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Urban air quality and associations with pediatric multiple sclerosis

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Abstract

Background: We previously identified air quality as a risk factor of interest for pediatric multiple sclerosis. The purpose of this study is to more closely examine the association between the six criteria air pollutants and pediatric MS as well as identify specific areas of toxic release using data from the Toxic Release Inventory. **Methods**: Pediatric MS cases ($N = 290$) and healthy controls ($N = 442$) were included as part of an ongoing case–control study. We used the National Emissions Inventory system to estimate particulate exposure by county of residence for each participant. Proximity to Toxic Release Inventory (TRI) sites was also assessed using ArcGIS mapping tools. Risk-Screening Environmental Indicators (RSEI) classified counties at risk to exposure of environmental toxic releases. **Results**: Fine particulate matter ($PM_{2.5}$), carbon monoxide (CO), sulfur dioxide (SO_2), and lead air emissions were associated with increased odds for pediatric MS ($P < 0.01$) for those residing within 20 miles of an MS center. Most study participants (75%) resided within 5 miles of at least one TRI site; however, the mean total pounds of stack air releases was higher for sites near MS cases (81,000 tons) compared to those near healthy controls (35,000 tons, $P = 0.002$). Average RSEI scores did not differ significantly between cases and controls. **Conclusion**: Out of several air pollutants examined, we show that fine particulate matter and three other criteria pollutants (SO_2, CO, and lead) were statistically associated with higher odds for pediatric MS.

Introduction

The contributions of physical environmental exposures to pediatric multiple sclerosis (MS) have not been extensively studied. Our prior work showed that of several categories of physical environment exposures (air, water, and land quality), air quality contributed to the odds for having pediatric MS.[1]

Air particulates consist of solids and liquids generally created through transportation and industrial sources. Chronic exposure has shown to cause epithelium and respiratory alterations[2] leading to other chronic health outcomes including nonfatal heart attacks,[3] stroke,[4] asthma,[5,6] and decreased lung function.[7,8] Fine particulate matter ($PM_{2.5}$) has also been associated with adverse neurological outcomes including cognitive delays in children,[9–11] dementia and Alzheimers,[12–14] and white matter abnormalities.[14–16] Animal studies show that long-term exposure to $PM_{2.5}$ can decrease total brain and white matter volumes.[17]

Although some adult MS studies have suggested a relationship between air constituents and MS,[18–20] not all of the Environmental Protection Agency (EPA) criteria air pollutants have been assessed, including fine $PM_{2.5}$, ground level ozone precursors, and lead. Furthermore, the proximity of MS patients to industrial facilities that release toxic chemicals into the air has yet to be explored. The purpose of this study is to more closely examine the association between the six criteria air pollutants (carbon monoxide, sulfur dioxide, particulate matter, ozone, nitrogen oxides, and lead) and pediatric MS. Furthermore, we evaluate the proximity to Toxic Release Inventory sites in relation to pediatric MS cases using geographic information systems (GIS).

Methods

Participants

Pediatric MS subjects (first clinical attack before 18 years of age) and healthy children seen at pediatric clinics at the same institutions were enrolled as part of an ongoing multicenter case–control study. Participants were included from 16 pediatric MS centers across the United States. Selection of the centers and confirmation of diagnosis has been previously described.[21] Healthy controls were frequency-matched to be similar to MS patients in age, sex, and race. The zip code of each subject's longest residence was entered into a database at time of enrollment and was geocoded using ArcGIS (ESRI). In order to help protect anonymity, the centroid of the county for the zip code was used as the reference point for location in map presentations. This study was approved by the institutional review boards at the participating sites. Consent and assent (when appropriate) were obtained for each subject.

