

Air Pollution and Risk of Parkinson's Disease in a Large Prospective Study of Men

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BACKGROUND: Exposure to air pollution has been implicated in a number of adverse health outcomes, and the effect of particulate matter (PM) on the brain is beginning to be recognized.

OBJECTIVES: We aimed to examine whether exposure to PM air pollution is related to risk of Parkinson's disease (PD) in the Health Professionals Follow-up Study (HPFS), a large prospective cohort of U.S. men.

METHODS: We prospectively followed 50,352 men in the HPFS, a large prospective cohort of U.S. men, and identified 550 incident PD cases. Cumulative average exposure to various size fractions of PM [PM₁₀ ($\leq 10 \mu\text{m}$ in diameter), PM_{2.5} ($\leq 2.5 \mu\text{m}$ in diameter), and PM_{2.5–10} (between 2.5 and 10 μm in diameter)] up to 2 years before the onset of PD was estimated using a spatiotemporal model by linking each participant's place of residence throughout the study with location-specific PM levels. We used multivariable Cox proportional hazards models to independently estimate the risk of PD associated with each size fraction of PM.

RESULTS: In models adjusted for age, smoking, region, and population density, we did not observe statistically significant associations between exposure to PM and PD risk. In analyses considering cumulative average PM exposure, the comparing the top to the bottom quintile of PM exposure was 0.85 [95% confidence interval (CI): (0.63, 1.15)] for PM₁₀, 0.97 [95% CI: (0.72, 1.32)] for PM_{2.5}, and 0.88 [95% CI: (0.64, 1.22)] for hazard ratio (HR) PM_{2.5–10}. The results did not change markedly when restricted to men who did not move during the study or when stratified by smoking status or population density.

CONCLUSIONS: In this study, we found no evidence that exposure to air pollution is a risk factor for PD in men. <https://doi.org/10.1289/EHP259>

Introduction

Evidence is rapidly growing on the negative health impacts of air pollution (Loomis et al. 2013; Wang et al. 2014). Research into the association between air pollution and neurological disease, particularly Parkinson's disease (PD), is limited. PD is the second most prevalent neurodegenerative disease, and it results in substantial personal and societal costs (Huse et al. 2005). Toxins in air pollution have been shown to promote inflammation and oxidative stress (Calderon-Garcidueñas et al. 2015), both of which are thought to contribute to PD (Andican et al. 2012). Inflammatory markers have been associated with elevated PD risk in epidemiological studies (Chen et al. 2008; Ton et al. 2012). Furthermore, urate, a strong antioxidant, has been shown to be neuroprotective in animal models (Haberman et al. 2007), and has been associated with reduced PD risk (Davis et al. 1996; de Lau et al. 2005; Weisskopf et al. 2007).

The epidemiologic literature on air pollution and PD is limited, although interest in this topic is growing. Here, we present the results from a large prospective study of U.S. male health professionals, the Health Professionals Follow-up Study (HPFS),

where we examined whether exposure to ambient particulate matter (PM), specifically particles smaller or equal to 10 μm in diameter (PM₁₀), particles smaller than 2.5 μm in diameter (PM_{2.5}), and particles between 2.5 and 10 μm in diameter (PM_{2.5–10}), is associated with risk of PD in men.

Methods

Study Population

The HPFS cohort (Grobbee et al. 1990) began in 1986, and consists of 51,529 dentists, podiatrists, pharmacists, veterinarians, and optometrists, recruited nationally and located throughout the United States, who were 40 to 75 years of age at the start of the study. The population was selected due to ease of tracking for follow-up, interest in investigating nutritional factors associated with disease, and level of health knowledge. The majority of participants are Caucasian (>91%), reflective of the racial/ethnic composition of the health professional occupations at the time the study began rather than any exclusion criteria established by investigators. The cohort has been followed by mailed questionnaires sent every 2 years to update exposure information and to ascertain nonfatal incident diseases. Response rates are over 93% at each follow-up cycle. The study was approved by an institutional review board at the Harvard School of Public Health, and each participant provided informed consent before the study began.

