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Original Contribution

Metal Emissions and Urban Incident Parkinson Disease: A Community Health Study of Medicare Beneficiaries by Using Geographic Information Systems

Allison W. Willis, Bradley A. Evanoff, Min Lian, Aiden Galarza, Andrew Wegrzyn, Mario Schootman, and Brad A. Racette*

* Correspondence to Dr. Brad A. Racette, Department of Neurology, School of Medicine, Washington University, 660 South Euclid Avenue, Campus Box 8111, St. Louis, MO 63110 (e-mail: racetteb@neuro.wustl.edu).

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Parkinson disease associated with farming and exposure to agricultural chemicals has been reported in numerous studies; little is known about Parkinson disease risk factors for those living in urban areas. The authors investigated the relation between copper, lead, or manganese emissions and Parkinson disease incidence in the urban United States, studying 29 million Medicare beneficiaries in the year 2003. Parkinson disease incidence was determined by using beneficiaries who had not changed residence since 1995. Over 35,000 nonmobile incident Parkinson disease cases, diagnosed by a neurologist, were identified for analysis. Age-, race-, and sex-standardized Parkinson disease incidence was compared between counties with high cumulative industrial release of copper, manganese, or lead (as reported to the Environmental Protection Agency) and counties with no/low reported release of all 3 metals. Parkinson disease incidence (per 100,000) in counties with no/low copper/lead/manganese release was 274.0 (95% confidence interval (CI): 226.8, 353.5). Incidence was greater in counties with high manganese release: 489.4 (95% CI: 368.3, 689.5) (relative risk = 1.78, 95% CI: 1.54, 2.07) and counties with high copper release: 304.2 (95% CI: 276.0, 336.8) (relative risk = 1.1, 95% CI: 0.94, 1.31). Urban Parkinson disease incidence is greater in counties with high reported industrial release of copper or manganese. Environmental exposure to metals may be a risk factor for Parkinson disease in urban areas.

copper; heavy metal poisoning, nervous system; incidence; lead; manganese; Parkinson disease; risk; urban population

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; IR, incidence ratio; RR, relative risk.

Parkinson disease is a common neurodegenerative disease with a suspected environmental cause in the majority of cases. Much research has focused on agriculture-related exposures, with findings of increased Parkinson disease risk attributable to pesticide exposure and proximity to pesticide-treated land (1). However, few studies have focused on the risks to people living in urban areas. A recent study found that most Medicare beneficiaries with Parkinson disease live in a metropolitan area and that Parkinson disease is nonrandomly distributed in the United States, with clustering of cases in the Midwest and East (2). The urban areas of these regions contain the majority of metal-emitting facilities in the United States. We therefore sought to investigate the risk of Parkinson disease attributable to urban metal emissions.

The metals chosen for this study—copper, lead, and manganese—have been associated with injury to some of the same neuronal pathways that are thought to be involved in Parkinson disease (3). Parkinsonism is a common feature of Wilson disease, characterized by copper accumulation in the basal ganglia. Copper dyshemostasis has also been demonstrated on laboratory investigation of Parkinson disease patients (4). Manganese is a basal ganglia toxin also associated with parkinsonism (5–8). A decreased ability to clear manganese from the body has been associated with progressive, levodopa-responsive parkinsonism (9), and increased

dietary manganese has been reported in patients with Parkinson disease (10). However, the role of manganese in the pathogenesis of Parkinson disease is controversial (11). Lead is a well-described neurotoxin with multiple clinical phenotypes, including parkinsonism in those exposed to lead compounds (12, 13). Finally, copper, lead, and manganese have been shown in vitro to accelerate or induce formation of alpha synuclein fibrils, the principle component of Lewy bodies that are the pathologic hallmark of Parkinson disease (9, 14).