Environmental data

National emissions inventory

The Environmental Protection Agency (EPA) has established six criteria air pollutants which are regularly recorded and monitored as part of the Clean Air Act and the National Ambient Air Quality Standards. Criteria air pollutants include carbon monoxide (CO), particulate matter and fine particulate matter (PM_{10}, $PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), lead, and ground level ozone (O_3). As part of this system, the National Emissions Inventory (NEI) system was created to provide comprehensive exposure estimates of these pollutants and other hazardous air pollutants. The NEI totals values from fixed location sources (point sources), nonpoint sources including vehicle emissions, nonroad sources including aircraft and marine vessels, and "event" sources such as wildfires and prescribed burns. Total emission estimates by county are provided every 3 years with the most recent dataset issued in 2014. The portions of the dataset utilized for this study included estimates on CO, PM_{10}, $PM_{2.5}$, SO_2, lead, NOx (including NO_2 and other nitric oxides), volatile organic carbons (precursors to ground level ozone), and carbon dioxide (CO_2). Using ArcGIS, participants were given emission estimates for each pollutant based on their county of longest residence.

Toxic release inventory

The EPA also tracks the management and environmental release of potentially harmful industrial chemicals through a system called the Toxic Release Inventory (TRI). Each year facilities are required to report how much of a chemical is released in to the environment and through which mechanism (air, water, or land release). The TRI database contains GIS locations for each facility as well as a total amount of chemicals released into the air, water, and land. Only air releases were considered for this study. Using a buffer tool within ArcGIS, each participant was given a numeric value of how many TRI reporting sites were within a 5-mile radius of the participant's residence. A summation of total air releases was created from those reporting sites within a 5-mile radius of the participant's home.

Risk-screening environmental indicators

Although the TRI reports total releases from facilities, not all chemicals are immediate threats to public health because of toxicity and breakdown of the chemical elements. The EPA created the Risk-Screening Environmental Indicators (RSEI) model to help identify toxic

substances released from TRI sites and estimate the potential for human exposure to those substances. The model incorporates information on the annual quantity, dispersion, and toxicity of each chemical released, creating a weighted score for each site. Scores were also created for each county based on the scores of the facilities within the county. A higher score suggests an area of higher "risk" than a lower score and indicates areas which need further investigation. The RSEI database was downloaded from the EPA website and geocoded in ArcGIS by county. Each participant was given a RSEI score based on their county of residence.

Data analysis

Each air pollutant was categorized into quartiles to compare differing levels of exposures, with the lowest exposure category as the reference. Logistic regression determined the odds of pediatric MS given the estimates of air pollutant exposure. Univariate analysis was performed for additional covariates to be considered in the final models. Population density of the county, median income level of the county, exposure to secondhand smoke in the home, age at disease onset, length of time at residence, and basic demographics such as age, gender, and race/ethnicity were considered for the final logistic regression models. Population density for the county of residence was determined by dividing the total population by the total square miles of the county. A Bonferroni correction was used and an odds ratio with a $P < 0.01$ was considered significant. As in our prior study,[1] subjects were stratified by proximity to the recruiting site as control patients were more likely to be recruited from areas proximal to MS Centers (pediatric MS clinics are tertiary referral centers). The median distance traveled for MS cases and controls was considered as the stratification point (20 miles).

Descriptive statistics were used to explain the number of TRI releases within a 5-mile radius of each participant, the total air releases from these facilities, and the RSEI scores for the counties of residence. Where appropriate, student *t*-tests were used to determine difference in mean values between cases and controls. For those participants who had TRI air releases within 5 miles of their residence, air releases were categorized into quartiles. Logistic regression was used to determine the odds for having pediatric MS in areas of higher air releases compared to areas of lower air release.

Results

We included 290 pediatric-onset MS cases and 442 healthy controls with valid U.S. zip codes in the database in this study. Table 1 displays the general characteristics of the study participants. Demographics were comparable between MS cases and healthy controls although MS cases were slightly older ($P = 0.07$) and more were Hispanic compared to healthy controls ($P < 0.001$). Compared to healthy controls, MS cases were more likely to travel longer distances to seek care at the pediatric referral centers (only 26% of cases were within 20 miles of recruiting centers compared to 71% of healthy controls).

NEI comparisons

Final logistic regression models were adjusted for age, ethnicity, secondhand smoke exposure in the home, referral site, and median household income and population density of the county of residence (Table 2).

