29 days up to and including the day of admission were significantly associated with an increased rate of hospitalizations for all neurologic diseases (RR=1.03; CI=1.00–1.05), and hospital admissions for Parkinson's disease (RR=1.06; CI=1.00–1.12). Although not statistically significant, an increased rate of hospital admissions for Alzheimer's disease was associated with increased $PM_{2.5}$ concentrations in the 365 days up to and including the day of admission (RR=1.16; CI=0.91–1.46), while an increased rate of dementia was associated with each IQR increase in $PM_{2.5}$ concentration in the 180 days up to and including the day of admission (RR=1.11; CI=0.92–1.34). Because 20% of neurologic hospitalizations (n=12,841) were among patients with two or more hospitalizations during the study, we re-ran the model described above using the first hospitalization only and then again with patients with only one hospitalization during the 2005–2016 study period. After doing so, elevated rates found with two or more hospitalizations included were lowered after considering the first hospitalization only and they were no longer statistically significant for any lag-outcome combination. Site-specific estimates for all lags are presented in Supplemental Table S3, and results for lag 0 and 0–13 days across all sites are shown in Supplemental Table S4.

Rate ratios (RR) and 95% confidence intervals (CI) of total and cause-specific neurodegenerative disease hospital admissions associated with each IQR increase in source-specific $PM_{2.5}$ concentration, by lag time and outcome, are shown in Table 5. For all neurologic admissions combined, some statistically significant associations were observed, but there were also some protective associations. For example, while an increased rate of neurologic hospitalizations was associated with each IQR increase in secondary sulfate contribution in the past 6 months (RR=1.09; CI=1.00–1.19) and each IQR increase in diesel contribution in the previous year (RR=2.02; CI=1.17–3.47), decreased hospital admission rates were associated with IQR increases in the contribution of secondary nitrate in the previous 29 days (RR=0.93; CI=0.88–0.99), and spark-ignition emissions (RR=0.81; CI=0.66–0.99) and biomass burning (RR=0.58; CI=0.31–1.06) in the previous 6 months. The directions and magnitudes of association were similar for Alzheimer's disease hospital admissions since they constitute the majority of total neurologic admissions, although the associations were less frequently statistically significant due to a smaller sample size.

Patterns for hospital admission rates of dementia and Parkinson's disease were inconsistent, with both adverse and protective associations, but none were statistically significant. Results for lag 0 and 0–13 days for each source specific $PM_{2.5}$ are shown in Supplemental Table S4.

DISCUSSION

For NYS residents living within 15 miles from $PM_{2.5}$ monitoring sites in six urban areas from 2005–2016, our study found little evidence to support the hypothesis that increased ambient $PM_{2.5}$ concentrations or individual source specific ambient $PM_{2.5}$ contributions were associated with increased rates of hospital admissions for neurodegenerative diseases. Among the many comparisons across lags and outcomes, elevated hospitalization rates were observed for all neurologic outcomes combined and Parkinson's disease in relation to $PM_{2.5}$ exposure in the previous 29 days but only when patients with two or more hospitalizations were considered, potentially suggesting a role of $PM_{2.5}$ in exacerbation of disease. However, analysis of individual source-specific ambient $PM_{2.5}$ contributions showed inconsistent results. Increased contributions of secondary sulfates and diesel were associated with increased rates of total neurodegenerative hospital admissions, but increased contributions of secondary nitrate, spark-ignition emissions, and biomass burning $PM_{2.5}$ were associated with decreased hospitalization rates.