Although there is reasonable evidence that exposure to copper, manganese, and lead is associated with the development of atypical parkinsonism syndromes, the data on metal exposure and idiopathic Parkinson disease are less clear. One study of the regional variation in Parkinson disease death rates found that the rate in areas with copper-processing industries was higher than that in areas without copper industries (15). Similarly, a case-control study investigated occupational metal exposure and found a higher risk of Parkinson disease in those exposed to copper, manganese, lead plus copper, and lead plus iron, but the number of subjects studied was small (16).

Most Parkinson disease patients do not work in metal (or agricultural) industries. Therefore, nonoccupational, passive community-level exposures are likely critical if metals play a role in Parkinson disease pathogenesis or alter risk in susceptible individuals. In this study, we used publicly available Environmental Protection Agency emissions data to test the hypothesis that living in an urban area with high industrial metal emission is associated with a higher risk of Parkinson disease.

MATERIALS AND METHODS

This study was approved by the Human Studies Committee at the Washington University School of Medicine and by the Centers for Medicare and Medicaid Services.

Study population

This study utilized Medicare research-identifiable files (17) that contain individual-level data on Medicare benefit recipients including *International Classification of Diseases,* Ninth Revision (ICD-9), codes, date of birth, race, sex, county, and zip code of residence. The study population included all Medicare part A beneficiaries living in the United States in the year 2003. We selected those who had been enrolled in Medicare part A since 1995 and resided in the same county at that time, hereafter referred to as ''nonmobile.'' From these, Parkinson disease cases were identified by ICD-9 code 332.0 (paralysis agitans), with incident Parkinson Disease cases further defined as those who had no Parkinson disease claims for 2 years prior to the incident date. Those beneficiaries who also had diagnoses of ''secondary parkinsonism'' (ICD-9 code 332.1) or ''other degenerative diseases of the basal ganglia'' (ICD-9 code 333.0) were excluded. Individuals with race declarations of ''Native American'' or ''other'' and those with missing data were not included because of small numbers of subjects or demographic ambiguity.

To designate a case as living in an ''urban'' county, we applied the US Department of Agriculture's Rural-Urban Continuum Code classification system, which defines rurality by absolute population and classifies each county in the United States by degree of rurality in a rank order fashion by using a rigorous 9-tier scale from a population less than 2,500 (''completely rural'') to a population greater than 1 million (''completely urban'') (18). Beneficiaries residing in a metropolitan county across the United States with greater than 250,000 people were included in this study, hereafter referred to as ''urban.'' Nonmetropolitan counties adjacent to urban centers, such as suburbs, were excluded because they may have only been recently urbanized and are more likely to be proximal to agricultural areas.

Metal emission data

The Toxic Release Inventory is a publicly available Environmental Protection Agency database that contains detailed information on selected chemical releases and waste management activities reported annually. This database was created in response to the Emergency Planning and Community Right-to-Know Act that was enacted in 1986. Facilities that meet release thresholds for any of 650 standard chemicals are required to submit detailed waste disposal records. The release threshold for copper, manganese, and lead during the study period (1988–1998) was 10,000 pounds (4,535.92 kg) per year.

We extracted Toxic Release Inventory facility location and onsite metal release data (in pounds) for copper, lead, and manganese for the United States from 1988 to 1998. Cumulative onsite metal release was calculated per county for this 10-year period. For each case, we ended the exposure period 5 years before incident diagnosis to allow for latency in symptom onset and seeking medical attention. Furthermore, a 6-[^{18}F]fluoro-L-dopa positron emission tomography study of a normal volunteer who then went on to develop idiopathic parkinsonism with reduced substantia nigral uptake consistent with Parkinson disease suggests a presymptomatic clinical and normal radiographic period of 3–5 years (19).

''Exposure'' categories based on quartiles of reported metal release were created. The <25th percentile of all 3 metals (corresponding to <100 pounds (<45.36 kg) of metal released) was designated the ''no copper, manganese, or lead'' exposure category, and counties that were in the >75th percentile of total reported metal release for each metal that were also in the <25th percentile for the other 2 metals were designated as ''high copper,'' ''high manganese,'' or ''high lead'' exposure categories. Counties in the >75th percentile of total reported metal release contained the majority of the highest emitting facilities for each metal, and this quartile was compared with the <25th percentile for all 3 metals in order to examine nonlinear trends in Parkinson disease incidence.