Exposure Assessment

Monthly exposures to ambient air pollution were estimated for each participant at the appropriate time-matched questionnaire mailing address using spatiotemporal models, discussed in detail elsewhere (Yanosky et al. 2014). In brief, generalized additive mixed models of PM₁₀ from 1988 through 2007 were developed for the continental United States, using monthly average PM₁₀

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data from the Environmental Protection Agency (EPA)'s Air Quality System (AQS), a nationwide network of continuous and filter-based monitors, as well as data from various other sources, including the Interagency Monitoring of Protected Visual Environments network, several Harvard-based research studies, and a geographic information system (GIS) for variables such as population density, distance to nearest road, elevation, and urban land use. The estimation of PM_{2.5} was similar; however, because EPA AQS monitoring data for PM_{2.5} were not available prior to 1999, separate models were created for pre- and post-1999 PM_{2.5}. To estimate PM_{2.5} prior to 1999, the model relied on measured PM₁₀ pre-1999 and the PM_{2.5} to PM₁₀ ratio from the spatiotemporal model post-1999, as well as estimated extinction coefficients from airport visibility data. PM_{2.5–10} was estimated by subtracting values for PM_{2.5} from those for PM₁₀. All models showed little bias and a high degree of precision when evaluated with a cross-validation approach, where a subsection of the monitors was held out to compare predicted and observed values (Puetz et al. 2011). Monthly exposures to ambient air pollution were estimated for each participant at the appropriate time-matched questionnaire mailing address, and were then summed to form a cumulative average exposure for each participant.

Parkinson's Disease Ascertainment

The ascertainment of PD cases was conducted as described previously (Ascherio et al. 2001; Gao et al. 2007; Gao et al. 2011). Briefly, in the HPFS, new cases of PD are reported on biennial questionnaires. When a participant reports PD, we then ask for consent to contact the treating neurologist. If consent is provided, we ask the treating neurologist to complete a questionnaire to confirm the PD diagnosis and to send a copy of the participant's medical record. During follow-up, 1,481 cohort participants self-reported PD; of these, 860 gave permission to view their medical record (the rest were either deceased, denied diagnosis, did not give permission, or we were unable to contact them), and medical records were obtained for 821 participants. The medical records were reviewed, blind to exposure status, by a movement disorder specialist (M.A.S.). A PD case was considered confirmed if the treating physician reported it as either definite or probable, or if the medical record included evidence of either a final diagnosis of PD made by a neurologist or evidence of two or more of the three cardinal signs of PD (bradykinesia, rigidity, rest tremor) in the absence of characteristics suggesting an alternate diagnosis. Additionally, we requested death certificates of all deceased study participants, and identified PD diagnoses that were not reported as part of regular study follow-up (fewer than 2% of all PD cases). Only definite and probable PD cases were used for our analyses, consistent with prior work (Ascherio et al. 2001; Gao et al. 2007).

Statistical Analysis

We used separate time-varying Cox proportional hazards models to model the association between exposure to each fraction of PM and incident PD. The timescale for the left-truncated survival model was age (months), and it is additionally stratified by calendar time in 2-year groups. Person-years of follow-up were accumulated from 1988 through the end of follow-up (30 June 2010), death, or date of PD diagnosis, whichever occurred earlier. We excluded participants who reported PD with onset before the start of follow-up ($n=55$), participants who died before the start of follow-up ($n=412$), and participants whose date of birth was not known ($n=152$). We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for each quintile of PM exposure, as well as in a linear model for each 10- $\mu\text{g}/\text{m}^3$ increase. Quintiles of PM were determined on the initial data set and were the same

for all analyses and sensitivity analyses (quintile ranges are listed in Tables 1–4). For tests of trend, we used the median value of each quintile as a continuous variable to minimize the influence of outliers. Deviations from linearity of continuous PM relationships were assessed with cubic regression splines (Durrleman and Simon 1989). Exposure to air pollution was included in the models as a time-varying variable: every 2 years, a new PM average was calculated as an average of all prior (back to 1988) 2-year PM estimates. The cumulative average of PM exposure was used in an attempt to capture any effects of PM on PD risk prior to onset. Our primary analyses were stratified by age in months and adjusted for calendar year, smoking (never/past/current), region of residence (Northeast, Midwest, West, and South), and median census tract population density (tract level), included in models as time-dependent variables.

Because the relevant etiologic period of air pollution exposure in PD is unknown, we conducted additional sensitivity analyses using PM levels in 2000 (the midpoint of the study) as the exposure of interest. Also, as longer cumulative exposure may be more important, we conducted additional sensitivity analyses among participants with 10 or more years of PM exposure data. We also conducted additional sensitivity analyses adding caffeine intake (<100 mg/day vs. over 100 mg/day) and median census tract income to the models. Additionally, we conducted sensitivity analyses restricted to men who did not move during the study (a move was defined as a change in latitude/longitude of greater than 5 kilometers during the study).