Multiple interconnected pathophysiologic mechanisms may explain associations between $PM_{2.5}$ concentrations and adverse neurological outcomes, such as the activation of microglia and neuroinflammation through direct (e.g. translocation to the brain) and indirect (e.g. peripheral inflammation) pathways (Jayaraj et al., 2017), alterations of dopamine and glutamate neurotransmitter systems (Allen et al., 2017), neuronal injury including white matter damage (Allen et al., 2017; Chen et al., 2015), lower total cerebral brain volume and covert brain infarcts (Wilker et al., 2015), and adverse vascular effects (Babadjouni et al., 2017; Weuve, 2014). Some studies of $PM_{2.5}$ and PM_{10} have reported an increased risk of Parkinson's disease associated with PM_{10} (Chen et al., 2017a; Liu et al., 2016) or $PM_{2.5}$ (Kioumourtzoglou et al., 2016; Kirrane et al., 2015; Lee et al., 2016; Liu et al., 2016), but other studies did not observe such associations (Guo et al., 2018; Palacios et al., 2017; Palacios et al., 2014b). Studies of cognitive decline in relation to particulate matter include a range of outcomes such as Alzheimer's disease (Jung et al., 2015; Kioumourtzoglou et al., 2016), dementia (Chen et al., 2017b; Kioumourtzoglou et al., 2016; Linares et al., 2017; Wu et al., 2015), mild cognitive impairment (Tzivian et al., 2016), and sub-clinical cognitive function (Ailshire and Clarke, 2015; Ailshire and Crimmins, 2014; Power et al., 2011). Most studies reported an adverse association with $PM_{2.5}$ (Ailshire and Clarke, 2015; Chen et al., 2017b; Jung et al., 2015; Tzivian et al., 2016), PM_{10} (Wu et al., 2015). However, some did not show a consistent exposure-response pattern (Ailshire and Crimmins, 2014) and one did not find an association between $PM_{2.5}$ and neurologic disease (Linares et al., 2017). Recent meta-analyses have summarized the evidence regarding air pollution and neurological disorders providing support for adverse associations (Fu et al., 2019; Kasdagli et al., 2019).

Perhaps most relevant to the current analysis are prospective population-based studies evaluating rates of either hospital admissions (Cerza et al., 2019; Kioumourtzoglou et al., 2016) or emergency department visits (Guo et al., 2018; Linares et al., 2017) due to

neurological diseases. Kioumourtzoglou and colleagues (Kioumourtzoglou et al., 2016) used hospital admission data from 1999–2010 for almost 10 million Medicare enrollees 65 years and older, living in 50 cities in the Northeastern United States. For each city, annual $PM_{2.5}$ averages (mean = 12.0 μg/m^3) were estimated using data from the U.S. EPA's Air Quality System which were then used to examine associations with hospital admission rates for Parkinson's disease (total number of admissions N=119,425), Alzheimer's disease (N=266,725), dementia (N=203,463), as well as cardiovascular and respiratory conditions. After hazard ratios were estimated for each city, they were pooled using random effects meta-analysis similar to procedures used in our study. For each 1 μg/m^3 increase in $PM_{2.5}$, an 8% increased rate of Parkinson's disease was observed (hazard ratio [HR] = 1.08; CI = 1.04–1.11). Adverse associations were also reported for Alzheimer's disease (HR = 1.15; CI = 1.11–1.19) and dementia (HR=1.08; CI=1.05–1.11). Linares and colleagues studied daily dementia-related emergency hospital admissions (N=1175) in Madrid, Spain from 2001–2009 in relation to noise pollution, air pollution, and daily temperature (Linares et al., 2017). Daily average $PM_{2.5}$ concentrations (mean = 17.1 μg/m^3) were obtained from the Madrid Municipal Air Quality Monitoring Grid, a network consisting of 27 urban monitoring sites. No association with $PM_{2.5}$ was found (no risk estimates were reported). Guo et al. examined 162,771 emergency department visits from 65 hospitals from the Emergency Medical Command Center in Guangzhou (2013–2015) (Guo et al., 2018). Daily average $PM_{2.5}$ concentrations (mean = 45.8 μg/m^3) were obtained from the Daily Quality Report of the Guangzhou Environmental Protection Bureau. They reported a 2.2% (95% CI = 0.63% −3.74%) increased rate of neurologic emergency department visits (ICD-10: codes G00–G99) associated with each 33.8 μg/m^3 increased $PM_{2.5}$ concentration at lag day 0 although this association did not remain after accounting for other pollutants. Unfortunately, no disease-specific associations were examined. Finally, Cerza and colleagues (Cerza et al., 2019) in a large administrative cohort in Rome identified 350,844 subjects without dementia (65–100 years of age) and followed them for 12 years to investigate the association between first hospitalization with primary or secondary diagnoses of dementia and air pollution concentrations (PM_{10}, $PM_{2.5}$, NOx, NO_2, and ozone) estimated from land use regression models. Mean exposure levels of the population at the time of inclusion into the study were 36.9 μg/m^3 for PM_{10} and 19.7 μg/m^3 for $PM_{2.5}$. $PM_{2.5}$ was not associated with an elevated rate of dementia (HR = 0.99; CI = 0.98–1.02 per 5 μg/m^3), Alzheimer's disease (HR = 0.91; CI = 0.85–0.97 per 5 μg/m^3), or senile dementia (HR = 0.98; CI = 0.92–1.03 per 5 μg/m^3), but was associated with an elevated rate of vascular dementia (HR = 1.07; CI = 1.01–1.12 per 5 μg/m^3). It should be noted that while ambient $PM_{2.5}$ exposure was not clearly associated with increased rates of neurologic hospital admissions in our study, the magnitude of associations where rates were elevated was similar to, and sometimes larger than, those reported in previous studies.