Parkinson disease incidence

Age-, sex-, and race-standardized Parkinson disease incidence was calculated by using nonmobile beneficiaries

Table 1. Neurologist-diagnosed, Incident, Nonmobile, Urban Parkinson Disease Cases and Noncases, US Medicare Beneficiaries, 2003

Characteristic	Incident Cases		Population	
	No.	%	No.	%
Sex				
Males	17,586	50.9	2,685,857	52.3
Females	16,998	49.1	2,452,791	47.7
Race				
White	31,284	90.5	4,732,665	92.1
Black	2,030	5.9	186,430	3.6
Hispanic	824	2.3	111,389	2.2
Asian	446	1.3	108,164	2.1
Age, years				
70–74	4,173	12.1	609,288	11.9
75–79	11,613	33.6	1,561,934	30.4
80–84	10,787	31.2	1,469,318	28.6
≥85	8,011	23.1	1,498,108	29.1
Total persons observed	34,584		5,138,648	
Total person-years observed	276,672		46,247,832	

and nonmobile, neurologist-diagnosed Parkinson disease cases living in high and no metal emission regions. Standardization was performed via the direct method, by using all nonmobile, urban Medicare beneficiaries in the study regions as the standard population. Relative risk was estimated by the standardized incidence ratio that was calculated according to standard methods by using the incidence in the no/low metal release regions as the reference group. We attempted a confirmatory analysis using hierarchical regression with demographic factors on the first level (with white males as the reference category) and county-level metal exposure category on the second level, with low/no metal output as the reference category. Regression coefficients were converted to odds ratios by using standard methods.

The primary analyses in this study were performed on cases that were diagnosed by a neurologist. Each patient's encounter in our data set contained the unique physician identification number of the treating physician, as well as his or her specialty, allowing us to extract those diagnoses made by a neurologist. Although this allows for greater diagnostic certainty, it can also introduce referral bias, particularly for studies of Parkinson disease (20). We therefore performed identical incidence and relative risk calculations using cases diagnosed by either a neurologist or internist for comparison, and we report those data also. These 2 specialist types generated greater than 95% of all Parkinson disease diagnosis claims in the study regions. We also investigated whether socioeconomic factors could potentially influence any findings by comparing educational level, marriage rates, income, home value, and poverty rates among study regions, using US Census data collected during the study period.

A geographic information system was used to spatially link the environmental and clinical data by county, allowing quantitative analysis of disease behavior in urban areas with high or low metal release.

Statistical analysis

Data manipulation and statistical analysis were performed with SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina), and SPSS, versions 15 and 17 (SPSS, Inc., Chicago, Illinois), software.

RESULTS

Study population demographics

Over 35,000 incident Parkinson disease cases met inclusion criteria in 1,046 counties across the United States. Whites comprised the majority of cases (89.3%), followed by blacks (5.9%), Hispanics (2.4%), and Asians (1.3%). The crude incidence ratios with whites as the reference group suggested a lower incidence among Asians and blacks but a similar rate among Hispanics, similar to our previous nationwide study of 450,000 Parkinson disease cases in the United States: blacks (incidence ratio (IR) = 0.60, 95% confidence interval (CI): 0.58, 0.63); Asians (IR = 0.62, 95% CI: 0.57, 0.68); and Hispanics (IR = 1.11, 95% CI: 1.04, 1.19) (2). The age-adjusted incidence in males was greater than that in females, similar to previous studies, with a sex incidence ratio of 142 males per 100 females (21). The study population characteristics are summarized in Table 1.

Although all study subjects had the same insurance and, theoretically, the same financial access to physician's services, marked differences in community socioeconomic profiles may be associated with dissimilar health-care–seeking behaviors. By use of US Census data collected during the study period, the following socioeconomic factors did not vary significantly among study regions: percentage with a high school education, percentage married (for either men or women), median household income, median home value, or percentage of individuals below the poverty line (2-sided $P > 0.05$) (22). There was also no apparent trend of lower socioeconomic status between low- and high-metal categories (Table 2).

