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Analysis of long- and medium-term particulate matter exposures and stroke in the US-based Health Professionals Follow-up Study

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Purpose: Stroke is a leading cause of mortality worldwide, and air pollution is the third largest contributor to global stroke burden. Existing studies investigating the association between long-term exposure to particulate matter (PM) and stroke incidence have been mixed and very little is known about the associations with medium-term exposures. Therefore, we wanted to evaluate these associations in an cohort of male health professionals.

Methods: We assessed the association of PM exposures in the previous 1 and 12 months with incident total, ischemic, and hemorrhagic stroke in 49,603 men in the prospective US-based Health Professionals' Follow-up Study 1988–2007. We used spatiotemporal prediction models to estimate monthly PM less than 10 (PM_{10}) and less than 2.5 ($PM_{2.5}$), and $PM_{2.5–10}$ at all mailing addresses. We used time-varying Cox proportional hazards models adjusted for potential confounders based on previous literature to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for each 10-μg/m^3 increase in exposure in the preceding 1 and 12 months. We explored possible effect modification by age, obesity, smoking, aspirin use, diet quality, physical activity, diabetes, and Census region.

Results: We observed 1,467 cases of incident stroke. Average levels of 12-month PM_{10}, $PM_{2.5–10}$, and $PM_{2.5}$ were 20.7, 8.4, and 12.3 μg/m^3, respectively. In multivariable adjusted models, we did not observe consistent associations between PM and overall or ischemic stroke. There was a suggestion of increased risk of hemorrhagic stroke (12-month PM_{10} multivariable HR: 1.13 [0.86, 1.48]; $PM_{2.5–10}$: 1.12 [0.78, 1.62]; $PM_{2.5}$:1.17 [0.76, 1.81], all per 10 μg/m^3). There was little evidence of effect modification.

Conclusions: We observed only weak evidence of an association between long-term exposure to PM and risks of overall incident stroke. There was a suggestion of increasing hemorrhagic stroke risk.

Keywords: Stoke; Incidence; Particulate matter; Air pollution; Cohort study

Introduction

Stroke is a leading cause of mortality in the United States and worldwide, with death rates of 45 and 110 per 100,000 inhabitants, respectively.[1,2] About 30% of strokes have been attributed to air pollution, making it the third largest contributor to global stroke burden.[3] In the last decade, a series of epidemiological studies have studied the association between short-term exposure to particulate matter (PM) and stroke incidence.[4–8] However, fewer studies to date have investigated the effect of medium- or long-term air pollution on stroke incidence, and the current evidence is inconsistent. Although higher risks were found in some studies,[9–16] other studies have been null.[17–19] As noted in a pair of recent meta-analyses, the inconsistency in results may be from the lack of well-defined outcomes or poorly measured confounding factors, such as smoking status and socioeconomic status (SES), although tests for heterogeneity in the more recent meta-analysis did not detect statistically significant differences between previous studies.[20,21] In the more recent meta-analysis, after excluding a study identified as an outlier, the relative risk (RR) of incident stroke studies was 1.13 (95% CI: 1.11, 1.15) per 10 μg/m^3 increase in particulate matter less than 2.5 μm

What this study adds

Previous studies have identified associations between long- and medium-term exposures to particulate matter (PM) air pollution and stroke. However, results have been somewhat inconsistent, especially by stroke subtype, and a recent meta-analysis called for papers with the ability to improve control for confounding. Even fewer studies have been able to examine associations for long- and medium-term exposures in the same cohort. These analyses were able to replicate previous work and assess stroke subtypes, all with extensive time-varying control for potential confounders. We were also able to assess a number of individual-level demographics and behaviors as effect modifiers.

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Statistical code can be requested from the corresponding author. Data access procedures and application forms for the Health Professionals' Follow-Up Study are available at https://sites.sph.harvard.edu/hpfs/for-collaborators/

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diameter ($PM_{2.5}$). In a subset of six studies that explored associations with stroke subtypes, the RR for ischemic stroke was 1.18 (95% CI: 1.14, 1.22) and the RR for hemorrhagic stroke was 1.10 (95% CI: 1.05, 1.16), with little evidence of heterogeneity. Results from studies published after the meta-analysis[14–16] have more consistently demonstrated positive associations between exposures to PM and stroke; however, these studies did not explore associations by stroke subtype.