No previous studies have specifically examined associations between multiple source-apportioned $PM_{2.5}$ contributions and neurodegenerative or neurocognitive outcomes (Colicino et al., 2014; Finkelstein and Jerrett, 2007; Palacios et al., 2014a; Power et al., 2011). In the Normative Aging Study of older men, Power et al. (Power et al., 2011) used 83 monitoring sites to estimate daily concentrations of ambient black carbon, and from those measurements estimated annual average ambient black carbon concentrations for each study

participant. For each doubling of black carbon concentration, the odds of having a mini-mental state examination score ≤ 25 (suggestive of cognitive impairment) increased by 30% (Power et al., 2011). In a follow up study in this population, Colicino and colleagues observed that this association appeared to be mostly confined to participants in a few specific mitochondrial haplotype groups that may confer susceptibility to oxidative stress induced by air pollution (Colicino et al., 2014). In a Nurses Health Study of Parkinson's disease, Palacios and coworkers used the National Air Toxics Assessment database to estimate annual average concentrations of airborne metals including arsenic, cadmium, chromium, nickel, manganese, antimony and lead (Palacios et al., 2014a). They found no statistically significant associations with any of the metals examined, although there was a suggestive positive dose-response trend for mercury exposure (Hazard Ratio [HR] = 1.33 [95% CI=0.99, 1.79] in the highest exposure quartile vs. the lowest exposure quartile; p_{trend}=0.10 based on linear model through quartile medians). Finkelstein and Jerrett linked neighborhood levels of ambient manganese in Hamilton, Canada as measured by the manganese fraction of total suspended particulate, to the risk of Parkinson's disease as identified from administrative databases of medication prescriptions and physicians' diagnoses (Finkelstein and Jerrett, 2007). They reported a 3% increase in odds of Parkinson's disease associated with each 10 ng/m^3 increase in total suspended particulate manganese concentration (Finkelstein and Jerrett, 2007). While we were not able to confirm the findings of these studies, together they suggest that source apportionment of PM in health studies may be useful in understanding what PM sources or components impact population health effects, which can be used to guide public health policies.

Previously, we observed increased rates of cardiac arrhythmia, ischemic stroke, and congestive heart failure hospitalizations associated with increased diesel, spark-ignition vehicle, road dust, secondary nitrate, and residual oil contributions, but not secondary sulfate or other source-specific $PM_{2.5}$ contributions (Rich et al., 2019). These findings suggest a role of New York State traffic emissions, residual oil, and non-traffic emissions such as brake and tire wear in the triggering of acute cardiovascular events. Although any air pollution effects on the cardiovascular system could increase susceptibility to dementia, our lack of associations between any source specific $PM_{2.5}$ contribution and neurodegenerative hospitalization rates (including Alzheimer's disease and dementia) is inconsistent with these findings. The role of methodological differences in exposure and outcome assessment in explaining inconsistency in study findings needs to be further investigated.

Strengths of our study included a large sample size, the use of uniformly collected and coded hospitalization data in New York State from 2005–2016, and a concurrent multi-year source apportionment analysis across urban centers in New York State. These strengths allowed an assessment of associations with $PM_{2.5}$ and mean $PM_{2.5}$ source contributions over 30, 180, and 365 days. However, there were also some limitations to consider. First, residential history was obtained at the time of hospitalization which may not accurately capture residential location for the entire year prior. Furthermore, cases within 15 miles of a $PM_{2.5}$ monitoring site were assigned the same exposure values for a specific day, regardless of how close they lived to the site. This exposure misclassification likely resulted in bias toward the null and underestimates of relative rates (Zeger et al. 2000).