Facility data

Reportable copper-, manganese-, and lead-releasing facilities were present in every state during the study period except Alaska (which had reportable lead release only). Twenty-six industries according to the North American Industry Classification System had reportable copper, manganese, or lead release (Table 3). The mean reported onsite metal release during the study period was 3.18 metric tons/year for copper, 1.22 metric tons/year for lead, and 1.90 metric tons/year for manganese.

Parkinson disease incidence in urban counties with metal-emitting facilities

The annual age-, race-, and sex-standardized Parkinson disease incidence in urban counties with high reported

Table 2. Population Socioeconomic Characteristics According to 2000 US Census Data Compared by Metal Exposure Category Region, US Medicare Beneficiaries, 2003

Socioeconomic Variable	Cumulative Metal Exposure Category				*P* Value
	Low Copper, Lead, and Manganese	High Copper	High Manganese	High Lead	
High school graduates, %	81.32	83.69	80.21	80.14	0.26
Married males, %	56.48	57.27	57.74	56.85	0.90
Married females, %	51.67	51.56	52.30	52.20	0.97
Median household income, dollars[a]	43,701.60	47,044.35	40,617.43	40,696.09	0.07
Median home value, dollars[a]	129,176.74	119,426.21	96,475.00	131,272.09	0.64
Individuals below poverty line, %	11.75	9.62	11.29	13.21	0.08

[a] In 2000 US dollars.

copper, manganese, or lead release was greater than in urban counties with no or low reported release of all 3 study metals (Table 4). The risk of Parkinson disease was elevated in counties with high reported manganese release (relative risk (RR) = 1.78, 95% CI: 1.54, 2.07). Counties with high reported copper (RR = 1.11, 95% CI: 0.94, 1.31) or lead (RR = 1.04, 95% CI: 0.88, 1.23) release did not show an elevation in Parkinson disease risk. Hierarchical regression analysis produced odds ratios that were in the same general direction of the primary analysis but with wide confidence intervals that spanned unity.

A sensitivity analysis of Parkinson disease cases that were diagnosed by either a neurologist or internal medicine specialist revealed a similar pattern of increased Parkinson disease incidence and elevated relative risk in each of the high metal regions compared with the reference group with no/low metal regions. However, the magnitude of difference in incidence and, subsequently, relative risk was more pronounced: for high reported release of manganese (RR = 2.50, 95% CI: 2.23, 2.82); for copper (RR = 1.64, 95% CI: 1.45, 1.86); and for lead (RR = 1.41, 95% CI: 1.24, 1.61). The magnitude and direction of the difference in incidence were also similar to our primary data when analyses were performed without regard to mobility status. Finally, although we chose to report the results using metal emission data ending 5 years prior to the incident date to account for possible disease latency, analysis using cumulative metal emission data from 1995 to 2003 did not change the direction or lessen the magnitude of our results.

DISCUSSION

In this study, we demonstrated a relation between community metal release and urban Parkinson disease rates, using over 35,000 nonmobile, neurologist-diagnosed incident Parkinson disease cases. Our data suggest that prolonged residence in an urban county with high long-term copper, manganese, or lead release is associated with increased Parkinson disease incidence and modestly increased risk of Parkinson disease. These data also demonstrate that there are significant differences in Parkinson disease incidence between races by using a nonmobile, neurologist-confirmed urban Parkinson disease study population. Interestingly, the data are strongest for manganese, which has been shown to affect basal ganglia pathways not primarily involved in Parkinson disease. Although the classic clinical phenotypes of high-level occupational manganese exposures appear to be distinct from Parkinson disease (7, 23), it is possible that chronic, lower-level residential exposures may be associated with a different clinical phenotype in susceptible individuals. Our primary data do not support a strong relation between incident Parkinson disease and industrial lead emissions; however, lead may still be a relevant basal ganglia neurotoxin and risk factor for Parkinson disease. Unlike manganese and copper, environmental lead exposure has multiple potential sources, such as lead paint, consumer products, and contaminated soil and water, that were not quantified in this study and may confound our results.