Because smoking is a well-known protective factor in PD epidemiology and may have modes of action that mimic air pollution, we conducted analyses stratified by smoking status (never/ever). We also conducted analyses stratified by tertile of census tract-level population density.

We used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) for all statistical analyses.

Results

The characteristics of the study population by quintile of PM_{2.5} are presented in Table 1; characteristics for PM₁₀ and PM_{2.5–10} were similar. Our study included 50,352 participants, and 550 PD cases were identified throughout follow-up. PM_{2.5} exposure was not associated with age, smoking status, caffeine or alcohol intake, or census tract income. As expected, participants living in census tracts with higher population density had higher PM exposure.

In models adjusted for age, time period, smoking, region, and population density, we observed no statistically significant associations between exposure to air pollution and PD risk (Table 2). The HR comparing the top to the bottom quintile of PM exposure was 0.85 (95% CI: 0.63, 1.15) for PM₁₀, 0.97 (95% CI: 0.72, 1.32) for PM_{2.5}, and 0.88 (95% CI: 0.64, 1.22) for PM_{2.5–10}. Likewise, in linear models calculating the association between each 10- $\mu\text{g}/\text{m}^3$ increase in PM, there was no association observed with PD [HR = 0.99 (95% CI: 0.97, 1.01)] for PM₁₀, 0.99 (95% CI: 0.97, 1.02) for PM_{2.5}, and 0.99 (95% CI: 0.96, 1.01) for PM_{2.5–10}. We used splines to test for linearity, and there was some evidence of a nonlinear relation for PM_{2.5–10} (test for curvature $p=0.04$), although the test for overall significance of the dose-response was not statistically significant ($p=0.13$). For PM₁₀ and PM_{2.5}, there was no evidence of deviations from linearity.

Results of sensitivity analyses using PM levels in 2000 as the exposure of interest were similar to the main results, and are presented in Table 3. Sensitivity analyses among participants with 10 or more years of PM exposure data also did not differ significantly from the main results, although the association, especially for PM₁₀ and PM_{2.5}, tended somewhat more in the direction of a "protective" effect of air pollution on PD risk. However, because none of the

Table 1. Age-standardized characteristics of the 50,352 Health Professionals Follow-up Study (HPFS) study participants at baseline in 1988 with respect to quintiles of PM_{2.5}.

Characteristic	Q1 Range: 3.1–9.9 µg/m ³	Q2 Range: 9.9–13.1 µg/m ³	Q3 Range: 13.1–16.3 µg/m ³	Q4 Range: 16.3–18.7 µg/m ³	Q5 Range: 18.7–29.2 µg/m ³
Age, years, mean ± SD	56.87 ± 10.15	56.35 ± 9.73	56.55 ± 9.86	56.87 ± 9.70	57.05 ± 9.57
Current smoker %	9.8	9.1	9.5	8.7	9.1
Pack-years, mean ± SD	12.1 ± 18.6	12.3 ± 18.9	12.5 ± 19.2	12.2 ± 18.4	11.7 ± 18.1
Caffeine, mg/day, mean ± SD	234.2 ± 238.0	231.4 ± 233.7	230.9 ± 225.4	221.1 ± 217.6	216.3 ± 217.2
Alcohol, gm/day, mean ± SD	11.7 ± 15.6	12.2 ± 16.3	11.7 ± 15.4	10.7 ± 14.9	10.5 ± 15.0
Census tract income ^b , USD, mean ± SD	51,886.8 ± 20,522.4	56,960.6 ± 25,969.7	64,808.6 ± 28,449.9	65,165.3 ± 30,314.9	60,040.2 ± 30,482.4
1988 tract population density (persons/tract), mean ± SD	2,703.9 ± 2,970.8	3,555.6 ± 4,779.8	3,075.6 ± 3,415.9	4,484.0 ± 6,474.6	10,887.0 ± 21,741.1
Region of United States (%)					
Northeast	0.9	8.9	36.4	36.2	35.0
Midwest	22.1	30.2	36.6	25.7	22.6
West	44.3	28.7	12.9	5.7	16.9
South	32.7	32.2	14.2	32.5	25.6

Note: Values are means SD or percentages and are standardized to the age distribution of the study population. Q, quintile; SD, standard deviation.

associations observed in this sensitivity analysis were strongly protective or statistically significant, they still contribute to the overall finding of no association between air pollution exposure and PD risk in this study. In sensitivity analyses where the models additionally included caffeine intake (<100 mg/day vs. over 100 mg/day) and median census tract, the results did not differ substantially from the main results. In analyses restricted to men who did not move throughout the study (427 PD cases), our results were not significantly different from our main analyses, and we did not observe any association with PD (Table 5).