Next, the PMF analyses of Squizzato et al. (Squizzato et al., 2018) were conducted as a single source apportionment across the entire 12 years of the study period (2005–2016), with individual sources identified and named based on an assumed common chemical composition across these 12 years. It is possible that if the source apportionments had been done for each individual time period (e.g. 2005–2007, 2008–2013, and 2014–2016) instead, daily contributions of individual source specific mass contributions (e.g. secondary sulfate) may have differed from those used in the current study. Any exposure misclassification likely resulted in biases toward the null and underestimates of relative rates (Zeger et al., 2000).

Third, there was a change in the hospital admission diagnosis codes used in SPARCS, from ICD9 to ICD10 codes starting Oct 1, 2015. However, this change likely did not greatly affect our associations, as the vast majority of our hospital admissions (almost 11 out of 12 years of study data) were coded using ICD9. In a sensitivity analysis excluding the 2015 data and rerunning the analyses, results remained similar and inference identical to the original findings.

Finally, hospitalizations due to neurologic conditions may be due to symptoms directly related to the neurologic disease, or they may reflect comorbidities (Arasalingam and Clarke, 2014; Bernardes et al., 2018; Lin et al., 2017; Oguh and Videnovic, 2012; Ronneikko et al., 2018), especially since about 80% of hospitalizations were among individuals age 70 or older. Heterogeneity in exacerbations of either neurologic symptoms or common comorbidities (e.g. essential hypertension) may make the index hospitalizations different disease events, resulting in outcome misclassification and a bias towards the null.

In conclusion, ambient $PM_{2.5}$ exposure and source apportioned ambient $PM_{2.5}$ contributions were not clearly associated with increased rates of hospital admissions due to Alzheimer's disease, dementia, or Parkinson's disease. Further studies with finer spatial resolution of air pollution data and less heterogeneity in outcome events, for example by studying spatial associations within our study areas, may be needed to detect such subtle associations, if they are indeed present.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Hospital admission characteristics for primary diagnosis of selected neurological diseases in six urban sites in New York State, 2005–2016

	Total		Alzheimer's Disease		Dementia		Parkinson's Disease	
	N	%	N	%	N	%	N	%
Total	63,287	100	35,706	100	16,366	100	11,215	100
Male	33,365	52.7	19,620	55.0	9,281	56.7	4,464	39.8
Age(years) Mean(SD)	77.2 (11.7)		77.5 (12.3)		79.2 (10.2)		73.5 (11.3)	
20–39	814	1.3	712	2.0	27	0.2	75	0.7
40–49	916	1.5	574	1.6	81	0.5	261	2.3
50–59	2,884	4.6	1,350	3.8	578	3.6	947	8.4
60–69	8,551	13.5	4,055	11.4	2,083	12.7	2,413	21.5
70–79	19,163	30.3	10,680	29.9	4,770	29.2	3,713	33.1
80+	30,959	48.9	18,335	51.4	8,818	53.9	3,806	33.9
Race/Ethnicity								
White	36,056	57.0	20,849	58.4	8,179	50.0	7,028	62.7
Black	13,427	21.2	7,193	20.2	4,568	27.9	1,666	14.9
American Indian	305	0.5	168	0.5	75	0.5	62	0.6
Asian	1,201	1.9	627	1.8	277	1.7	297	2.7
Native Hawaiian	9	0.01	3	0.01	4	0.02	2	0.02
Hispanic	6,358	10.1	3,712	10.4	1,653	10.1	993	8.9
Year								
2005	5,527	8.7	3,005	8.4	1,610	9.8	912	8.1
2006	5,570	8.8	3,312	9.3	1,378	8.4	880	7.9
2007	5,552	8.8	3,255	9.1	1,400	8.6	897	8.0
2008	5,857	9.3	3,430	9.6	1,551	9.5	876	7.8
2009	5,642	8.9	3,298	9.2	1,428	8.7	916	8.2
2010	5,535	8.8	3,337	9.4	1,274	7.8	924	8.2
2011	5,249	8.3	3,271	9.2	1,110	6.8	868	7.7
2012	4,914	7.8	3,068	8.6	864	5.3	982	8.8
2013	4,709	7.4	2,904	8.1	867	5.3	938	8.4
2014	4,166	6.6	2,622	7.3	686	4.2	858	7.7

