



ENVIRONMENTAL HEALTH PERSPECTIVES

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<http://dx.doi.org/10.1289/ehp.1307218>

Received: 13 June 2013

Accepted: 3 June 2014

Advance Publication: 6 June 2014

A Prospective Analysis of Airborne Metal Exposures and Risk of Parkinson Disease in the Nurses Health Study Cohort

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Running title: Airborne Metals and Parkinson Disease

Acknowledgments: This work was supported by K01 (1K01ES019183) from the NIEHS/NIH to Natalia Palacios Dr. Schwarzschild receives funding from the DoD (W81XWH-11-1-0150), Dr. Ascheiro receives funding from the NIH, Dr. Gao receives funding from the NIH (NIH/NINDS grant 5R01NS062879-03) and Dr. Laden receives funding from the NIH (NIEHS R01 ES017017 and NCI P01 CA87969). The authors would like to acknowledge Leslie Unger for administrative support and Dr. Eilis O'Reilly for statistical advice.

Competing financial interests: none

Abstract

Background: Exposure to metals has been implicated in the pathogenesis of Parkinson disease (PD).

Objectives: We sought to examine in a large prospective study of female nurses whether exposure to airborne metals was associated with risk of PD.

Methods: We linked the Environmental Protection Agency's Air Toxics tract-level data with the Nurses Health Study, a prospective cohort of female nurses. Over the course of 18 years of follow-up from 1990 to 2008, we identified 425 incident cases of PD. We examined the association of risk of PD with the following metals that were part of the first EPA collections in 1990, 1996, and 1999: arsenic, antimony, cadmium, chromium, lead, manganese, mercury and nickel, as well as total (sum) metal exposure. To estimate Hazard Ratios (HRs) and 95% confidence intervals (CI), we used the Cox Proportional Hazards model adjusting for age, smoking, and population density.

Results: In adjusted models, the HR for the highest compared with the lowest quartile of each metal ranged from 0.78 (95% CI: 0.59, 1.04) for chromium to 1.33 (95% CI: 0.98, 1.79) for mercury.

Conclusions: Overall, we found limited evidence for the association between adulthood ambient exposure to metals and risk of PD. The results for mercury need to be confirmed in future studies.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, after Alzheimer's Disease (Lang and Lozano 1998). Exposure to metals has been implicated in the pathogenesis of PD. Manganese intoxication is recognized as a cause of parkinsonism at high levels of exposure (Jankovic 2005; Guilarte 2010). However, the pathology of manganese intoxication is distinct from PD (Jankovic 2005) and the causal association of exposure to manganese with PD continues to be debated (Fryzek et al. 2005; Fored et al. 2006; Mortimer et al. 2012). For example, a study that compared the food habits of 250 patients and 388 controls found that a high intake of iron, combined with a high manganese intake, was significantly associated with PD (Powers et al. 2003). Another study in Quebec, Canada, a slightly higher, although not statistically significant risk of PD was observed among participants with occupational exposure to manganese, iron and aluminum (Zayed et al. 1990). At the same time, many studies of manganese and PD have been null (Hertzman et al. 1994; Seidler et al. 1996; Semchuk et al. 1993; Vieregge et al. 1995).

There has also been some evidence of onset of PD following occupational (Kuhn et al. 1998; Coon et al. 2006) as well as non-occupational (Weisskopf et al. 2010) exposure to high levels of lead. Increased brain iron levels have been found in PD patients by some investigators, although this has not been confirmed in all studies (Logroscino et al. 2006; Logroscino et al. 2008; Logroscino et al. 1998). Some, but not all studies have reported positive associations between PD and exposure to copper (Gorell et al. 1997). Furthermore mercury measured in blood, urine and hair has been positively associated with PD (Ngim and Devathanan 1989).

To our knowledge, to date only two epidemiologic studies have assessed exposure to airborne metals and PD in non-occupational cohorts. A case-control study in Canada by Finkelstein et al.

reported a modest association between airborne manganese and PD (Finkelstein and Jerrett 2007). In a study of US Medicare beneficiaries, Willis et al. used county-level data from the Environmental Protection Agency (EPA) Toxic Release Inventory on copper, lead, and manganese and found significant associations between residing in urban counties with high levels of release of manganese and PD (Willis et al. 2010).

