Long-Term Exposure to Ambient Particulate Matter and Stroke Etiology: Results from the Women's Health Initiative

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ABSTRACT

Background: Ambient particulate matter (PM) air pollution is a leading cause of global disability and accounts for an annual 2.9 million deaths globally. PM is established as an important risk factor for cardiovascular disease, however the evidence supporting a link specifically between long-term exposure to ambient PM and incident stroke is less clear. We sought to evaluate the association of long-term exposure to different size fractions of ambient PM with incident stroke (overall and by etiologic subtypes) and cerebrovascular deaths within the Women's Health Initiative, a large prospective study of older women in the US.

Methods: We studied 155,410 postmenopausal women without previous cerebrovascular disease enrolled into the study between 1993-1998, with follow-up through 2010. We assessed geocoded participant address-specific concentrations of ambient PM (fine [$PM_{2.5}$], respirable [PM_{10}] and coarse [$PM_{10-2.5}$]), as well as nitrogen dioxide [NO_2]) using spatiotemporal models. We classified hospitalization events into ischemic, hemorrhagic, or other/unclassified stroke. Cerebrovascular mortality was defined as death from any stroke etiology. We used Cox proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals, adjusting for individual and neighborhood-level characteristics.

Results: During a median follow-up time of 15 years, participants experienced 4,556 cerebrovascular events. The hazard ratio for all cerebrovascular events was 2.14 (95% CI: 1.87, 2.44) comparing the top versus bottom quartiles of $PM_{2.5}$. Similarly, there was a statistically significant increase in events comparing the top versus bottom quartiles of PM_{10} and NO_2 (HR: 1.17; 95% CI: 1.03, 1.33 and HR:1.26; 95% CI: 1.12, 1.42). The strength of association did not

vary substantially by stroke etiology. There was little evidence of an association between PM_{coarse} and incident cerebrovascular events.

Conclusions: Long-term exposure to fine ($PM_{2.5}$) and respirable (PM_{10}) particulate matter as well as NO_2 was associated with a significant increase of cerebrovascular events among postmenopausal women. Strength of the associations were consistent by stroke etiology.

Keywords: air pollution; particulate matter; stroke; cerebrovascular disease; ischemic stroke; hemorrhagic stroke

Non-standard abbreviations and acronyms: PM: particulate matter, WHI: Women's Health Initiative, IQR: interquartile range, NSES: neighborhood socioeconomic status, HR: hazard ratio, CI: confidence interval

INTRODUCTION

Ambient particulate matter (PM) air pollution is a leading cause of disability and accounts for an estimated 2.9 million deaths per year globally[1]. Estimates from the Global Burden of Disease suggest that 977,000 (approximately one-third) of these excess deaths are due to ischemic heart disease with an additional 184,000 (6.3%) excess deaths due to ischemic stroke and 226,000 (7.7%) due to intracerebral hemorrhage.[1] An earlier analysis by Global Burden of Disease investigators reported that ambient air pollution was a leading cause of global stroke-related disability-adjusted life-years, accounting for an estimated 16% of all stroke-related disability-adjusted life-years.[2,3]

These estimates of population attributable numbers or fractions explicitly assume the presence of a relationship between exposure and specific health end points. PM has been established as an important risk factor for cardiovascular disease with extensive evidence of adverse health effects of both long-term exposures (over the course of months to years, on which the Global Burden of Disease estimates are based) and short-term exposures (on the order of hours to days).[4–6] On the other hand, the evidence supporting a link specifically between long-term exposure to ambient PM and incident stroke is less clear.[7] For example, prospective cohort studies in North America[8,9], Europe[10,11], and Asia[12–14], provide important evidence supporting an association between long-term exposure to ambient fine ($PM_{2.5}$) and/or respirable (PM_{10}) particulate matter and either incident stroke or cerebrovascular mortality. However, a number of other studies report either no association or suggestive positive associations with wide confidence intervals that include the null hypothesis of no association.[10,15–20] A few additional studies have only

found associations among specific subgroups of participants such as women[16], those with specific stroke subtypes, particularly those that examine ischemic stroke events[21,22], or other subsets of the study population.[16–18]

This heterogeneity across prior studies suggests the need for additional prospective cohort studies to examine the effects of long-term exposure to air pollution across different cerebrovascular outcomes. While the pathophysiologic mechanisms that link air pollution to stroke and cerebrovascular events are still largely unknown, mechanisms may differ by etiologic sub-type. [7] Accordingly, our goal was to evaluate the association between long-term exposure to $PM_{2.5}$ and PM_{10} and incident stroke (overall and by etiologic subtypes) and cerebrovascular deaths within the context of the Women's Health Initiative, a large prospective cohort study of post-menopausal women across the United States with 17 years of follow-up data and more than 4,400 documented cerebrovascular events. We hypothesized that long-term average concentrations of ambient $PM_{2.5}$ and PM_{10} at the residence would be associated with incident cerebrovascular events. In secondary analyses we additionally considered the association between ambient concentrations of coarse particulate matter (PM_{coarse}) and NO_2 (a marker of traffic pollution) and cerebrovascular events.