	Total		Alzheimer's Disease		Dementia		Parkinson's Disease	
	N	%	N	%	N	%	N	%
2015	4,773	7.5	2,521	7.1	1,283	7.8	969	8.6
2016	5,793	9.2	1,683	4.7	2.915	17.8	1,195	10.7
Season of admission								
Fall	15,769	24.9	7,495	24.7	4,115	25.1	2,805	25.0
Spring	16,199	25.6	7,825	25.8	4,185	25.6	2,822	25.2
Summer	15,882	25.1	7,657	25.2	3,952	24.2	2,980	26.6
Winter	15,437	24.4	7,385	24.3	4,114	25.1	2,608	23.3
Length of stay (days) Mean(SD)	10.7 (21.9)		10.8 (20.8)		13.4 (29.3)		6.3 (10.2)	

Table 2.

Distribution of $PM_{2.5}$ concentrations ($\mu g/m^3$) for different lags, by study site, 2005–2016 *

Site/Lag	Mean(SD)	Median	IQR
Albany			
0–29	8.6(2.7)	8.1	3.6
0–179	8.6(1.7)	8.4	2.4
0–364	8.7(1.6)	8.3	2.4
Buffalo			
0–29	9.8(2.9)	9.5	3.8
0–179	9.9(1.9)	9.7	2.3
0–364	10.0(1.7)	9.6	2.3
Rochester			
0–29	8.6(2.6)	8.1	3.3
0–179	8.6(1.7)	8.3	2.3
0–364	8.8(1.5)	8.3	2.1
Bronx			
0–29	10.3(3.1)	9.8	4.4
0–179	10.4(2.1)	10	3.9
0–364	10.5(2.0)	10	4.1
Manhattan			
0–29	11.7(3.1)	11.2	4.1
0–179	11.8(2.0)	11.7	3.1
0–364	11.9(1.9)	11.6	3.1
Queens			
0–29	9.5(2.9)	9.0	3.8
0–179	9.6(1.8)	9.3	2.9
0–364	9.7(1.7)	9.4	3.2

* IQR=Interquartile range, SD=Standard deviation

Table 3.

Distribution of $PM_{2.5}$ contributions ($\mu g/m^3$) for different $PM_{2.5}$ sources in New York State, 2005–2016 *

$PM_{2.5}$ Source	Lag 0–29			Lag 0–179			Lag 0–364		
	Mean(SD)	Median	IQR	Mean(SD)	Median	IQR	Mean(SD)	Median	IQR
Road Dust (RD)	0.32 (0.29)	0.24	0.29	0.33 (0.24)	0.26	0.27	0.33 (0.22)	0.26	0.28
Secondary Sulfate (AS)	2.98 (2.57)	2.41	2.33	3.00 (1.72)	2.68	1.86	2.98 (1.33)	2.84	1.57
Secondary Nitrate (AN)	1.55 (1.64)	0.99	1.89	1.51 (1.07)	1.31	1.41	1.54 (0.74)	1.41	0.88
Diesel (DIE)	0.97 (0.64)	0.79	0.7	0.97 (0.52)	0.8	0.72	0.96 (0.47)	0.78	0.71
Spark-Ignition Emissions (GAS)	1.65 (1.12)	1.44	1.54	1.63 (0.80)	1.47	1.17	1.60 (0.66)	1.5	0.92
Biomass Burning (BB)	0.49 (0.43)	0.39	0.44	0.48 (0.29)	0.4	0.37	0.48 (0.25)	0.42	0.35
Pyrolized Organic Rich (OP)	1.14 (0.99)	0.88	0.99	1.17 (0.79)	0.98	0.76	1.22 (0.73)	1.04	0.61

* IQR=Interquartile range, SD=Standard deviation

Table 4.