In this prospective cohort study, we evaluated long- and medium-term exposure to PM less than 10, less than 2.5, and between 2.5 and 10 μm in diameter (PM_{10}, $PM_{2.5}$, $PM_{2.5–10}$), and total, ischemic, and hemorrhagic stroke incidence in the US-based nationwide, prospective, Health Professionals' Follow-up Study (HPFS). Importantly, using the detailed information available in HPFS, we were able to control for, and assess effect modification by each of a variety of time-varying individual-level characteristics, including smoking status, body mass index (BMI), physical activity, diet quality, current medication use, and individual and area-level socioeconomic status. Finally, to date, with the exception of our previous work in HPFS, most of the US-based studies of the impacts of long-term PM exposure on stroke risk have been conducted in cohorts only (or mostly) composed of women, so exploring these associations in a cohort of US men is novel.

Methods

Study population

The HPFS is an ongoing cohort composed of 51,529 male dentists, pharmacists, optometrists, osteopath physicians, podiatrists, and veterinarians in the United States, who responded to a mailed questionnaire in 1986. The participants were 40 years of age through 75 years at enrollment. Follow-up questionnaires including questions about demographics, diagnosed diseases, medical history, and lifestyle factors are mailed to participants every 2 years, and questionnaires collecting detailed diet information are administered every 4 years. The response rate is generally above 90% for each cycle. For this analysis, we restricted the study population to those participants whose addresses were in the conterminous United States during the follow-up and had no history of stroke or myocardial infarction (MI) before the start of follow-up. This study was approved by the Harvard T.H. Chan School of Public Health Human Subjects Committee and the Brigham and Women's Hospital Institutional Review Board, and consent was implied through return of the questionnaires.

Outcome assessment

The primary endpoint was defined as the first occurrence of fatal or nonfatal stroke (*International Classification of Disease*, Ninth (ICD9) Edition codes of 430-437). Strokes were self-reported by participants on each biennial questionnaire and further confirmed using a standardized approach. For participants who gave consent, medical records were reviewed by study physicians who were blinded to exposure. Diagnoses were made on the basis of the National Survey of Stroke criteria when there was a neurologic deficit with sudden or rapid onset persisting for more than 24 hours duration or until death.[22] Confirmed strokes were then classified as ischemic, hemorrhagic, or unknown type accordingly.[22] Fatal events were confirmed by searches of the National Death Index or reporting from next of kin, coworkers, or postal authorities.[23] Cases for which medical records or death certificates were not available were classified as stroke of unspecified type.

Exposure assessment

The mailing addresses for each questionnaire were geocoded to obtain latitude and longitude. Addresses were an unknown mix of work and residential addresses, as participants were able to receive their questionnaires at the address of their choice. Spatiotemporal generalized additive mixed models (GAMMs) were used to estimate the long-term exposure to ambient particulate matter at each mailing address in the conterminous United States from January 1988 to December 2007. Details of these models have been provided elsewhere.[24] Briefly, the models were based on PM monitoring data obtained from US EPA and various other sources, such as the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, and included time-varying spatial smooths of monitoring site geographic coordinates, GIS-based time-invariant geographical covariates, and time-varying meteorological covariates to predict monthly average outdoor concentrations of PM_{10} and $PM_{2.5}$. The geographical covariates included urban land use within 1 km, elevation, distance to nearest road by road class (A1–A3), tract- and county-level population density, and point-source emissions density, whereas the meteorological covariates included monthly average wind speed, temperature, percentage of stagnant days, and monthly total precipitation. Because they included GIS-based time-invariant geographical covariates, the spatial resolution of the models was high, with areas near roadways exhibiting spatial gradients down to several to tens of meters. Separate models for $PM_{2.5}$ were created for 1988–1998 and 1999 onward with different methods to account for the availability of $PM_{2.5}$ monitoring data. Thus, $PM_{2.5}$ levels from 1988 to 1998, $PM_{2.5}$ levels from 1999 to 2007, and PM_{10} levels from 1988 to 2007 were predicted from three separate models (due to availability of monitoring data). $PM_{2.5–10}$ levels were then calculated by subtracting predicted $PM_{2.5}$ from predicted PM_{10}. The models have been shown to have moderate to high predictive accuracy assessed with cross-validation R^2 of ranging from 0.58 to 0.77, from models leaving out 10% of the data. The monthly spatiotemporal predictions were used to create 1- and 12-month moving average exposures for each participant throughout the study.