We did not observe any statistically significant interactions with smoking status (Table 4). When we stratified our analyses by population density, we saw no evidence for effect modification by population density (Figure 1).

Discussion

In this study, we did not observe an association between exposure to ambient air pollution measured as cumulative exposure to

PM₁₀, PM_{2.5}, and PM_{2.5–10} at the participant's mailing address and risk of PD in a U.S.-based study of men. In analyses considering cumulative average PM exposure, the HR comparing the top to the bottom quintile of PM exposure was 0.85 (95% CI: 0.63, 1.15) for PM₁₀, 0.97 (95% CI: 0.72, 1.32) for PM_{2.5}, and 0.88 (95% CI: 0.64, 1.22) for PM_{2.5–10}. These findings were similar to those we have previously published on exposure to PM and PD risk in the Nurses' Health Study (NHS), a similarly designed study of women (Palacios et al. 2014a).

PM₁₀ describes all particles that are smaller than 10 µm in diameter, these particles are considered small enough to pass through the throat or the nose and enter the lungs, thus potentially causing harm to human health. (PM). Thus, PM₁₀ encompasses both inhalable coarse particles (PM_{2.5–10}) and fine particles (PM_{2.5}). Inhalable coarse particles, PM_{2.5–10}, come primarily from agricultural, mining and construction sources (Kagan and Maddison 1992). Fine particles, PM_{2.5}, are mostly combustion-derived particles and are produced from the burning of coal, wood and fuel oil and from motor vehicle emissions.

Table 2. Exposure to cumulative average of PM₁₀, PM_{2.5}, and PM_{2.5–10} and risk of Parkinson's disease (PD) in the health professionals follow-up study.

Exposure	Person-years	Cases	Age adjusted ^a		Multivariable ^b		
			HR	95% CI	HR	95% CI	p-trend
PM ₁₀							
Quintiles of PM ₁₀							
Q1: 7.4–21.8 µg/m ³	187,789	121	1.00	Ref	1.00	Ref	
Q2: 21.8–24.9 µg/m ³	190,039	109	0.93	(0.72, 1.21)	0.98	(0.75, 1.28)	
Q3: 24.9–27.7 µg/m ³	189,973	112	0.95	(0.74, 1.24)	1.04	(0.79, 1.35)	
Q4: 27.7–31.7 µg/m ³	189,573	117	0.95	(0.74, 1.23)	1.04	(0.80, 1.36)	
Q5: 31.7–81.3 µg/m ³	188,104	91	0.77	(0.58, 1.01)	0.85	(0.63, 1.15)	0.33
Linear ^c	945,478	550	0.98	(0.97, 1.00)	0.99	(0.97, 1.01)	
PM _{2.5}							
Quintiles PM _{2.5}							
Q1: 3.1–9.9 µg/m ³	187,997	98	1.00	Ref	1.00	Ref	
Q2: 9.9–13.1 µg/m ³	189,818	114	1.22	(0.93, 1.60)	1.22	(0.92, 1.61)	
Q3: 13.1–16.3 µg/m ³	189,880	125	1.29	(0.98, 1.68)	1.24	(0.93, 1.64)	
Q4: 16.3–18.7 µg/m ³	189,949	119	1.23	(0.94, 1.60)	1.21	(0.91, 1.62)	
Q5: 18.7–29.2 µg/m ³	187,836	94	0.96	(0.72–1.27)	0.97	(0.72, 1.32)	0.61
Linear ^c	945,478	550	0.99	(0.97, 1.02)	0.99	(0.97, 1.02)	
PM _{2.5–10}							
Quintiles of PM _{2.5–10}							
Q1: 1.6–7.9 µg/m ³	188,998	133	1.00	(Ref)	1.00	(Ref)	
Q2: 7.9–10.4 µg/m ³	190,395	110	0.79	(0.61, 1.02)	0.84	(0.65, 1.09)	
Q3: 10.4–13.0 µg/m ³	188,336	112	0.80	(0.62, 1.03)	0.89	(0.68, 1.16)	
Q4: 13.0–16.8 µg/m ³	188,815	93	0.69	(0.53, 0.90)	0.78	(0.58, 1.04)	
Q5: 16.8–59.7 µg/m ³	188,935	102	0.77	(0.60–1.00)	0.88	(0.64, 1.22)	0.57
Linear ^c	945,478	550	0.98	(0.97, 0.99)	0.99	(0.96, 1.01)	

Note: CI, confidence interval; HR, hazard ratio; PM, particulate matter; PY, person-years; Ref, reference.