Rate ratio (95% confidence interval (CI)) of total and cause-specific neurological disease hospital admissions associated with each interquartile range (IQR) increase in $PM_{2.5}$ concentration, by lag time and outcome, 2005–2016

Outcome/Lag	IQR (μg/m^3)	Rate Ratio[¥] (95% CI)	p-value[*]
Total			
0–29	3.6	1.03 (1.00, 1.05)	**0.017**
0–179	2.4	1.04 (0.95, 1.14)	0.448
0–364	2.4	1.06 (0.89, 1.27)	0.512
Alzheimer's disease			
0–29	3.6	1.02 (0.99, 1.05)	0.182
0–179	2.4	1.01 (0.90, 1.14)	0.878
0–364	2.4	1.16 (0.91, 1.46)	0.229
Dementia			
0–29	3.6	1.02 (0.97, 1.06)	0.499
0–179	2.4	1.11 (0.92, 1.34)	0.259
0–364	2.4	1.02 (0.71, 1.46)	0.934
Parkinson' disease			
0–29	3.6	1.06 (1.00, 1.12)	**0.035**
0–179	2.4	0.98 (0.79, 1.22)	0.838
0–364	2.4	0.88 (0.57, 1.35)	0.562

[¥] Models adjusted for temperature (4df) and relative humidity using natural splines (3df); RR estimates in *italics* showed statistically significant ($p<0.05$) heterogeneity in RR estimates across sites

[*] P values in bold indicate statistically significant associations at $\alpha=0.05$

[†] Site-specific estimates per IQR: Albany RR=1.07 (CI=0.94–1.22); Buffalo RR=0.91 (CI=0.83–1.01); Rochester RR=0.86 (CI=0.75–0.99); Bronx RR=1.04 (CI=0.99–1.10); Manhattan RR=0.97 (CI=0.92–1.03); Queens RR=1.03 (CI=0.98–1.08)

[‡] Site-specific estimates per IQR: Albany RR=0.93 (CI=0.85–1.02); Buffalo RR=1.00 (CI=0.91–1.09); Rochester RR=0.99 (CI=0.90–1.09); Bronx RR=0.99 (CI=0.95–1.04); Manhattan RR=1.00 (CI=0.91–1.09); Queens RR=1.08 (CI=1.03–1.14)

Table 5.

Rate ratio (95% confidence interval (CI)) of total and cause-specific neurological disease hospital admissions associated with each interquartile range (IQR) increase in $PM_{2.5}$ source concentration, by lag time and outcome, 2005–2016