Covariates

We hypothesized several *a priori* risk factors for stroke or predictors of exposure may potentially confound the association between long-term PM and stroke incidence, including current age, race (White vs. non-White), body mass index (BMI [<25 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2], alcohol consumption [0, 0.1–4.9, 5.0–14.9, or ≥15 g/day], physical activity [<3 metabolic equivalent of task (MET)-hrs/wk, 3–9 MET-hrs/wk, 9–18 MET-hrs/wk, 18–27 MET-hrs/wk, and ≥27 MET-hrs/wk], smoking status [never, current, and former], total pack-years [continuous], diet quality [continuous Alternate Healthy Eating Index, AHEI] not including alcohol[25]), neighborhood and individual-level socioeconomic status, season (spring, summer, fall, winter), comorbidities (yes/no for each of diabetes, hypertension, and hypercholesterolemia), current medication use (yes/no for each of aspirin, antidepressants, antihypertensive, and cholesterol lowering medication), and family history of stroke, MI, or any cardiovascular disease.[10,11,18,19,26] Census tract-level

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median household income (continuous) and median home value (continuous) were included as measures of neighborhood socioeconomic status. Census tract population density (rural, suburban, urban), and region (Northeast, Midwest, West, and South) were included to adjust for large-scale spatial patterns in exposure and risk. Marital status (married yes/no) and living arrangement (alone or with others), employment status (full-time employed, part-time employed, and retired/unemployed/on disability leave, and occupation (dentist, pharmacist, optometrist, osteopath physician, podiatrist, or veterinarian) were included as measures of individual-level socioeconomic status. Missing indicators were created to adjust for missing data in each potential confounder. Time-varying potential effect modifiers were selected based on the literature. These included age (in 5-year groups), obesity, smoking status, current aspirin use, diet quality (AHEI tertiles), physical activity, diabetes, Census tract median income (in tertiles), and Census region (Northeast, Midwest, West, South).

Statistical analysis

Individuals contributed person-months of follow-up from 1988 through the end of follow-up, month of incident stroke or other cardiovascular event, death, loss to follow-up, or the end of this study (December 2007), whichever came first. As noted earlier, individuals who died or had a cardiovascular event before the start of follow-up were excluded. We used time-varying Cox proportional hazards models stratified by age (in months) and calendar year (continuous) to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between time-varying averages of each size fraction of PM and stroke incidence. Deviations from linearity were examined using cubic splines. The analyses were performed separately for the different time-varying exposure windows (1 and 12 months) and results are reported for a 10-$\mu g/m^3$ increase in each PM metric to facilitate comparisons with previous studies.

The basic model was adjusted for age, race, calendar year, season, and Census region. In multivariable models, we further included all potential confounders listed earlier. To determine the impact of specific confounders, or groups of confounders, on the exposure-response functions, we added them to the basic models. We tested each potential effect modifier by adding a multiplicative interaction term to the multivariable model and calculating strata-specific estimates.

To determine the robustness of our findings to different outcome definitions, we included sensitivity analyses restricting our analyses of total stroke to only those cases where a subtype was known, and to stroke cases where all requested medical records were available and the case was classified as definite.

All analyses were conducted with SAS software (SAS Institute, Inc., version 9.4), and we considered an alpha level of 0.05 when determining statistical significance of the main effects or interaction terms.

Results

During follow-up, a total of 49,603 HPFS participants were eligible for analysis. Among those men, 1,467 developed stroke during 9,178,732 person-months of follow-up, including 848 ischemic and 230 hemorrhagic strokes. Age-standardized characteristics of the study population overall and by tertile of 12-month moving average $PM_{2.5–10}$ and $PM_{2.5}$ are presented in Table 1.

During follow-up, participants were 64.2 (SD = 10.3) years old on average and were predominantly White, married, dentists, or veterinarians, and most were never or former smokers. Most (82%) lived in nonrural areas and were distributed across the different regions of the United States (eFigure S1; http://links.lww.com/EE/A165). More than half of the men reported moderately high or high levels of exercise; however, 56% were overweight or obese. Comorbidities and medication use related to hypertension and hypercholesterolemia were common among participants.