In this study, we examined the association between Census tract-level air emissions of antimony, arsenic, cadmium, chromium, lead, manganese, mercury, and nickel, as well as total (sum) metal exposure, and risk of PD in a large prospective cohort of female nurses.

Methods

Study population

This study was conducted using data from the Nurses Health Study (NHS), an ongoing prospective cohort of female nurses initiated in 1976 and followed with biennial questionnaires collecting residential location and information on lifestyle factors and health outcomes. Residential locations were available throughout follow-up only, they were not available during childhood in this cohort. At the initiation of the cohort in 1976, the 121,701 study participants were between 30 and 55 years of age and resided in 11 states (California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New York, New Jersey, Pennsylvania, Ohio, and Texas). For each follow-up cycle, the rate of follow up has been above 90%. State, county, and Census tract of residence was derived from the residential address updated every two years. Detailed description of the cohort is provided elsewhere (Colditz et al. 1997). Data on airborne metal exposures were available for 97,430 women at baseline in 1990.

PD ascertainment

A question regarding PD onset and diagnosis was first asked in 1994 and has been asked every 2 years since. The ascertainment method for PD in this study has been described in detail previously (Ascherio et al. 2001). Briefly, each study participant who reports PD is sent a written request for consent to contact her treating neurologist (or internist if the neurologist is not available). Once consent is provided by the participant, the doctor is contacted for a copy of the medical record and asked to complete a questionnaire documenting the likelihood of the diagnosis of PD. The medical records are reviewed by a neurologist movement disorder specialist (M.A.S.) who is blinded to the exposure status of the participant. We considered confirmed cases to be participants with medical record evidence of a final diagnosis of PD by a treating neurologist, or medical record evidence of at least two cardinal signs of PD (bradykinesia, rigidity, or rest tremor) in the absence of information suggesting an alternate diagnosis. Women who self-reported a PD diagnosis before 1990, or had evidence in their medical record indicating onset before 1990, were excluded from the study.

Airborne metals exposure ascertainment

We used data on antimony, arsenic, cadmium, chromium, lead, manganese, mercury, and nickel exposure from the National Air Toxics Assessments (NATA)(NATA) NATA includes data on emissions of hazardous air pollutants (HAPs) from a variety of sources including major stationary sources (such as factories), other sources (such as dry cleaners, small manufacturers, and wildfires) and traffic sources (cars, boats). The EPA created this inventory by, first, drawing on data from state and local air pollution inventories, and if those were not available, on existing databases related to EPA's air toxics regulatory program, followed by the EPA Toxic Release inventory. NATA uses a complex dispersion model, ASPEN, which estimates annual average

annual concentrations of the HAPs for each census tract in the contiguous US and Puerto Rico. The model incorporates information about the rate, location, and height of release; meteorological factors; and pollutant-specific factors such as radioactive decay, deposition, and secondary formation. HAP data were downloaded from the EPA website on June 23, 2010(EPA) and additional archived data were received on compact disc from the EPA. HAPs data from 1990, 1996, and 1999 were available. We linked the HAP data with the NHS, using US Census state, county and tract identifiers. We used updated metal exposure in our analyses: metal values measured in 1990 were assigned for cases with onset prior to 1996, metal measures in 1996 were assigned for cases with onset between 1996 and 2000, and metal measures in 1999 were assigned for cases with onset after 2000. We estimated associations between PD and the following metals available in all years: antimony, arsenic, cadmium, chromium, lead, manganese, mercury and nickel. Although the EPA specifically advises against combining metal concentrations measured at different time periods (EPA), we performed a sensitivity analysis of associations with estimates of cumulative airborne metal exposures based on updated measurements at each time period, which is of interest because of the long pre-clinical phase of PD..