Total CO emissions were estimated for a total of 54 sources within the NEI dataset. The largest sources of CO emissions were from nondiesel road vehicles, nonroad equipment, fires, and biogenic processes. For study participants who lived within 20 miles of referral centers, an increased odds for pediatric MS was shown with each increasing quartile compared to the lowest reference quartile (OR range~ 3.8–5.5, $P < 0.01$). No differences were seen for participants who reside more than 20 miles from the referral center.

Forty-eight sources contributed to the total emissions of $PM_{2.5}$ with the largest sources consisting of combustion sources, agriculture dust, and unpaved roads. Other large contributors were prescribed fires, wildfires, and electric generation from coal. For the participants near to the referral site, the increase in odds for MS was statistically significant, ranging from four to seven times in the higher emission quartiles ($P < 0.01$). The relationships were not statistically significant for those residing more than 20 miles from a referral site.

SO_2 emissions were totaled from 44 sources, mostly impacted by industrial processes such as cement manufacturing, chemical manufacturing, nonferrous metal industries, and petroleum refineries. Logistic regression models again showed increased odds for pediatric MS only for those living within 20 miles of a recruiting center. Each of the higher quartiles of exposure indicated a three- to fourfold increase in odds for MS compared to the lowest quartile of exposure ($P < 0.01$).

Lead emissions were totaled from 40 sources and the largest emissions were through construction dust, coal electric generation plants, both ferrous and nonferrous industrial processes, and mobile aircraft which still uses leaded gasoline for fuel. The logistic regression analyses indicated that for those living within 20 miles of a referral center, the odds for having pediatric MS increased by

Table 1. Demographics and characteristics of study participants.

	Within 20 miles of recruiting center			More than 20 miles from recruiting center		
	MS cases (*N* = 76)	Healthy controls (*N* = 311)	*P*-value	MS cases (*N* = 208)	Healthy controls (*N* = 126)	*P*-value
Age, years						
Mean (SD)	14.7 (3.4)	13.5 (4.1)	0.018	14.2 (3.3)	14.4 (3.7)	0.590
Female, *N*(%)	48 (63%)	178 (57%)	0.348	131 (63%)	77 (37%)	0.230
Race, *N*(%)						
American Indian or Alaska Native	4 (5%)	3 (1%)	<0.001	4 (2%)	4 (3%)	0.227
Asian	2 (3%)	16 (5%)		10 (5%)	6 (5%)	
Black	14 (18%)	70 (23%)		29 (14%)	7 (6%)	
White	42 (55%)	191 (61%)		141 (68%)	97 (77%)	
Mixed race	4 (5%)	23 (7%)		13 (6%)	6 (5%)	
Unknown	10 (13%)	8 (3%)		11 (5%)	6 (5%)	
Ethnicity, *N*(%)						
Hispanic	28 (37%)	51 (16%)	<0.001	58 (28%)	29 (23%)	0.346
Non-Hispanic	45 (59%)	250 (80%)		143 (69%)	95 (75%)	
Unknown	3 (4%)	10 (3%)		7 (3%)	2 (2%)	
Median household income, County of Residence						
Mean (SD)	$65,618	$64,978	0.758	$59,259	$60,572	0.445
Time at residence, years						
Mean (SD)	5.6 (4.6)	6.4 (4.7)		6.6 (4.5)	6.1 (4.4)	0.472
Population density[1], County of Residence						
Mean (SD)	3043 (4140)	3877 (5894)	0.244	3374 (10522)	881 (3209)	0.010
Disease duration, years						
Mean (Range)	0.5 (0.7)			0.5 (0.8)		

[1]Total population count of the county divided by the total land area of the county in square miles.

5–10 in the upper emissions quartiles compared to the lowest emissions quartile ($P < 0.01$).

The relationships between the other pollutants (CO_2, NOx, PM_{10}, and VOCs) and the odds for MS were not statistically significant.

Toxic release inventory and RSEI scores

Out of all participants, 217 of the MS cases (75%) and 321 of the healthy controls (73%) lived within 5 miles of at least one TRI reporting site (Table 3). The average number of chemical releases occurring within the 5 mile radius was similar between cases and controls, and total releases ranged from 1 to 580 releases in 2014. The total pounds of stack air releases by these facilities was significantly higher near MS cases where sites reported over 81,000 tons of stack air releases compared to a little over 35,000 tons near healthy controls ($P = 0.002$). Average fugitive air releases, which do not occur through a confined system for air release, were also higher in those facilities near MS cases, although the difference was not statistically significant at the 0.01 level ($P = 0.057$).