^aadjusted for age and time period.

^badjusted for age, time period, smoking (status and pack-years), region (Northeast, Midwest, West, and South) and census tract population density.

^cLinear models represent HR per 10-µg/m³ increase in PM.

Table 3. Exposure to PM₁₀, PM_{2.5}, and PM_{2.5–10} in the year 2000 and risk of Parkinson's disease (PD) in the health professionals follow-up study.

Exposure	Person-years	Cases	Age adjusted ^a		Multivariable ^b		
			HR	95% CI	HR	95% CI	<i>p</i> -trend
PM ₁₀							
Quintiles of PM ₁₀							
Q1: 7.4–21.8 µg/m ³	190,377	126	1.00	Ref	1.00	Ref	0.07
Q2: 21.8–24.9 µg/m ³	188,529	127	1.01	(0.79, 1.30)	1.06	(0.82, 1.38)	
Q3: 24.9–27.7 µg/m ³	189,113	115	0.94	(0.73, 1.21)	1.00	(0.76, 1.31)	
Q4: 27.7–31.7 µg/m ³	189,374	93	0.74	(0.57, 0.97)	0.81	(0.60, 1.08)	
Q5: 31.7–81.3 µg/m ³	186,970	89	0.74	(0.56, 0.97)	0.83	(0.62, 1.12)	
Linear ^c	923,899	550	0.97	(0.96, 0.99)	0.98	(0.96, 0.99)	
PM _{2.5}							
Quintiles PM _{2.5}							
Q1: 3.1–9.9 µg/m ³	187,550	110	1.00	Ref	1.00	Ref	0.25
Q2: 9.9–13.1 µg/m ³	190,954	133	1.24	(0.96, 1.60)	1.22	(0.94, 1.60)	
Q3: 13.1–16.3 µg/m ³	187,141	106	1.02	(0.78, 1.33)	1.01	(0.75, 1.35)	
Q4: 16.3–18.7 µg/m ³	188,643	115	1.06	(0.82, 1.38)	1.08	(0.81, 1.44)	
Q5: 18.7–29.2 µg/m ³	188,074	86	0.83	(0.63, 1.11)	0.88	(0.65, 1.19)	
Linear ^c	944,362	550	0.97	(0.95, 1.00)	0.98	(0.95, 1.00)	
PM _{2.5–10}							
Quintiles of PM _{2.5–10}							
Q1: 1.6–7.9 µg/m ³	189,550	127	1.00	Ref	1.00	Ref	0.68
Q2: 7.9–10.4 µg/m ³	190,954	107	0.83	(0.64, 1.08)	0.88	(0.68, 1.14)	
Q3: 10.4–13.0 µg/m ³	187,141	111	0.82	(0.64, 1.07)	0.89	(0.68, 1.16)	
Q4: 13.0–16.8 µg/m ³	188,643	104	0.79	(0.61, 1.03)	0.89	(0.68, 1.16)	
Q5: 16.8–59.7 µg/m ³	188,074	101	0.81	(0.62, 1.05)	0.92	(0.68, 1.18)	
Linear ^c	923,899	550	0.97	(0.95, 0.99)	0.98	(0.96, 1.00)	

Note: CI, confidence interval; HR, hazard ratio; PM, particulate matter; PY, person-years; Ref, reference.

^aadjusted for age and time period.

^badjusted for age, time period, smoking (status and pack-years), region (Northeast, Midwest, West, and South) and census tract population density.

^cLinear models represent HR per 10-µg/m³ increase in PM.