Statistical analyses

We used Cox proportional hazards models adjusted for age in months (crude model), as well as a multivariable model adjusted additionally for smoking (one variable defined as never/past/current and another continuous pack years variable at baseline) and Census tract-level population density (calculated as the number of people in the tract divided by the square miles of the tract, in quartiles) to calculate Hazard Ratios (HRs) for the association between exposure to airborne metals and risk of PD. We also conducted sensitivity analyses further adjusting for tract-level income (quartiles). Person-years of follow-up were calculated from baseline in 1990,

through the end of follow-up (June 30, 2008), death, or date of PD onset, whichever occurred earlier. The relationship between PD onset and metals exposure was examined for each metal individually, coded in quartiles (using cutoffs based on the exposure distribution over the entire study period) or continuously in separate models. Because smoking has been established as protective against PD based in multiple epidemiologic studies,(Hernán et al. 2001) we performed additional analyses stratified by smoking status at baseline (ever vs. never smoker) and tested for interaction between each of the metals and smoking, by using the likelihood ratio test to compare a model that included a product term between smoking (ever/never) and the metal coded as an ordinal variable to a model without such a term. We also conducted additional analyses stratified by population density in 1990, the time of the metal exposure assessment, to examine the potential interaction of rural vs. urban living with the effects of airborne metals. In these analyses, women residing in counties with over 250,000 inhabitants were considered urban dwellers while those in counties with fewer than 250,000 inhabitants were considered rural dwellers.

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA) for all analyses. All analyses were conducted at the 0.05 alpha level and all test were two-sided. P-values for trend test based on linear model through the quartile medians. All members of the NHS provide informed consent. The study was approved by the institutional review of Brigham and Women's Hospital. Informed consent was implied through the return of questionnaires.

Results

Between study baseline in 1990 and end of the study in 2008, we confirmed 425 cases of PD with data available on metal exposures. Table 1 shows the baseline characteristics of the study participants. Age, BMI, and smoking did not differ with quartile of total metal exposure

(constructed as the sum of all metals in the study). Participants residing in Census tracts with the lowest quartile of metal exposure also lived in tracts with the lowest median family income and lowest population density. Metal exposures were highly inter-correlated (Table 2), with Spearman correlation coefficients ranging from 0.38 to 0.68.

Metals exposures were not significantly associated with PD (Table 3) in age adjusted or multivariable (age, smoking and population density) adjusted models. In the main analyses, there was a suggestion of a positive monotonic association with exposure to mercury (the HR comparing to the top quartile of mercury exposure to the bottom quartile was 1.33 (95% CI: 0.98-1.79; p-trend: 0.10).

Because at the census tract level total metal exposure was correlated with income (Table 1), we conducted additional sensitivity analyses adjusted for income. This adjustment did not substantially influence the results (data not shown). The results of sensitivity analyses that used cumulative updating were not significantly different from our primary analysis: mercury was still the only metal that gave a suggestion of an association with PD risk (p-trend = 0.14) in these analyses (data not shown).

In analyses stratified by smoking (Table 4), we did not observe statistically significant effect modification by smoking of associations with any of the metals. Among never smokers we observed a significant increasing risk of PD with higher mercury exposure (HR comparing top to bottom quartile: 1.68; 95% CI: 1.11-1.25; p-trend = 0.04) but not among ever smokers (HR:0.99; 95% CI: 0.63-1.55; p-trend: 0.85), the p for interaction with smoking was not significant (p-int: 0.29). We did not observe evidence of interactions between smoking and any of the other metals in the study.

In analyses stratified by population density (Table 5), we observed a marginally significant interaction for arsenic (p-int: 0.06) consistent with evidence of a negative association among those living in less densely populated counties versus a weak positive association in highly populated counties. For most of the metals in the study, the relative risks among participants living in urban counties were higher than among those living in rural counties, although, none of the other interaction tests were significant. The relative risk was particularly high for mercury exposure among those living in urban counties (HR comparing top quartile of exposure to bottom quartile was 1.84 (95% CI: 1.13-2.99; p-trend: 0.14), although risk was also elevated in the low population density group (HR: 1.32; 95% CI: 0.79-1.29) and the p-value did not indicate an interaction (p-interaction: 0.86)..

Discussion

In this prospective cohort study of female nurses, we did not observe a statistically significant association between EPA HAP modeled concentrations overall and risk of PD. In adjusted models, the HR for the highest compared to the lowest quartiles of each metal ranged from 0.78 (95% CI: 0.59, 1.04) for chromium to 1.33 (95% CI: 0.98, 1.79) for mercury. The association with mercury was stronger in non-smokers as well as among participants living in urban counties.