The average RSEI score for MS cases and healthy controls was not significantly different (Table 3). However, when stratifying by proximity to referral site, the average RSEI score for cases was almost five times the average score of the healthy controls ($P < 0.001$) for those living within 20 miles of the referral centers (data not shown). The values were not significantly different for those living outside the 20 mile radius.

Discussion

We showed that of several air constituents examined, four showed strong associations with pediatric MS when compared to healthy controls for those participants who lived within 20 miles of a referral center. Emissions of CO, $PM_{2.5}$, SO_2, and lead were all significantly related to higher odds for pediatric MS in the upper quartiles of emissions compared to the lowest quartile of emissions.

Although MS cases and controls resided near a similar number of TRI sites on average, MS cases lived near TRI sites which produced significantly higher stack air releases than healthy controls ($P = 0.002$). The proximity of these TRI sites may contribute to the increased odds for MS demonstrated when comparing higher levels of emissions for participants close to referral centers. Confirmations by the worsening RSEI score among the group helped

Table 2. Quartiles of air constituents and the odds for pediatric multiple sclerosis, stratified by proximity to recruiting center and adjusted for age, ethnicity, median household income, population density, and secondhand smoke exposure at home.

	Number HC/MS	Within 20 miles OR (95%CI)	More than 20 miles, OR (95%CI)
Carbon monoxide (CO), tons			
Reference (<35,609)	105/79	-	-
2 (35,609–62,903)	107/72	5.11 (1.76, 14.8)[1]	0.59 (0.32, 1.11)
3 (62,903–136,625)	92/87	5.45 (1.80, 16.5)[1]	0.88 (0.44,1.77)
4 (≥136,625)	138/52	3.85 (1.34, 11.1)[1]	0.51 (0.21, 1.24)
Carbon dioxide (CO_2), tons			
Reference (<1,899,668)	96/88	-	-
2 (1,899,668–2,872,181)	115/66	0.55 (0.19, 1.66)	0.73 (0.39, 1.39)
3 (2,872,181–6,248,662)	91/76	1.05 (0.38, 2.85)	0.86 (0.42, 1.74)
4 (≥6,248,662)	140/60	0.92 (0.36, 2.35)	0.69 (0.27, 1.76)
Nitrogen oxides (NOx), tons			
Reference (<8257)	92/95	-	-
2 (13,287–8527)	121/51	0.48 (0.14, 1.65)	0.86 (0.42, 1.74)
3 (24,169–13,287)	102/88	1.28 (0.41, 4.00)	0.98 (0.51, 1.88)
4 (≥24,169)	127/56	0.73 (0.23, 2.35)	0.87 (0.39, 1.94)
Sulfur dioxide (SO_2), tons			
Reference (<377)	113/69	-	-
2 (377–1314)	98/86	4.06 (1.42, 11.1)[1]	0.74 (0.41, 1.35)
3 (1314–5632)	98/82	3.99 (1.54, 10.4)[1]	1.40 (0.66, 2.94)
4 (≥5632)	133/153	3.14 (1.13, 8.72)	0.76 (0.35, 1.65)
Particulate matter (PM_{10}), tons			
Reference (<5888)	88/61	-	-
2 (12,251–5888)	124/91	1.32 (0.52, 3.36)	1.29 (0.72, 2.29)
3 (23,065–12,251)	114/67	1.88 (0.73, 4.81)	1.89 (0.93, 3.85)
4 (≥23,065)	116/71	1.29 (0.48, 1.24)	1.48 (0.76, 2.87)
Fine particulate matter ($PM_{2.5}$), tons			
Reference (<1874)	120/59	-	-
2 (3340–1874)	93/86	6.03 (2.15, 16.9)[1]	1.13 (0.63, 2.04)
3 (5997–3440)	105/73	7.53 (2.69, 21.1)[1]	1.42 (0.72, 2.82)
4 (≥5997)	124/72	3.96 (1.42, 11.1)[1]	1.36 (0.65, 2.86)
Volatile organic compounds (VOCs)			
Reference (<13,358)	107/59	-	-
2 (13,358–21,200)	105/84	3.45 (1.18, 10.1)	1.33 (0.64, 2.77)
3 (21,200–41,010)	109/82	4.88 (1.89, 12.6)	0.58 (0.31, 1.11)
4 (≥41,010)	121/65	2.48 (0.73, 8.36)	0.64 (0.31, 1.31)
Lead, pounds			
Reference (<0.167)	110/68		
2 (0.167–0.440)	90/98	10.1 (3.3, 30.7)[1]	0.97 (0.52, 1.81)
3 (0.440–1.10)	114/61	5.37 (1.85, 15.6)[1]	0.43 (0.22, 0.82)
4 (≥1.10)	128/63	6.16 (2.10, 18.1)[1]	0.69 (0.30, 1.60)