Participants who were exposed to higher levels of ambient PM were more likely to be unmarried and living alone, have more pack-years of cigarette smoking, consume less alcohol, perform less intense exercise, and have fewer comorbidities and medication use, but overall most individual characteristics were similar across all exposure categories. The differences in neighborhood characteristic distributions across all exposure groups were more pronounced: men in high exposure groups were more likely to live in urban areas with lower median household income and higher median home value.

Distributions of the exposures of interest throughout follow-up and correlations between each of them are presented in eTables S1 and S2; http://links.lww.com/EE/A165. The median (12.22 $\mu g/m^3$) and mean (12.27 $\mu g/m^3$) levels of 12-month moving average $PM_{2.5}$ were close to the current US EPA annual average standards (12 $\mu g/m^3$),[27] and there were wide distributions of each of the size fractions. Correlations between the 1- and 12-month moving averages were around 0.7 to 0.8 for each size fraction. Within each exposure window, PM_{10} and $PM_{2.5–10}$ were strongly correlated ($r \approx 0.8$), PM_{10} and $PM_{2.5}$ were moderately correlated ($r \approx 0.6$), and $PM_{2.5–10}$ and $PM_{2.5}$ were weakly correlated ($r \approx 0.1$).

The HRs and 95% CIs for incident stroke for a 10 $\mu g/m^3$ increase in each of the PM exposures are summarized in Table 2. We observed no evidence of nonlinearity for the associations between the 1- and 12-month time-varying averages of each size fraction of PM and all types of stroke (eFigure S2; http://links.lww.com/EE/A165), and therefore present linear exposure-response results. In basic models adjusted for age, race, calendar year, season, and Census region of residence, there was no evidence of associations between any of the PM size fractions with overall stroke or ischemic stroke. There was little evidence of confounding, comparing the basic and multivariable model results (Table 2), or the impact of including individual confounders (e.g., BMI) or groups of confounders (e.g., individual and neighborhood level SES) to the basic model (Figure 1). We observed suggestive positive associations between hemorrhagic stroke and each size fraction of PM exposure over the last 12 months in multivariable models (HR: 1.13, 95% CI: 0.86, 1.48 for PM_{10}; HR: 1.12, 95% CI: 0.78, 1.62 for $PM_{2.5–10}$; HR: 1.17, 95% CI: 0.76, 1.81 for $PM_{2.5}$). Patterns were similar in models for 1-month exposures, although the associations for hemorrhagic stroke were attenuated.

The tests for interaction showed little evidence of effect modification (eTable S3; http://links.lww.com/EE/A165). Among the stratified models examined, only participants with a prior history of diabetes appeared to be at a greater risk of total stroke. In sensitivity analyses, results were similar in models restricted to stroke cases with known subtypes and in models restricted to definite cases (eTable S4; http://links.lww.com/EE/A165).

Discussion

In this prospective cohort study, we did not find evidence supporting the presence of associations between long-term exposure to PM and incident stroke. In analysis restricted to specific stroke subtypes, there was some suggestion of a higher risk associated with hemorrhagic stroke, but the estimates were imprecise and equally consistent with the null hypothesis of no association. The results were consistent across PM size fractions and time periods.

Our findings are generally consistent with several previous studies. However, our HR = 1.05 (95% CI: 0.88, 1.25) for 12-month average $PM_{2.5}$ and total stroke is lower than a recent meta-estimate (RR = 1.13, 95% CI: 1.11, 1.15)[21] of other

Table 1.

Age-standardized characteristics of 49,603 participants of the Health Professionals' Follow-Up Study (HPFS) throughout follow-up (1988–2007) overall and by tertile of 12-month moving average ambient exposure to $PM_{2.5-10}$ and $PM_{2.5}$