To our knowledge, to date there have only been two studies of ambient air pollution and risk of PD. In Hamilton, Ontario, in a case-control study designed to examine the association between traffic pollution in general and PD, Finkelstein et al. observed a modest increase in risk of PD among individuals with higher exposure to airborne manganese (Finkelstein and Jerrett 2007). However, this study identified cases using prescription data from a drug registry or a physician diagnosis code from the Ontario Health Insurance Plan, resulting in potential inclusion of

subjects with manganism and not true PD, and thus potentially augmenting the association seen for manganese. In contrast, our study relied on PD cases confirmed through neurologist medical record review.

In a study Willis et al. (Willis et al. 2010) used physician disease codes to identify over 35,000 incident PD cases in a database of 29 Million Medicare beneficiaries of PD and compared the risk of PD among participants living in urban counties with high versus low cumulative industrial release of copper, manganese, or lead based on GIS-derived estimates from the EPA Toxic Release Inventory (TRI). A major advantage of that study was its large sample size. Willis et al found that participants residing in counties with in the highest 25% of manganese release had an almost 80% higher risk of PD compared to those living in the counties with the lowest 25% for lead, copper and manganese release. However, this study relied only on direct emissions data from the EPA TRI as their exposure. As discussed in the Methods, the EPA TRI data contribute to the NATA HAPs data used in our study; however, the NATA data are also supplemented by data from local air pollution inventories and other EPA air toxics databases. The TRI are raw emissions data, while the NATA data used in our study include a dispersion model that accounts for dispersion of air pollution, including across tract and county lines. Thus, the NATA data should provide a more accurate measure of exposure to the metals than the TRI data. Also, the smallest geographic unit in the Willis study was county, while we were able to estimate pollution concentration estimates at the Census tract level. In contrast to Willis et al, we did not observe an association between higher exposure to airborne manganese and risk of PD. Our primary analyses were not restricted to urban or rural areas, but we conducted additional analyses stratified by low vs. high population density (dichotomized in the same way as Willis et al, where counties with over 250,000 inhabitants were considered urban). In our study, for most

metals, the observed HRs associated with metal exposure were higher in the high population density strata than in the low population density strata, although with the exception of arsenic, for which we observed a marginally significant p-interaction of 0.06, none of the other test for interaction were significant. Also, our study included only women, and all the participants were nurses. We cannot therefore exclude the possibility that our results would have been different had our study focused on men or on individuals occupationally exposed to pesticides or other chemicals. An interaction between manganese containing fungicides and paraquat, for example, has been reported in animal models of PD (Thiruchelvam et al. 2000). Likewise, in humans, simultaneous exposure to maneb and paraquat in participants 60 years old or younger was associated with a 4.17 odds of PD, while exposure to either pesticide alone was associated with a 2.27 odds of PD (Costello et al. 2009).

The association between exposure to mercury and PD in the present study is supported by some (Ngim and Devathanan 1989; Seidler et al. 1996), but not all (Wechsler et al. 1991; Semchuk et al. 1993) prior studies. The association with mercury was stronger among never smokers and dwellers of urban counties (with over 250,000 inhabitants). Mercury is a heavy metal, and could contribute to oxidative damage in the substantia nigra, however, other heavy metals, such as iron (Lezak 1995), could also have this effect, so it is unclear why we saw an association with PD with mercury but not other heavy metals in this study.

One limitation of our work is that the levels of airborne metals were not measured directly, but rather were based on linkage with the EPA HAP modeled concentrations. The use of Census tract-level modeled estimates of air pollution may have obscured a true association between airborne metals and PD. Additionally, Parkinson disease is thought to have a long pre-clinical period and thus the ideal measure of exposure would have been a cumulative lifetime exposure

to airborne metals. However, only HAPs measures in 1990, 1996, and 1999 were available, and according to the EPA, it was not advisable to combine the data into cumulative analyses. Thus in our primary analyses, we used exposure from only one time point for each PD case, as appropriate. This could have potentially biased our results. We did however, as mentioned in the methods section, conduct analyses, combining the three separate metals assessments into a cumulative measure, and confirmed that these results did not differ from the results of our primary analyses (data not shown). Also, it is not known how much time the participants spent inside as opposed to outside their homes, and the HAP dataset is only a measure of outdoor exposures. Penetration of outdoor pollutants indoors is possible, but is dependent on the ventilation rates of the individual dwellings.