$PM_{2.5}$ Source	IQR * ($\mu g/m^3$)	Total			Alzheimer's Disease			Dementia			Parkinson's Disease		
		N	Rate Ratio¥ (95% CI)	P*	N	Rate Ratio¥ (95% CI)	P*	N	Rate Ratio¥ (95% CI)	P*	N	Rate Ratio¥ (95% CI)	P*
Road Dust (RD)													
0–29	4.2	56,542	0.96 (0.74, 1.25)	0.77	31,852	0.85 (0.60, 1.20)	0.37	14,790	1.24 (0.75, 2.06)	0.40	9,900	0.90 (0.49, 1.66)	0.74
0–179	2	56,726	0.77 (0.39, 1.51)	0.44	32,133	0.98 (0.41, 2.36)	0.96	14,650	0.81 (0.20, 3.29)	0.77	9,943	0.22 (0.05, 1.08)	0.062
0–364	1.3	54,729	0.57 (0.21, 1.57)	0.28	31,095	0.30 (0.08, 1.15)	0.080	14,054	3.40 (0.45, 25.63)	0.24	9,580	0.27 (0.03, 2.79)	0.27
Secondary Sulfate (AS)													
0–29	4.2	56,542	1.02 (0.99, 1.04)	0.30	31,852	1.01 (0.98, 1.05)	0.47	14,790	1.01 (0.95, 1.07)	0.74	9,900	1.02 (0.95, 1.09)	0.57
0–179	2	56,726	1.09 (1.00, 1.19)	0.042	32,133	1.07 (0.95, 1.20)	0.25	14,650	1.13 (0.94, 1.35)	0.19	9,943	1.13 (0.93, 1.38)	0.21
0–364	1.3	54,729	1.01 (0.89, 1.14)	0.88	31,095	1.01 (0.86, 1.19)	0.90	14,054	0.93 (0.71, 1.22)	0.61	9,580	1.10 (0.84, 1.43)	0.50
Secondary Nitrate (AN)													
0–29	4.2	56,542	0.93 (0.88, 0.99)	0.015	31,852	0.97 (0.90, 1.04)	0.39	14,790	0.87 (0.78, 0.98)	0.021	9,900	0.89 (0.78, 1.02)	0.083
0–179	2	56,726	0.91 (0.77, 1.08)	0.29	32,133	1.05 (0.85, 1.30)	0.68	14,650	0.80 (0.57, 1.13)	0.20	9,943	0.73 (0.49, 1.08)	0.12
0–364	1.3	54,729	0.95 (0.75, 1.20)	0.66	31,095	0.97 (0.72, 1.32)	0.86	14,054	0.88 (0.54, 1.43)	0.60	9,580	1.03 (0.58, 1.83)	0.92
Diesel (DIE)													
0–29	4.2	56,542	0.95 (0.83, 1.09)	0.46	31,852	1.04 (0.87, 1.24)	0.67	14,790	0.80 (0.61, 1.05)	0.11	9,900	0.89 (0.64, 1.22)	0.47
0–179	2	56,726	0.97 (0.66, 1.43)	0.87	32,133	1.36 (0.82, 2.27)	0.23	14,650	0.71 (0.32, 1.56)	0.39	9,943	0.54 (0.22, 1.35)	0.19
0–364	1.3	54,729	2.02 (1.17, 3.47)	0.011	31,095	1.83 (0.90, 3.71)	0.093	14,054	2.45 (0.78, 7.72)	0.13	9,580	2.06 (0.56, 7.50)	0.28
Spark-Ignition Emissions (GAS)													
0–29	4.2	56,542	0.97 (0.91, 1.05)	0.48	31,852	0.97 (0.88, 1.07)	0.54	14,790	0.96 (0.84, 1.11)	0.60	9,900	1.04 (0.88, 1.22)	0.67
0–179	2	56,726	0.81 (0.66, 0.99)	0.037	32,133	0.76 (0.58, 0.98)	0.038	14,650	0.71 (0.47, 1.07)	0.11	9,943	1.11 (0.70, 1.75)	0.66
0–364	1.3	54,729	0.96 (0.75, 1.23)	0.75	31,095	0.77 (0.56, 1.06)	0.11	14,054	1.35 (0.79, 2.33)	0.28	9,580	1.38 (0.78, 2.44)	0.27
Biomass burning (BB)													
0–29	4.2	56,542	0.96 (0.80, 1.17)	0.70	31,852	0.96 (0.75, 1.22)	0.72	14,790	0.70 (0.46, 1.06)	0.092	9,900	1.49 (0.95, 2.32)	0.081
0–179	2	56,726	0.58 (0.31, 1.06)	0.076	32,133	0.50 (0.23, 1.09)	0.083	14,650	0.40 (0.10, 1.51)	0.18	9,943	1.73 (0.40, 7.42)	0.46
0–364	1.3	54,729	0.93 (0.38, 2.28)	0.88	31,095	1.15 (0.36, 3.63)	0.81	14,054	0.79 (0.12, 5.33)	0.81	9,580	0.90 (0.11, 7.45)	0.92
Pyrolized Organic Rich (OP)													

$PM_{2.5}$ Source	IQR * ($\mu g/m^3$)	Total			Alzheimer's Disease			Dementia			Parkinson's Disease		
		N	Rate Ratio¥ (95% CI)	P*	N	Rate Ratio¥ (95% CI)	P*	N	Rate Ratio¥ (95% CI)	P*	N	Rate Ratio¥ (95% CI)	P*
0–29	3.8	39,029	1.01 (0.93, 1.09)	0.89	21,603	1.04 (0.94, 1.16)	0.41	10,388	0.97 (0.83, 1.14)	0.73	7,038	0.91 (0.74, 1.10)	0.32
0–179	1.5	41,343	1.00 (0.88, 1.14)	0.95	23,005	1.05 (0.89, 1.24)	0.55	10,915	1.05 (0.81, 1.36)	0.72	7,423	0.86 (0.63, 1.18)	0.36
0–364	0.9	42,054	1.09 (0.95, 1.25)	0.22	23,467	1.15 (0.96, 1.37)	0.13	11,072	1.24 (0.94, 1.64)	0.13	7,515	0.80 (0.57, 1.14)	0.22

¥Models adjusted for day of the week, public holidays, time trend (4df/year), temperature (4df) and relative humidity using natural splines (3df); RR estimates in *italics* showed statistically significant ($p<0.05$) heterogeneity in RR estimates across site