		12-month moving average ambient $PM_{2.5-10}$			12-month moving average ambient $PM_{2.5}$		
	All	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Participants, N	49,603	31,259	41,954	37,225	28,274	38,686	32,290
Person-months	9,178,732	3,059,577	3,059,578	3,059,577	3,059,577	3,059,578	3,059,577
Current age, yr*	64.2 ± 10.3	66.4 ± 9.8	64.1 ± 10.4	62.2 ± 10.3	65.3 ± 10.4	64.5 ± 10.2	62.9 ± 10.2
Race, %							
White	91	92	91	90	92	92	89
Married, %	69	70	70	69	71	70	68
Living alone, %	10	7	10	14	9	9	13
Employment status, %							
Full-time employed	43	43	43	44	41	44	45
Part-time employed	9	9	9	9	9	9	10
Retired/unemployed/on disability	48	48	48	47	50	47	45
Specific occupation, %							
Dentist	58	56	58	59	55	57	61
Hospital pharmacist	1	1	1	1	1	1	1
Pharmacist	7	8	7	7	6	8	8
Optometrist	7	7	7	7	7	7	7
Osteopath physician	4	4	4	4	4	4	4
Podiatrist	3	3	3	3	2	3	4
Veterinarian	20	21	20	19	25	20	16
Smoking status, %							
Never	39	39	38	41	40	39	39
Current	6	5	6	6	6	6	7
Former	41	40	42	41	40	41	42
Pack-years	11.6 ± 17.9	10.7 ± 16.9	12.0 ± 18.1	12.1 ± 18.6	11.0 ± 17.4	11.5 ± 17.8	18.4
Alcohol consumption, g/d (%)							
0 (none)	24	23	24	27	25	24	25
0.1–4.9 (low)	23	23	24	23	21	23	25
5.0–14.9 (moderate)	26	27	26	25	26	27	26
≥15 (high)	25	26	25	24	27	25	23
Body mass index, kg/m^2 (%)							
<25 (underweight/normal)	39	38	40	40	40	39	40
25-29.9 (overweight)	45	46	45	43	45	46	43
≥30 (Obese)	11	13	11	10	11	12	11
Physical activity, MET-hrs/wk (%)							
<3 (low)	10	9	10	10	9	10	11
3-9 (moderately low)	12	11	12	13	11	12	14
9-18 (moderate)	14	14	14	15	14	15	15
18-27 (moderately high)	12	12	12	12	11	12	12
≥27 (high)	38	40	38	37	42	38	35
AHEI score	49.8 ± 11.2	49.9 ± 11.2	49.5 ± 11.1	49.8 ± 11.3	49.9 ± 11.3	49.7 ± 11.2	49.8 ± 11.1
Family history of CVD, %	12	12	12	11	11	12	12
Comorbidities, %							
Diabetes	6	7	6	6	6	6	7
Hypertension	36	38	36	34	35	36	35
Hypercholesterolemia	42	46	42	39	43	43	41

(*Continued*)

Table 1.
(Continued)

	All	12-month moving average ambient $PM_{2.5-10}$			12-month moving average ambient $PM_{2.5}$		
		Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Current medication use, %							
Aspirin	38	41	38	35	40	39	36
Antidepressants	3	3	3	2	3	3	2
Antihypertensive	20	21	20	19	20	21	20
Cholesterol lowering	12	15	11	9	13	13	10
Census tract population density, %							
Rural	18	25	17	13	28	17	9
Suburban	36	44	37	27	35	40	33
Urban	46	30	47	60	38	43	58
Census region, %							
Northeast	22	38	21	8	12	29	25
Midwest	26	27	26	26	19	29	30
West	23	9	17	43	41	13	15
South	29	26	36	24	28	29	29
Census tract SES							
Median household income, USD$	62,783 ± 28,713	65,660± 27,934	62,571± 28,526	60,424± 29,554	58,275± 24,895	65,206± 29,434	64,854± 31,036
Median home value, USD$	178,188 ± 146,654	171,020± 117,657	174,709± 144,321	189,880± 173,762	169,639± 138,842	179,324± 142,430	185,743± 158,667

Values are means ± SD or percentages and are standardized to the age distribution of the study population and participants may be in multiple exposure categories throughout follow-up.
*Values are not age adjusted.