The strengths of this study include its large size and a long, prospective follow-up, which included a large number of PD cases confirmed through neurologist medical record review. The study area included the whole contiguous United States allowing for a wide range of exposure values for the airborne metals of interest. Among the limitations, our study included only women who were unlikely to be occupationally exposed to metals, pesticides or other toxins that might interact with metals. However, this aspect of our study is also an advantage as this is one of the few studies of airborne metal exposure in a non-occupational cohort.

Conclusion

Overall, we found little evidence that airborne metals exposures were associated with PD in this large prospective cohort of female nurses. There was limited evidence of an association between mercury exposure and PD, particularly among never smokers, and among participants living in counties with populations $\geq 250,000$ persons. The results suggest that exposure to airborne metals is by itself unlikely to be a major cause of PD among US women without occupational exposures

to metals. The lack of association with most metals in this study as well the observed association with mercury needs to be confirmed in future studies.

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Table 1. Age-standardized characteristics at study baseline in 1990 of the 97,430 female study participants by quartile of total metal exposure (n, mean \pm SD, or percentage, as indicated).

Characteristic	Quartile1	Quartile 2	Quartile 3	Quartile 4
Age (years)	57.8 \pm 7.2	57.6 \pm 7.2	57.7 \pm 7.1	58.0 \pm 7.1
Pack years smoking	11.8 \pm 18.1	12.4 \pm 18.5	12.0 \pm 18.4	11.3 \pm 18.0
BMI	25.9 \pm 4.9	25.8 \pm 4.9	25.9 \pm 4.9	25.9 \pm 5.0
Never smoker, %	45	42	43	44
Median tract household income 1990	55211 \pm 9501	66534 \pm 25586	68866 \pm 27274	66096 \pm 27507
Median tract population density 1990 (average persons/square mile)	1450 \pm 3840	2783 \pm 4458	4010 \pm 6770	8008 \pm 15744
Urban dwelling (% living in county with over 250,000 inhabitants)	30	70	80	80

Table 2. Spearman correlations between the metals examined in this study.

Metal	Antimony	Arsenic	Cadmium	Chromium	Lead	Manganese	Mercury	Nickel
Antimony	1.00	0.57	0.52	0.38	0.54	0.54	0.50	0.60
Arsenic		1.00	0.68	0.54	0.66	0.61	0.61	0.62
Cadmium			1.00	0.51	0.64	0.59	0.66	0.58
Chromium				1.00	0.55	0.50	0.44	0.55
Lead					1.00	0.65	0.57	0.57
Manganese						1.00	0.47	0.52
Mercury							1.00	0.58
Nickel								1.00

Table 3. Exposure to individual metal HAPs^a and risk of Parkinson Disease among participants on the Nurses Health Study (N = 97,430), Follow-up 1990-2008, by quartile of each metal exposure.

Metal HAP	Median conc., µg/m³	Person years	Cases	HR (95% CI): age-adjusted	HR (95% CI): fully adjusted^b	p-trend^c
Antimony						
Q1	0.000034	463350	113	1.00 (Ref)	1.00 (Ref)	
Q2	0.000138	450715	104	0.97 (0.74, 1.27)	0.98 (0.75, 1.28)	
Q3	0.000287	444776	104	1.00 (0.76, 1.30)	1.01 (0.77, 1.33)	
Q4	0.000682	426213	104	1.01 (0.77, 1.32)	1.04 (0.78, 1.38)	0.70
Arsenic						
Q1	0.000073	457965	117	1.00 (Ref)	1.00 (Ref)	
Q2	0.000173	494663	94	0.84 (0.64, 1.10)	0.86 (0.65, 1.13)	
Q3	0.000293	447912	112	1.01 (0.78, 1.30)	1.03 (0.78, 1.37)	
Q4	0.000610	424514	102	0.94 (0.72, 1.23)	0.95 (0.71, 1.27)	0.95
Cadmium						
Q1	0.000025	443659	120	1.00 (Ref)	1.00 (Ref)	
Q2	0.000097	442193	95	1.06 (0.82, 1.38)	1.08 (0.83, 1.42)	
Q3	0.000204	448139	116	1.02 (0.78, 1.32)	1.04 (0.79, 1.38)	
Q4	0.000474	451063	94	0.90 (0.68, 1.19)	0.90 (0.67, 1.22)	0.26
Chromium						
Q1	0.000165	443659	120	1.00 (Ref)	1.00 (Ref)	
Q2	0.000478	442193	95	0.86 (0.67, 1.10)	0.86 (0.67, 1.11)	
Q3	0.000926	448139	116	1.05 (0.83, 1.33)	1.05 (0.82, 1.34)	
Q4	0.001961	451063	94	0.80 (0.61, 1.03)	0.78 (0.59, 1.04)	0.11
Lead						
Q1	0.001971	459922	117	1.00 (Ref)	1.00 (Ref)	
Q2	0.002896	452125	100	0.91 (0.70, 1.19)	0.92 (0.70, 1.22)	
Q3	0.004890	442968	108	0.99 (0.76, 1.28)	0.99 (0.75, 1.31)	
Q4	0.010354	430039	100	0.91 (0.70, 1.19)	0.90 (0.67, 1.22)	0.54