The potential role of heavy metals, including copper, lead, and manganese, in the pathophysiology of Parkinson disease is supported by multiple studies demonstrating a role of these metals in tissue models of Parkinson disease. Some metal ions (including copper and manganese) accelerate the fibrillation of alpha-synuclein, excessive aggregation of which is a critical pathogenic event in numerous neurodegenerative diseases (24, 25). Furthermore, these metals have also been shown to increase the binding of herbicides (another important potential Parkinson disease risk factor group) to alpha-synuclein and to have a synergistic effect on alpha-synuclein when coupled with pesticides (26). Although the molecular basis of neuronal death in Parkinson disease is yet unknown, many studies support a critical role of oxidative stress resulting in dopaminergic neuronal degeneration (27, 28). Consequently, oxidation-reduction active metal ions, such as copper and manganese, are compelling etiologic agents to increase free radical production or to initiate a cascade of cellular reactions leading to dopaminergic cell death (29).

An important strength of this study is that it focuses on passive, community-level metal exposures, which are likely the most important neurotoxic exposures, given the marked heterogeneity in occupational and other demographic factors seen in Parkinson disease patients (1, 30). In addition, our study investigated the relation between incident Parkinson disease and toxin releases throughout the entire United States, as opposed to most previous studies of Parkinson disease prevalence or case-control studies conducted in single Parkinson centers. We chose to use a nonmobile, long-term resident study population to minimize

Table 3. Cumulative Onsite Copper, Manganese, or Lead Release Reported to the US Environmental Protection Agency, 1988–1998

TRI NAICS Code (Industry Description)	Cumulative Reported Onsite Metal Release, Metric Tons		
	Copper	Lead	Manganese
311 (food/beverages/ tobacco)	722.2	59.1	96.1
313 (textiles)	7.2	69.4	0.1
315 (apparel)	0.00	No facilities	No facilities
316 (leather)	0.9	No facilities	4.5
321 (wood products)	17.1	6.0	3.8
322 (paper)	15.9	1.4	2,193.1
323 (printing and publishing)	77.8	2.5	0.5
324 (petroleum)	32.7	196.8	189.5
325 (chemicals)	1,362.1	1,192.2	22,141.1
326 (plastics and rubber)	108.4	31.6	3.0
327 (stone/clay/glass)	79.4	284.2	764.2
3273 (cement)	7.3	1,069.8	1,373.3
331 (primary metals)	73,190.8	35,041.4	83,602.2
332 (fabricated metals)	1,841.6	1,140.7	4,732.3
333 (machinery)	657.3	111.7	1,493.5
334 (computers/ electronic products)	285.2	112.5	14.0
335 (electrical equipment)	966.0	2,493.0	466.3
336 (transportation equipment)	946.6	318.2	1,449.0
337 (furniture)	9.0	2.9	19.3
339 (miscellaneous manufacturing)	112.4	44.4	33.4
562 (hazardous waste)	1,549.9	11,074.0	3,759.1
2121 (coal mining)	0.0	0.0	0.7
2122 (metal mining)	250,837.2	399.8	5,364.5
2211 (electric utilities)	354.3	193.2	975.2
4246 (chemical wholesalers)	0.1	0.0	0.2
4247 (petroleum bulk terminals)	0.0	0.0	0.0
No TRI NAICS code	635.0	527.1	226.2

Abbreviations: NAICS, North American Industry Classification System; TRI, Toxic Release Inventory.