studies. Compared with a previous study by Puett et al.[28] in the HPFS, we observed generally larger estimates of effect with a longer study period and more cases; however, the results still did not reach statistical significance. Our findings are also comparable to a study conducted among women in the Nurses' Health Study (NHS), in which each 10 μg/m^3 increase in 12-month average PM_{10}, $PM_{2.5–10}$, and $PM_{2.5}$ (estimated from the same model used in these analyses) was associated with HRs of 1.03 (95% CI: 0.99, 1.12), 1.05 (95% CI: 0.95, 1.16), and 1.03 (95% CI: 0.92, 1.15), respectively, for incident stroke.[26] Some studies only reported risks for total stroke incidence,[18,19,26] but many have also investigated hemorrhagic and ischemic stroke subtypes.[17,29–31] The trend of larger effect estimates for hemorrhagic stroke risks has been relatively consistently observed, but the effect estimates have varied widely, likely due to the variation of study designs, lag periods, and population characteristics. However, some studies have also observed higher risks of ischemic stroke than hemorrhagic stroke.[32,33] Estimating the effects of stroke subtypes has been challenging in this and other studies, due to the additional information needed to subtype cases. Our HR = 1.17 (95% CI: 0.76, 1.81) for $PM_{2.5}$ and hemorrhagic stroke is somewhat higher than a recent meta-estimate (RR = 1.10, 95% CI: 1.05, 1.16)[21]; however, our HR = 0.99 (95% CI: 0.79, 1.25) for $PM_{2.5}$ and ischemic stroke is much lower than a recent meta-estimate (RR = 1.18, 95% CI: 1.14, 1.22).[21]

The associations from our multivariable models are weaker than those from previous cohort studies that also included men. Stockfelt et al.[18] reported HRs for incident stroke in men of 1.13 (95% CI: 0.56, 2.28) and 1.13 (95% CI: 0.57, 2.24) per 5 μg/m^3 increase in PM_{10} and $PM_{2.5}$ exposure over the last 5 years. These estimates were lower than those observed for woman in the same analyses. Another study for incident stroke within the European Study of Cohorts for Air Pollution Effects (ESCAPE) Project observed that increases in annual PM_{10}, $PM_{2.5–10}$, and $PM_{2.5}$ exposure was associated with incident stroke HRs of 1.11 (95% CI: 0.90, 1.36, per 10 μg/m^3), 1.02 (95% CI: 0.90, 1.16, per 5 μg/m^3), and 1.19 (95% CI: 0.88, 1.62, per 5 μg/m^3), respectively, with no evidence of effect modification by sex.[19] In an update as part of the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project, each 5 μg/m^3 increase in $PM_{2.5}$ was associated with an HR = 1.10 (95% CI: 1.01, 1.21), and results stratified by sex were not presented. The different findings between cohorts may result from sex differences in susceptibility to the effect of air pollution-mediated stroke, geographic differences in PM sources and composition, or methodologic differences in exposure assessment among studies. Many studies have reported stronger associations between long-term air pollution and cardiovascular health outcomes among women.[12,28,34–36] Physiological factors like smaller airways and lower erythrocyte levels have been hypothesized to result in greater deposition of inhaled particles and stronger effects of air pollution on blood viscosity.[37] However, many of the studies of stroke that examined effect modification by sex did not report any evidence of modification, although in recent studies in Taiwan and Canada, associations appeared stronger in men.[15,16]

We observed stronger associations with 12-month averages than 1-month averages (Table 2). This is consistent with the findings of other studies that have examined different time windows, where the strongest effects were usually observed for exposure in the last couple of years.[15,18,37,38] This might be expected since long-term effects are usually characterized by progression of atherosclerosis.[39]

The mechanisms through which air pollution may impact cardiovascular disease risk broadly have been extensively reviewed.[21,37] Briefly, inflammation, oxidative stress, and atherosclerosis have been consistently shown to be elevated with increasing exposures to air pollution, especially among older adults.[37,40–44] Ischemic strokes occur when blood flow to the brain is impaired by a blood clot, while the rarer hemorrhagic

Table 2.

Associations between medium- and long-term exposures to PM per 10 μg/m³ increase and incident stroke 1988–2007 among 49,603 participants of the Health Professionals' Follow-Up Study (HPFS), with 9,178,732 person-months of follow-up