METHODS

Study population

The Women's Health Initiative (WHI) enrolled post-menopausal women aged 50 to 79 into either the WHI Observational Study (WHI-OS) or one or more of three WHI Clinical Trials (WHI-CT) between 1993 and 1998, as previously described.[23–25] Briefly, the WHI-OS is a longitudinal cohort designed to examine causes of morbidity and mortality in postmenopausal women.[23] The WHI-CT examined the effects of menopausal hormone therapy (HT), calcium and vitamin D supplementation (CaD), and a low-fat dietary modification (DM).[24]

Of the 93,676 WHI-OS and 68,132 WHI-CT participants enrolled, we included all participants except those with history of cerebrovascular events at enrollment (n=2,156), those with missing stroke etiology (n=56), and those missing exposure data (n=4,176). Our final analytical sample included 155,410 women.

Exposure Assessment

Participant's addresses were recorded at the time of enrollment, confirmed at each follow-up visit, and reviewed at least annually with participants as part of cohort retention activities. Addresses were then geocoded using a previously described protocol.[26] For each address, annual average geocoded participant address-specific concentrations of different size fractions of particulate matter ($PM_{2.5}$, PM_{10}) were estimated. Estimates from 1993-1998 were obtained using a national spatiotemporal model of annual average concentrations of pollutants. For years 1999-2013, a national model was built using partial least squares and universal kriging to predict average concentrations of $PM_{2.5}$.[27,28] Predictions were made using data collected in the continental United States from IMPROVE and CSN monitors, and geographic covariates such as

distance to roadway, population density, and Normalized Difference Vegetation Index. PM_{10} was based on a national model similar to that of $PM_{2.5}$, described above. We calculated PM_{coarse} ($PM_{10-2.5}$) from the difference between estimates of PM_{10} and $PM_{2.5}$.[29] We additionally estimated annual average geocoded participant address-specific concentrations of NO_2, which were derived from similar national models with the addition of station monitor data. Residential addresses were updated at each annual follow-up, and time-varying estimates of pollutant exposure were calculated annually for each participant as an average of the current and previous year pollutant predictions weighted by time spent at each address during each year measured.

Outcome Assessment

We followed participants for clinical outcomes through the end of the WHI Extension I study (December 2010) or the date of the first stroke event. Hospitalization events were first identified using medical records and potential stroke events were adjudicated by physicians and classified into ischemic stroke, hemorrhagic stroke, or other/unclassified stroke. The WHI criteria for clinical endpoints were adapted from standardized criteria as previously reported.[30]

We defined cerebrovascular mortality as death from any stroke etiology and first obtained as part of routine participant follow-up that included reports from family or next of kin, obituaries, and data linkage with the National Death Index.[30] Death certificates and hospital records were obtained when possible, and all events were adjudicated by trained reviewers. Cerebrovascular events included cerebrovascular death and all-cause stroke hospitalizations.

173 *Covariate data*

174

175 We collected sociodemographic characteristics, lifestyle factors, medical history, and health
176 status using self-reported standardized questionnaires at enrollment. We defined race-ethnicity as
177 White, African American/Black, and Other (where 'other' included Hispanic or Latina, Asian,
178 Pacific Islander, American Indian, and Other). Education was defined as completing a college
179 degree versus having less than a college degree. Household income was obtained through self-
180 report. Employment status was dichotomized into working outside the home versus not working
181 outside the home at baseline. We categorized smoking status as never smoker (<100 lifetime
182 cigarettes) and ever smoker (≥ 100 lifetime cigarettes). Alcohol consumption was reported as
183 servings per week, where servings were defined as 12 oz. of beer, 6 oz. of wine, or 1.5 oz. of
184 liquor. High cholesterol and diabetes were defined as a self-reported physician diagnosis, and
185 hypertension at enrollment was defined as using antihypertensive medication or elevated blood
186 pressure (systolic≥140 or diastolic≥90 mmHg). We calculated body mass index (BMI, in kg/m^2)
187 at baseline and subsequent follow-up visits. Physical activity was defined as Metabolic
188 Equivalent (MET) hours per week, calculated using a questionnaire which collects frequency,
189 duration, and pace of self-reported activities.[31]

190

191 We calculated neighborhood socioeconomic status (NSES) as a summary z-score derived at the
192 census tract level as a neighborhood measure of wealth, education, and occupation,[32] based on
193 data came the American Community Survey Crosswalk from the US Census.