Metal HAP	Median conc., µg/m³	Person years	Cases	HR (95% CI): age-adjusted	HR (95% CI): fully adjusted^b	p-trend^c
Manganese						
Q1	0.001109	459870	101	1.00 (Ref)	1.00 (Ref)	
Q2	0.002488	457074	128	1.30 (1.00, 1.68)	1.30 (1.00, 1.70)	
Q3	0.004118	442783	96	0.99 (0.75, 1.32)	1.01 (0.75, 1.35)	
Q4	0.007797	425327	100	1.05 (0.79, 1.38)	1.04 (0.77, 1.40)	0.58
Mercury						
Q1	0.001543	449057	96	1.00 (Ref)	1.00 (Ref)	
Q2	0.001649	454765	106	1.14 (0.87, 1.50)	1.15 (0.87, 1.52)	
Q3	0.001867	457804	111	1.20 (0.92, 1.58)	1.24 (0.93, 1.65)	
Q4	0.002405	423428	112	1.28 (0.97, 1.68)	1.33 (0.99, 1.79)	0.10
Nickel						
Q1	0.000873	456523	109	1.00 (Ref)	1.00 (Ref)	
Q2	0.002485	448290	118	1.15 (0.88, 1.48)	1.02 (0.76, 1.34)	
Q3	0.004934	451511	107	1.02 (0.78, 1.33)	0.91 (0.67, 1.24)	
Q4	0.011718	428731	91	0.91 (0.68, 1.20)	1.01 (0.79, 1.24)	0.25

^aHAP metal levels were obtained from the EPA. The EPA estimates HAPS for each census tract in the contiguous US and Puerto Rico using a model incorporates information about the rate, location and height of release, meteorological factors and pollutant-specific factors such as radioactive decay, deposition and secondary formation. HAPs data from 1990, 1996 and 1999 were available. We used updated metal exposure incorporating all years of HAP measurement in our analyses. ^bAdjusted for age and smoking (never/past/current, and pack years) and population density (quartiles). ^cp-trends based on linear model through the quartile medians.

Table 4. Exposure to individual metal HAPs^a and risk of Parkinson Disease among participants on the Nurses Health Study (N = 97,430), Follow-up 1990-2008, by quartile of each metal exposure stratified by smoking status.