[1]Bonferoni adjusted significance ($P < 0.01$).

distinguish whether the nearby stack releases did actually present health risks. The difference in average RSEI score between MS cases and controls living near referral centers indicates that MS cases were more likely to live in a higher risk environment based on chemicals released from TRI facilities close to their areas of residence.

Our findings are consistent with several adult MS studies which have shown an association between MS and air constituents including PM_{10}, SO_2, NO_2, and CO. A more recent study using the Nurses' Health Study showed conflicting results, quintiles of PM_{10} and $PM_{2.5}$ were not statistically associated with MS risk.[22] To our knowledge, the current study is the first to have looked at potential sources through industrial output and examine childhood exposure and MS risk. In other adult MS studies, increased exposure to larger particulate matter (PM_{10}) was related to both increased risk for MS in adults[20,23] and MS relapse using hospitalization records.[18,19,24];

Table 3. Comparison of toxic release inventory releases (2014) and county of residence Risk Severity Index Scores between pediatric MS cases and healthy controls.

	MS cases $N = 290$	Healthy controls $N = 442$	*P*-value
Participants with TRI sites within 5 miles of residence, *N* (%)	217 (75%)	321 (73%)	
Number of TRI site with chemical releases, Mean [Range]	20 (44) Range [1–563]	17 (37) Range [1–580]	0.900
Total releases by all sources[2] in lbs for facilities within 5 miles, Mean (SD)	207,672 (41,433)	206,985 (38,713)	0.990
Total stack air releases[3] in lbs for facilities within 5 miles	81,532 (15,732)	35,355 (5772)	0.002[1]
Total fugitive air releases[4] in lbs for facilities within 5 miles	34,293 (11,460)	12,062 (5721)	0.057
Average RSEI score for county of residence, all participants	2733736 (542519)	1750258 (330923)	0.102
Average RSEI score for county of residence, within 20 mi recruiting site	6,188,463 (1,573,489)	1,706,977 (383,796)	<0.001[1]
Average RSEI score for county of residence, more than 20 mi recruiting site	1,501,063 (450,251)	1,857,609 (650,657)	0.6435

[1]Significant at the 0.05 level.
[2]All sources include releases into water, land, and air.
[3]Stack releases are releases from TRI facilities through stacks and confined air release systems.
[4]Fugitive air releases are from unintended releases through building spills and leaks.

however, in the present study the increase in odds for each quartile of PM_{10} was not statistically significant. Furthermore, we showed that fine particulate matter was related to pediatric MS in the three upper quartiles compared to the lowest exposure reference category. The discrepancy in findings potentially points to a more clear definition of the effects of particulate size in MS, since we distinguish fine particles (2.5 μm) from larger particles up to 10 μm.