	PM_{10} (μg/m³)		$PM_{2.5-10}$ (μg/m³)		$PM_{2.5}$ (μg/m³)	
Outcome	12 month	1 month	12 month	1 month	12 month	1 month
Total stroke (1,467 cases)						
Basic model* HR (95% CI)	1.02 (0.93, 1.13)	0.99 (0.92, 1.07)	1.02 (0.89, 1.18)	1.02 (0.92, 1.14)	1.03 (0.87, 1.21)	0.95 (0.84, 1.07)
Multivariable model† HR (95% CI)	1.04 (0.93, 1.15)	1.00 (0.92, 1.08)	1.04 (0.90, 1.20)	1.03 (0.92, 1.16)	1.05 (0.88, 1.25)	0.95 (0.84, 1.08)
Hemorrhagic stroke (230 cases)						
Basic model* HR (95% CI)	1.12 (0.87, 1.45)	1.04 (0.85, 1.28)	1.15 (0.80, 1.65)	1.00 (0.74, 1.35)	1.13 (0.74, 1.71)	1.10 (0.81, 1.50)
Multivariable model† HR (95% CI)	1.13 (0.86, 1.48)	1.04 (0.84, 1.28)	1.12 (0.78, 1.62)	0.98 (0.73, 1.33)	1.17 (0.76, 1.81)	1.12 (0.82, 1.53)
Ischemic stroke (848 cases)						
Basic model* HR (95% CI)	0.95 (0.83, 1.08)	0.99 (0.89, 1.09)	0.97 (0.78, 1.20)	0.98 (0.84, 1.13)	0.97 (0.78, 1.20)	1.00 (0.85, 1.17)
Multivariable model† HR (95% CI)	0.96 (0.84, 1.11)	1.00 (0.90, 1.11)	0.99 (0.79, 1.25)	0.99 (0.85, 1.15)	0.99 (0.79, 1.25)	1.01 (0.86, 1.19)

*Models adjusted for age (in months), race (White, non-White), calendar year (continuous), season (spring, summer, fall, winter), and Census region (Northeast, Midwest, West, South).
†Models additionally adjusted for smoking status (current, former, never) and pack-years (continuous), alcohol consumption ((0, 0.1–4.9, 5.0–14.9, or ≥15 g/day), BMI (<25 kg/m², 25–29.9 kg/m², and ≥30 kg/m²), physical activity (<3, 3–8.9, 9–17.9, 29–26.9, ≥27 MET-hrs/week), diet quality (continuous Alternate Healthy Eating Index [AHEI] not including alcohol (McCullough and Willett, 2006), family history of CVD (yes/no), comorbidities (yes/no for each of diabetes, hypertension, and hypercholesterolemia), current medication use (yes/no for each of aspirin, antidepressants, antihypertensive, and cholesterol lowering medication), individual (marital status [married yes/no], living arrangement [alone, with others], employment status [full time, part time, retired/unemployed/disabled], and occupation), and area-level socioeconomic status (Census tract median household income and median home value), and Census tract population density.