Metal HAP	Never smoker: person years	Never smoker: cases	Never smoker: HR (95% CI) ^b	Never smoker: p-trend ^c	Ever smoker: person years	Ever smoker: cases	Ever smoker: HR (95% CI) ^b	Ever smoker: p-trend ^c	p-int.
Antimony									
Q1	205420	60	1.00 (Ref)		249179	53	1.00 (Ref)		
Q2	198308	61	1.06 (0.74, 1.52)		241434	43	0.88 (0.59, 1.33)		
Q3	193544	51	0.90 (0.61, 1.32)		236848	53	1.15 (0.78, 1.71)		
Q4	184744	55	0.99 (0.67, 1.47)	0.95	217866	48	1.10 (0.73, 1.67)	0.48	0.58
Arsenic									
Q1	210463	63	1.00 (Ref)		237236	48	1.00 (Ref)		
Q2	194833	48	0.83 (0.56, 1.23)		245601	42	0.88 (0.58, 1.32)		
Q3	186002	60	1.08 (0.73, 1.59)		244303	42	0.94 (0.61, 1.43)		
Q4	190718	56	0.96 (0.64, 1.43)	0.94	218188	51	0.92 (0.59, 1.42)	0.90	0.97
Cadmium									
Q1	209521	60	1.00 (Ref)		234166	51	1.00 (Ref)		
Q2	957711	59	1.06 (0.73, 1.54)		244381	54	1.08 (0.73, 1.62)		
Q3	185869	53	0.99 (0.66, 1.48)		251031	54	1.04 (0.68, 1.59)		
Q4	190854	55	0.97 (0.66, 1.46)	0.84	215750	38	0.80 (0.50, 1.27)	0.18	0.46
Chromium									
Q1	202837	65	1.00 (Ref)		229154	55	1.00 (Ref)		
Q2	189959	50	0.86 (0.61, 1.23)		238065	44	0.82 (0.56, 1.19)		
Q3	190332	61	1.10 (0.78, 1.55)		242816	55	0.97 (0.66, 1.40)		
Q4	198888	51	0.81 (0.55, 1.20)	0.33	235293	43	0.74 (0.49, 1.13)	0.24	0.92
Lead									
Q1	208472	64	1.00 (Ref)		239836	53	1.00 (Ref)		
Q2	190940	47	0.81 (0.55, 1.20)		248120	53	1.02 (0.68, 1.54)		
Q3	189998	61	1.01 (0.69, 1.50)		238962	46	0.92 (0.59, 1.42)		
Q4	192605	55	0.81 (0.54, 1.20)	0.90	218411	45	0.92 (0.58, 1.44)	0.63	0.86
Manganese									
Q1	198449	52	1.00 (Ref)		252400	49	1.00 (Ref)		
Q2	197675	73	1.37 (0.95, 1.96)		247611	54	1.19 (0.80, 1.77)		
Q3	192392	51	0.96 (0.64, 1.44)		232493	45	1.08 (0.71, 1.65)		
Q4	193500	51	0.92 (0.61, 1.40)	0.98	212824	49	1.20 (0.78, 1.84)	0.37	0.49

Metal HAP	Never smoker: person years	Never smoker: cases	Never smoker: HR (95% CI) ^b	Never smoker: p-trend ^c	Ever smoker: person years	Ever smoker: cases	Ever smoker: HR (95% CI) ^b	Ever smoker: p-trend ^c	p-int.
Mercury									
Q1	206460	47	1.00 (Ref)		217568	49	1.00 (Ref)		
Q2	199558	63	1.46 (0.99, 2.16)		245796	43	0.84 (0.56, 1.29)		
Q3	191627	52	1.30 (0.85, 1.98)		255953	58	1.10 (0.73, 1.67)		
Q4	184371	65	1.68 (1.11, 2.55)	0.04	226011	47	0.99 (0.63, 1.55)	0.85	0.29
Nickel									
Q1	211260	57	1.00 (Ref)		234868	52	1.00 (Ref)		
Q2	195949	63	1.21 (0.83, 1.76)		239515	55	1.09 (0.74, 1.63)		
Q3	191980	59	1.13 (0.76, 1.68)		245360	48	0.91 (0.59, 1.40)		
Q4	182828	48	0.96 (0.62, 1.47)	0.46	225585	42	0.86 (0.55, 1.35)	0.36	0.90

^aHAP metal levels were obtained from the EPA. The EPA estimates HAPS for each census tract in the contiguous US and Puerto Rico using a model incorporates information about the rate, location and height of release, meteorological factors and pollutant-specific factors such as radioactive decay, deposition and secondary formation. HAPs data from 1990, 1996 and 1999 were available. We used updated metal exposure incorporating all years of HAP measurement in our analyses. ^bAdjusted for age and population density (quartiles). ^cp-trends based on linear model through the quartile medians.

Table 5. Exposure to individual metal HAPs^a and risk of Parkinson Disease among participants on the Nurses Health Study (N = 97,430), Follow-up 1990-2008, by quartile of each metal exposure stratified by county-level population density low (<250,000 persons per county) vs. high (≥250,000 persons per county).