Particulate matter is created largely from combustion through industry and transportation sources. It consists of a combination of gases, several of which were presented in this study. Our results show that fine particulate matter is significantly related to MS in urban settings. Sources comprised of CO, SO_2, and lead were of specific importance. At present, two main theories hypothesize the biological mechanism behind particulates and neurological and immunological outcomes. First, inhalation of these particles causes a release of proinflammatory cytokines and could contribute to allergic sensitization. This could also lead to oxidative stress and permeability in the epithelial walls allowing access of foreign particles into the blood stream.[2] Furthermore, pollutants might stimulate immune response with activating potentially auto-aggressive T-cells to enter the central nervous system.[25] Second, the inhaled particles could be translocated through the olfactory system and cross the blood–brain barrier. In animal studies, Oberdorster et al. (2004) demonstrated that a significant increase in particles were found in the olfactory bulb following exposure to fine particulates. Furthermore, 2 days following the exposure, an increase in the number of these particles was found in the cerebrum and cerebellum. The authors hypothesized that the translocation of the particles to the central nervous system (CNS) could be through the olfactory mucosa into the cerebral spinal fluid.[26] These translocations have been demonstrated in other animal studies as well which assessed the pathways of various metal compounds.[27,28]

The increased odds for pediatric MS related to increased lead exposure warrants further investigation. Although exposure to lead has been implicated with poor neurocognitive outcomes, little research has examined the potential contribution of lead exposure to MS. A study in Taiwan showed that increased lead in the soil was correlated with a higher incidence of MS (age and gender standardized), but the study was not able to assess other sources of lead exposure. Another study examined the prevalence of MS in relation to a lead smelting plant in Jefferson Country, Missouri. They were unable to find any significant clustering of cases near the smelting plant, but again did not take into account other sources of exposure such as through air or drinking water systems which may exist near the plant. Given our findings, more research should be done which takes into account various exposures of lead from the total environment as in mice exposed to lead acetate, the lead enhanced the immunogenicity of myelin basic protein and glial fibrillary acidic protein, two important neural system proteins.[29]

The strengths of our study include the use of multiple tools to identify potential exposures that are close to the residential location of study participants. The NEI estimates air pollutants using multiple source techniques, which includes large source emissions and smaller more local sources. We were also able to adjust for variables which may confound the relationships between air pollution and MS such as tobacco smoke exposure in the home and median income of the county of residence. Adjusting for proximity to the recruiting center allowed us to better compare our study participants who were in more urban settings compared to those in more suburban

and rural settings. Our results indicate that the odds for MS increased in the more urban settings with increased levels of air pollution.

Our study has limitations. Environmental data from the NEI were utilized from the 2014 analysis. Although the NEI is a comprehensive estimate from several exposure sources, we had to assume that the exposures in 2014 were similar to those in other years. EPA trend data have shown that particulate matter concentration has slightly decreased since 2000, but the decrease slowed between 2010 and 2014 when participants were diagnosed.[30] Also, the environmental sources for the NEI and RSEI were only estimated at the county level, limiting detailed exposure estimates; however, both measures account for a comprehensive list of potential exposures, rather than one point source measure, which provides a strong estimate of what a person would be exposed to within their neighborhood. Using GIS analysis, we were also able to analyze TRI facilities that were in close proximity to the study participants, which helped look at environmental exposures which were closer to their residences. Finally, we acknowledge that some referral bias may be present with the participants in this study, however, with the rarity of MS in children, population-based studies would be challenging.

Conclusions

Our findings of increased odds for pediatric MS in regions with higher $PM_{2.5}$ and acidic gases contribute to the increasing number of associations between air pollutants and adverse health outcomes.

Author contributions

All coauthors contributed to acquisition of the data and editing of the manuscript. Dr. Lavery conceptualized and designed the analysis for this study, drafted the initial manuscript and submitted the final manuscript. Drs. Waldman, Waubant, and Casper contributed to the conception and design of the analysis for this study.

Conflict of interest

The authors have no conflicts of interest for the current article. Dr. Bianca Weinstock-Guttman has received grant support from Biogen Idec, Teva Neuroscience, EMD Serono, Novartis, Genzyme & Sanofi and Genentech, Celgene and Mallinckrodt Pharmaceuticals, Inc. Dr. Benjamin Greenberg received grant support from Biogen, Acorda, Chugai, Medimmune, Genentech, NIH, Guthy Jackson Charitable Foundation, and PCORI. Dr. Amy Waldman received funding from the NIH-NINDS, Biogen, and foundation support. The remaining authors have no disclosures to report.

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