The potential effects of air pollution on neurological disease broadly and PD in particular are just beginning to be understood. Finkelstein and colleagues (Finkelstein and Jerrett 2007) found that although markers of traffic derived air pollution did not predict PD risk, risk was increased among participants with higher manganese (Mn) exposure (HR:1.03; 95% CI:1.00–1.07) for each 10-ng/m³ increase in Mn concentration) (Finkelstein and Jerrett 2007). Willis and colleagues linked airborne metal exposure data throughout the United States to the Medicare beneficiaries database, and reported that incidence of PD was elevated in urban counties with higher industrial release of both copper and manganese (Willis et al. 2010). Our group recently published on the association between airborne metals and risk of PD in the NHS, a similarly designed study of women (Palacios et al. 2014b),

showing a potential association with airborne tract-level mercury exposure and PD risk in women (Palacios et al. 2014a). In a separate paper, we also reported a lack of an association between PM air pollution and PD risk in the NHS cohort (Palacios et al. 2014a), a cohort of women with similar design to the present study. In a recent study, Ritz et al. (2016) found that modeled ambient air pollution from traffic sources (particularly NO₂) was associated with a 9% increase in PD risk per interquartile range, with some evidence of effect modification by urbanicity: the odds ratio (OR) associated with NO₂ exposure for long-term residents of the capital city (Copenhagen, Denmark) was higher (OR = 1.21; 95% CI: 1.11–1.31) than that in provincial towns (OR = 1.10; 95% CI: 0.97–1.26), and no association was seen among residents of rural areas. Our finding of a lack of effect

Table 4. Exposure to particulate matter (PM) and risk of Parkinson's disease (PD) in the health professionals follow-up study, stratified by smoking status.

Exposure	Never Smokers				Ever Smokers				<i>p</i> -int
	PY	Cases	HR ^a	95% CI	PY	Cases	HR ^a	95% CI	
Quintiles PM ₁₀									
7.4–21.8 µg/m ³	92,609	62	1.00	Ref	103,446	61	1.00	Ref	
21.8–24.9 µg/m ³	93,454	64	1.11	(0.77, 1.59)	105,880	50	0.88	(0.60, 1.29)	
24.9–27.7 µg/m ³	93,601	58	1.05	(0.72, 1.53)	105,526	58	1.02	(0.70, 1.48)	
27.7–31.7 µg/m ³	93,427	67	1.17	(0.81, 1.70)	104,968	54	0.92	(0.62, 1.36)	
31.7–81.3 µg/m ³	98,692	57	0.95	(0.63, 1.42)	99,965	39	0.78	(0.50, 1.21)	0.47
Quintiles PM _{2.5}									
3.1–9.9 µg/m ³	95,009	52	1.00	Ref	101,526	47	1.00	Ref	
9.9–13.1 µg/m ³	9,5637	62	1.29	(0.88, 1.89)	103,402	55	1.10	(0.74, 1.65)	
13.1–16.3 µg/m ³	93,935	70	1.32	(0.89, 1.94)	104,798	57	1.08	(0.72, 1.64)	
16.3–18.7 µg/m ³	92,795	72	1.40	(0.95, 2.08)	106,348	57	1.07	(0.70, 1.63)	
18.7–29.2 µg/m ³	94,406	52	0.98	(0.65, 1.49)	103,711	46	0.91	(0.58, 1.41)	0.78
Quintiles PM _{2.5–10}									
1.6–7.9 µg/m ³	93,485	74	1.00	Ref	104,476	65	1.00	Ref	
0.9–10.4 µg/m ³	91,695	64	0.77	(0.55, 1.09)	107,611	51	0.79	(0.54, 1.15)	
10.4–13.0 µg/m ³	90,836	55	0.77	(0.51, 1.15)	106,781	61	0.92	(0.63, 1.33)	
13.0–16.8 µg/m ³	93,763	46	0.80	(0.57, 1.12)	10,3928	47	0.80	(0.53, 1.21)	
16.8–59.7 µg/m ³	102,004	69	0.86	(0.62, 1.18)	96,988	38	0.77	(0.47, 1.25)	0.65

Note: CI, confidence interval; HR, hazard ratio; PM, particulate matter; PY, person-years; Ref, reference.

^aadjusted for age, time period, smoking (status and pack-years), region (Northeast, Midwest, West, and South) and census tract population density.

Table 5. Exposure to PM₁₀, PM_{2.5}, and PM_{2.5–10} and risk of Parkinson's disease (PD) in the health professionals follow-up study among nonmovers.