Metal HAP	Low population density: person years	Low population density: cases	Low population density: HR (95% CI) ^b	Low population density: p-trend ^c	High population density: person years	High population density: cases	High population density: HR (95% CI) ^b	High population density: p-trend ^c	High population density: p-int
Antimony									
Q1	256829	68	1.00 (Ref)		206521	45	1.00 (Ref)		
Q2	179049	61	1.13 (0.79, 1.64)		271666	53	0.92 (0.62, 1.37)		
Q3	113333	26	0.93 (0.59, 1.48)		331443	78	1.10 (0.76, 1.58)		
Q4	64700	14	0.88 (0.49, 1.59)	0.19	361513	90	1.10 (0.77, 1.60)	0.35	0.21
Arsenic									
Q1	307615	90	1.00 (Ref)		150351	27	1.00 (Ref)		
Q2	150741	35	0.84 (0.56, 1.26)		303922	59	1.06 (0.67, 1.68)		
Q3	80920	20	0.91 (0.55, 1.51)		366992	92	1.33 (0.85, 2.07)		
Q4	74637	14	0.65 (0.36, 1.15)	0.15	349877	88	1.28 (0.81, 2.01)	0.37	0.06
Cadmium									
Q1	305054	84	1.00 (Ref)		149459	27	1.00 (Ref)		
Q2	154477	42	1.08 (0.74, 1.59)		298153	71	1.27 (0.81, 1.99)		
Q3	75229	15	0.81 (0.46, 1.42)		377375	93	1.26 (0.81, 1.96)		
Q4	79151	18	0.86 (0.51, 1.45)	0.45	346155	75	1.03 (0.65, 1.64)	0.43	0.60
Chromium									
Q1	298746	86	1.00 (Ref)		144913	34	1.00 (Ref)		
Q2	161051	38	0.87 (0.60, 1.27)		281142	57	0.92 (0.64, 1.32)		
Q3	84838	23	0.99 (0.63, 1.55)		363301	93	1.15 (0.82, 1.61)		
Q4	69277	12	0.63 (0.34, 1.17)	0.19	381786	82	0.88 (0.61, 1.27)	0.35	0.31
Lead									
Q1	319326	90	1.00 (Ref)		140596	27	1.00 (Ref)		
Q2	148960	38	1.02 (0.69, 1.50)		303166	62	0.99 (0.62, 1.57)		
Q3	92101	21	0.90 (0.55, 1.47)		350867	87	1.15 (0.73, 1.80)		
Q4	53525	10	0.71 (0.36, 1.38)	0.26	376514	90	1.04 (0.65, 1.65)	0.84	0.17

Metal HAP	Low population density: person years	Low population density: cases	Low population density: HR (95% CI)^b	Low population density: p-trend^c	High population density: person years	High population density: cases	High population density: HR (95% CI)^b	High population density: p-trend^c	High population density: p-int
Manganese									
Q1	266167	64	1.00 (Ref)		193703	37	1.00 (Ref)		
Q2	161175	50	1.32 (0.90, 1.91)		295899	78	1.36 (0.91, 2.02)		
Q3	101067	24	1.02 (0.63, 1.64)		341716	72	1.05 (0.70, 1.58)		
Q4	85503	21	1.02 (0.61, 1.69)	0.61	339824	79	1.08 (0.72, 1.63)	0.70	0.91
Mercury									
Q1	285651	75	1.00 (Ref)		163406	21	1.00 (Ref)		
Q2	174527	41	0.99 (0.67, 1.46)		280238	65	1.77 (1.08, 2.89)		
Q3	92534	23	1.09 (0.67, 1.77)		365271	88	1.80 (1.11, 2.91)		
Q4	61201	20	1.32 (0.79, 2.19)	0.29	362227	92	1.84 (1.13, 2.99)	0.14	0.86
Nickel									
Q1	312521	82	1.00 (Ref)		144002	27	1.00 (Ref)		
Q2	157280	45	1.21 (0.82, 1.76)		291010	73	1.27 (0.81, 1.98)		
Q3	82026	18	0.95 (0.56, 1.61)		369485	89	1.14 (0.73, 1.78)		
Q4	62086	14	0.93 (0.52, 1.65)	0.66	366645	77	1.00 (0.63, 1.58)	0.33	0.84

^aHAP metal levels were obtained from the EPA. The EPA estimates HAPS for each census tract in the contiguous US and Puerto Rico using a model incorporates information about the rate, location and height of release, meteorological factors and pollutant-specific factors such as radioactive decay, deposition and secondary formation. HAPs data from 1990, 1996 and 1999 were available. We used updated metal exposure incorporating all years of HAP measurement in our analyses. ^bAdjusted for age and smoking (never, past current and pack-years). ^cp-trends based on linear model through the quartile medians.