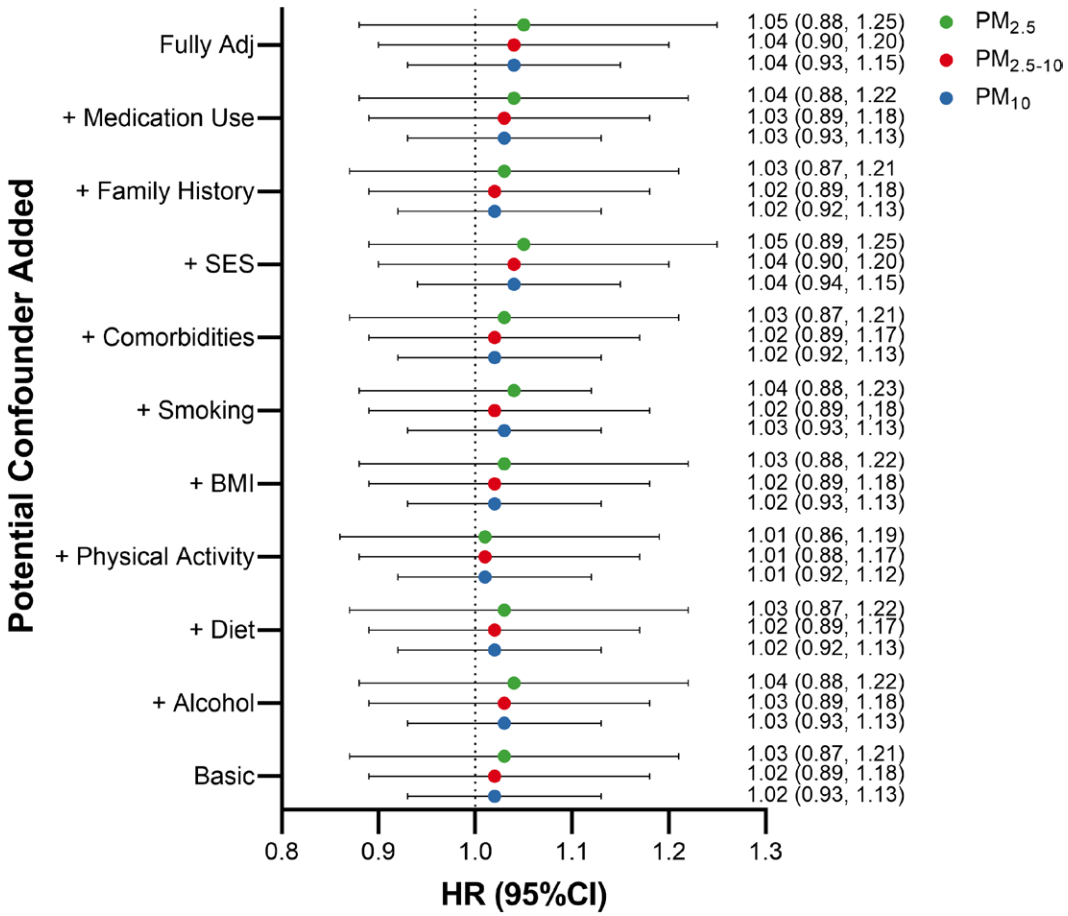

Figure 1. Impact of adding each confounder or group of confounders to the basic model on the risk of total stroke (cases = 1,467) with 12-month moving average exposures to PM_{10}, $PM_{2.5-10}$, or $PM_{2.5}$. SES denotes the inclusion of both individual- and neighborhood-level SES variables.

strokes occur when a blood vessel bursts, resulting in bleeding in the brain. Thus, the mechanisms through which air pollution exposures may act is likely different for these different subtypes. For example, air pollution may impact hemorrhagic stroke through increases in blood pressure and hypertension, although impacts on ischemic stroke may be more

likely to work through atherosclerosis and changes in blood coagulation.[21,37,43]

Several limitations of this study should be mentioned. Although we were able to predict PM levels at each address, exposure misclassification could still be raised by our lack of information on individuals' time-activity patterns and building characteristics that influence indoor infiltration of ambient PM. Given that our exposure predictions are made at the address-level, this may be a larger issue than it would be in studies where predictions are made over a larger spatial scale that may more fully cover each individuals' activity space. Also, the HPFS mailing addresses are a mix of work and home addresses, which may add additional nondifferential exposure misclassification and partially explain our generally nonstatistically significant results. We also only have address information in adulthood for these participants, which does not allow us to consider the impact of exposures before enrollment into the cohort on risk of stroke. The number of cases classified as unknown could potentially induce bias in the subtype-specific models, if there are geographic patterns to the availability of information needed to assign subtypes. There may also be other geographically varying predictors of stroke, or stroke subtypes, that we were unable to control for in this study, as it has been shown that incidence of ischemic and hemorrhagic stroke have different geographic patterns.[45] Results from our sensitivity models excluding those cases were similar, as were those from models restricted to definite cases, however, so this may not be a major weakness. We also lacked information on important risk factors for stroke, such as blood pressure measurements and incidence of atrial fibrillation, which, along with other unmeasured factors, may have resulted in unmeasured confounding. Another important limitation to be considered is generalizability. The HPFS was limited to men with relatively high socioeconomic status and there are only a small percentage of minority participants. Therefore, our results may not be generalizable to general populations with more diverse characteristics or populations with much higher or lower PM exposures.

Our study has some important strengths. The analysis used high quality exposure estimates from high-resolution models that incorporate geographic and meteorological predictors, as well as well-validated cases of stroke incidence. Additionally, we were able to collect information on a wide variety of time-varying covariates during the long time period of intensive follow-up, allowing us to reduce the potential residual confounding and perform stratified analyses to explore potentially susceptible subpopulations.

In conclusion, in this prospective cohort study among men in the US-based HPFS, we observed suggestive positive associations between long-term exposure to PM and risk of hemorrhagic, but not total or ischemic strokes. Overall, our study adds to the growing literature on the associations between long-term exposure to air pollution and risks of incident stroke, but the findings, especially for specific stroke subtypes, still need more investigation.

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