Exposure	PY	Cases	Multivariable ^a		
			HR	95% CI	p-trend
Quintiles of PM ₁₀					
7.4–21.8 µg/m ³	149,434	96	1.00	Ref	
21.8–24.9 µg/m ³	146,735	81	0.98	(0.72, 1.33)	
24.9–27.7 µg/m ³	148,683	80	0.98	(0.72, 1.34)	
27.7–31.7 µg/m ³	150,814	99	1.14	(0.85, 1.54)	
31.7–81.3 µg/m ³	153,144	71	0.88	(0.62, 1.24)	0.62
Quintiles of PM _{2.5}					
3.1–9.9 µg/m ³	146,665	84	1.00	Ref	
9.9–13.1 µg/m ³	145,982	87	1.14	(0.84, 1.56)	
13.1–16.3 µg/m ³	147,473	97	1.16	(0.84, 1.60)	
16.3–18.7 µg/m ³	151,200	82	0.96	(0.69, 1.34)	
18.7–29.2 µg/m ³	157,492	77	0.89	(0.63, 1.25)	0.18
Quintiles of PM _{2.5–10}					
1.6–7.9 µg/m ³	155,118	95	1.00	Ref	
7.9–10.4 µg/m ³	150,279	86	1.01	(0.75, 1.37)	
10.4–13.0 µg/m ³	144,904	86	1.10	(0.80, 1.50)	
13.0–16.8 µg/m ³	147,449	76	1.00	(0.71, 1.39)	
16.8–59.7 µg/m ³	151,062	84	1.21	(0.85, 1.73)	0.27

Note: Nonmovers were defined as participants whose address changed by less than 5 km during the study. CI, confidence interval; HR, hazard ratio; PM, particulate matter; PY, person-years; Ref, reference.

^aAdjusted for age, time period, smoking (status and pack-years), region (Northeast, Midwest, West, and South) and census tract population density.

modification by population density is not consistent with this finding. One possible reason for this is that Ritz et al. (2016) focused on pollution from traffic sources (particular NO₂), while our study examines PM, which is a complex mixture and represents other components in addition to traffic air pollution. A recently published study by Liu et al. (2016) examined PM₁₀, PM_{2.5}, and NO₂ relation to PD risk within the NIH–AARP Diet and Health Study. The main finding from that work is of no association between PM air pollution and PD, and it is in agreement with our results. However, in subgroup analyses, Liu et al. (2016) reported significant positive associations between PM₁₀ among women and moderate evidence for an increased risk associated with exposure PM_{2.5} among smokers. As our study included only men, it is in agreement with Liu et al. (2016) as to no association between exposure to PM air pollution and PD risk in men. We also conducted analyses stratified by smoking, one of the best-known protective factors for PD (Hernán et al. 2001; Morozova et al. 2008; O'Reilly et al. 2009). In our study, smoking did not appear to modify the lack of association between air pollution and risk of PD, which is somewhat contradictory to the findings by Liu et al. (2016). However, in the study by Liu et al. (2016), the finding of an increased risk among never smokers is of marginal significance, is not consistent across quintiles or in the linear model, and may be due to chance. More work on understanding the impact of exposure to air pollution among specific subgroups, such as nonsmokers, is needed.

A major strength of our study is the careful ascertainment of PD in the HPFS cohort. The ascertainment of PD cases was conducted as described in “Methods” and in previous studies (Ascherio et al. 2001; Gao et al. 2007; Gao et al. 2011), and included contacting the treating neurologist for each patient self-reporting PD, as well as confirmation by a study neurologist (M.A.S.) of the information reported by the patient's treating neurologist. However, it is still possible that PD cases, due to their onset of ill health, might be somewhat less likely to complete questionnaires. To address this, we examined death certificates for all study participants, and ascertained PD cases after death. Fewer than 2% of PD cases in this study were ascertained after death. Thus, the large majority (over 98%) of