Table 4. Age-, Race-, and Sex-standardized Annual Incidence (per 100,000) of Nonmobile Parkinson Disease Cases Living in Urban Counties With No Versus High Reported Copper, Manganese, and Lead Metal Release, US Medicare Beneficiaries, 2003

Exposure Category	Incidence	95% Confidence Interval	Relative Risk	95% Confidence Interval
No reported copper, manganese, or lead[a]	274.0	226.8, 353.5		
High reported copper release	304.2	276.0, 336.8	1.11	0.94, 1.31
High reported manganese release	489.4	368.3, 689.5	1.78	1.54, 2.07
High reported lead release	285.7	249.3, 337.5	1.04	0.88, 1.23

[a] Less than 100 pounds (45.36 kg) of reported copper, manganese, or lead release.

the likelihood that a subject may have moved in or out of an exposed county and minimized ''exposure'' misclassification. Similarly, we used cumulative metal emissions as a surrogate for long-term metal exposures that are likely more objective than subject-reported residential exposures to neurotoxins. Furthermore, we included Parkinson disease cases diagnosed by a neurologist, similar to many previous Parkinson disease environmental epidemiology studies, to minimize disease misclassification. However, the direction of the relation between Parkinson disease incidence and community copper, lead, or manganese release persists when nonneurologist diagnoses are included in the analysis, suggesting that these results are not likely due to selection or referral bias. Finally, the similarity of socioeconomic factors including education, income, and property values between metal-emitting and -nonemitting areas further supports the hypothesis that metal emissions, and not population demographic differences, may be a key factor accounting for the difference in the observed Parkinson disease rates.

There are several limitations to this study, similar to those encountered by previous Parkinson disease environmental risk studies. Most importantly, we do not have individual biomarker-proven exposure data, so other risk factors associated with living in these areas may explain the findings. We also used a basic exposure metric of metals released instead of direct environmental metal measurements. All individuals in a given county were assigned to the same exposure category, without regard for proximity to metal-emitting facilities, which could cause individual variation in actual exposure. Moreover, our methods assume that exposure within a building, neighborhood, county, or region is relatively homogeneous, but the degree to which these exposures reflect actual individual exposures is unclear. Finally, although we adjusted for known confounders, the possibility of yet undiscovered confounding variables that increase the likelihood of both living in a high emission area and being diagnosed with Parkinson disease may exist. These limitations would likely attenuate the observed exposure-risk relation, suggesting that the true elevation in disease risk may actually be higher than that found in this study. Future studies incorporating individual-level residential data may allow for more exact exposure assessments.

Although diagnosis by a neurologist should certainly allow for acceptable case identification, Parkinson-plus syndromes, such as multiple system atrophy or progressive supranuclear palsy, may initially resemble idiopathic Parkinson disease. However, these diseases are quite rare (31) and would be unlikely to alter our results significantly. Although there is some degree of diagnostic uncertainty in any clinical diagnosis, the Centers for Medicare and

Medicaid require neurologists to provide proof of completion of a neurology residency and valid state medical licensure to provide services as a neurologist. The American Academy of Neurology considers recognition of idiopathic Parkinson disease as a core competency. Nonetheless, misdiagnosis of atypical parkinsonism as Parkinson disease is a possible bias if substandard neurologists provide care more often to those living in high metal emission areas, independent of community wealth and education (which did not differ across exposure categories).

In conclusion, we present data suggesting that long-term residence in counties with high cumulative industrial copper or manganese release is associated with an increased Parkinson disease incidence and modestly increased Parkinson disease risk. Future studies with more sophisticated environmental heavy metal measurements, exposure modeling, and case confirmation may allow us to clarify the proportion of Parkinson disease risk conferred by passive metal exposure. Furthermore, the role of heterogeneous toxin exposures (metal-metal, metal-pesticide) is likely critical to the pathogenesis of Parkinson disease and most likely will also be the subject of future studies.

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Author affiliations: Department of Neurology, School of Medicine, Washington University, St. Louis, Missouri (Allison W. Willis, Aiden Galarza, Andrew Wegrzyn, Brad A. Racette); and Department of Internal Medicine, School of Medicine, Washington University, St. Louis, Missouri (Bradley A. Evanoff, Min Lian, Mario Schootman).

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