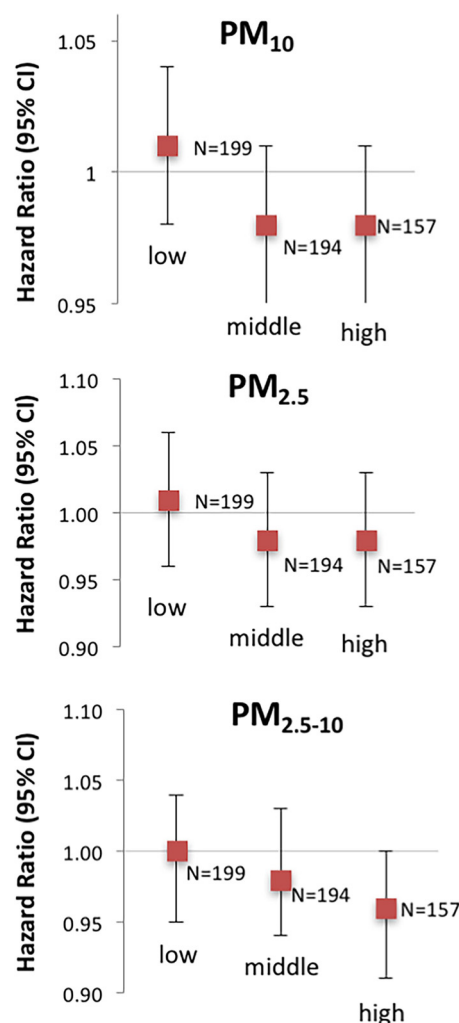


Figure 1. Association between particulate matter (PM) and Parkinson's disease (PD) risk, stratified by tertile of tract-level population density. Hazard ratio per linear 10-µg/m³ increase PM₁₀, PM_{2.5}, and PM_{2.5–10} by tract-level population density tertile (low, middle, high) adjusted for age, time period, smoking (status and pack-years), and region (Northeast, Midwest, West, and South).

PD cases were reported in life, indicating that selective nonresponse due to PD, if present, would have a minimal impact on the study.

Another advantage of our study is that the exposure models are based on a comprehensive prediction model of PM, which allowed us to estimate air pollution levels for an entire nonoccupationally exposed cohort based on participants' questionnaire mailing addresses. Our air pollution models take advantage of GIS-based spatiotemporal statistics with GIS covariates, and allow us to account for small-scale variation in pollution exposure around each study participant's address. Additionally, our biennial collection of addresses allows us to estimate pollution levels at each address where each study participant resided during follow-up.

The primary challenge of this study was the measurement of long-term exposure of air pollution. Our study is based on modeled estimates of ambient air pollution exposure in a large population of U.S. men. We did not have personal air pollution measurements or indoor air pollution measures for our study participants, and we did not know how much time they spent indoors vs. outdoors at their address. The use of ambient outdoor PM exposure could have attenuated our estimates towards the null compared to estimates that would have been expected with personal

PM monitoring (Kioumourtoglou et al. 2014). However, the exposure of interest in this study is outdoor PM and not personal PM exposure, and PM is regulated based on its outdoor ambient levels; we believe that outdoor ambient PM is an appropriate metric for this study. Furthermore, the addresses provided in the HPFS were either business or residential addresses, and, with the exception of 1988, when type of address was asked of the participants, we did not have information on which of the two were provided. The models used to estimate air pollution exposure have been shown to have little bias and high precision (Hart et al. 2015). However, some misclassification of the biologically relevant levels of individual exposure is inevitable, and could have attenuated our estimate of the association between air pollution and PD risk toward the null. We were also not able to account for occupational exposure to air pollution (if any), or other potential neurotoxins among our study participants, but we do not expect significant on-the-job exposure to air pollution given the occupational nature of this cohort. Exposure to neurotoxins, if any, would have to be correlated with exposure to ambient air pollution, which is not likely. Also, because this study was based in the United States, air pollution levels studied here are lower than those experienced by people in other, more polluted areas of the world.

Furthermore, the most relevant exposure window that needs to be considered in order to detect any potential association between pollution (or any other toxin) and PD is currently unknown. A recent study of smoking, the exposure with the best documented link to this disease, and PD showed smoking up to 20 years prior to onset was associated with PD risk, and the most recent exposure (up to or nearly up to the onset of symptoms) was the most strongly associated with risk of PD (Thacker et al. 2007). Because we only had residential history starting in 1986 (the inception of the cohort) and our air pollution models only started in 1988 due to the availability of monitoring data, we were only able to estimate exposure during adulthood for our study participants. Although this has not been determined, it is possible that the relevant etiological period may be much earlier in life, including childhood, or for a longer period than we were able to capture in this study. The analyses of men who did not move during the study attempt to address this concern, making the assumption that these men were also more likely to maintain a single address prior to study baseline than those who had moved during the study. Furthermore, because the study participants were highly educated and primarily Caucasian male health professionals of relatively high socioeconomic status, the results of this study may not be generalizable to the wider United States and world population.

The advantages of this study include a prospective design, large size, and a high follow-up rate. The study also benefited from rigorous follow-up for PD. The study participants' addresses, and thus the modeled air pollution estimates, were located throughout the continental United States, giving us a wide range in levels of air pollution exposure for our study.

Conclusions

In summary, overall the results of this large cohort study of male health professionals do not support an effect of air pollution on PD risk in men.

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