194

195 *Statistical Methods*

We used multiple imputation by chained equations in order to include in the analyses participants with missing covariate data on income (missing 6.7%), education (missing 0.7%), race-ethnicity (missing 0.2%), high cholesterol (missing 5.9%), hypertension (missing 0.8%), alcohol use (missing 0.3%), smoking (missing 0.8%), MET (missing 4.7%), diabetes (missing 0.1%), marital status (missing 0.5%), family history of stroke (missing 5.7%), employment status (missing 6.6%), NSES z-score (missing 0.01%), and BMI (missing 0.1%). All covariates and pollutants were included in the imputation model regardless of whether they were missing any values, while outcome was not included in the imputation model. We implemented this approach using the R *mice* package (version 2.46.0)[33] and used 10 imputations.

To estimate the hazard ratio (HR) and 95% confidence interval (CI) for incident cerebrovascular events associated with an IQR shift in each pollutant we used time-varying Cox proportional hazards models. In all models, air pollution was considered a time-varying exposure. We adjusted for potential confounders including age, race, smoking, education, income, marital status, employment status, BMI, high cholesterol, diabetes, and hypertension at enrollment, family history of stroke, alcohol consumption, physical activity, WHI study component (HT or OS), and WHI center, all which were considered time-fixed at enrollment and not allowed to vary over time. We allowed NSES measures to be time-varying as to reflect address changes over time. We additionally adjusted for $PM_{2.5}$ in models with PM_{coarse} as the exposure. Pollutant estimates were modeled as continuous variables (per interquartile range (IQR)) and repeated using quartiles of pollutants. Quartiles were calculated using pollution data at enrollment due to the overall decreasing trend in pollutant concentrations over time.

Additionally, we looked to see whether the association between ambient air pollution and cerebrovascular outcomes varied across strata of age, race, education, BMI, region, smoking, MET, high cholesterol, hypertension, and diabetes by adding interaction terms to our main models. Interaction terms with a p-value <0.10 were considered potentially statistically significant.

All analyses were run in R version 3.4.3 with packages *survival* v.2.41-3.[34,35]

RESULTS

At enrollment, the 155,410 post-menopausal women included in these analyses had a mean age of 63.2 ± 7.2 years (mean ± standard deviation (SD)) and were predominantly White (84%), without a college degree (60%), and married or living with a partner (62%) (Table 1).

Geocoded participant address-specific mean annual $PM_{2.5}$ concentrations at enrollment ranged from 3.0 to 25.2 $\mu g/m^3$ with a mean ± SD of 14.2 ± 2.8 $\mu g/m^3$ (Table 2). Participants living in areas with the highest concentrations of $PM_{2.5}$ were more likely to be African American or Black (18% vs 2% in the upper versus lower quartiles of $PM_{2.5}$), college educated (41% vs 34%), current smoker (8% vs 6%), and have hypertension (34% vs 32%) (Table 1). $PM_{2.5}$ concentrations were moderately correlated with PM_{10} (r=0.56) and NO_2 (r=0.66) and uncorrelated with PM_{coarse} (r=0.07) (Supplemental Table S1).

242 During a median follow-up time of 14.9 years, study participants experienced 4,556 documented
243 cerebrovascular events, including 2,946 ischemic stroke hospitalizations, 666 hemorrhagic stroke
244 hospitalizations, 605 stroke hospitalizations of undetermined etiology, and 946 cerebrovascular
245 deaths. In models adjusting for individual and neighborhood-level characteristics, the hazard
246 ratio of cerebrovascular events increased monotonically with increasing quartiles of $PM_{2.5}$ (Table
247 3). A linear association was apparent and statistically significant for all outcomes of interest. For
248 example, the hazard ratio for all cerebrovascular events was 2.14 (95% CI: 1.87, 2.44)
249 comparing the top versus bottom quartiles of $PM_{2.5}$. In models considering PM2.5 as a linear
250 continuous variable, the hazard ratio for an IQR (3.5 $\mu g/m^3$) shift in PM2.5 ranged from 1.13
251 (95% CI: 1.06, 1.19) to 1.18 (95% CI: 1.11, 1.26) dependent on event type (Figure 1,
252 Supplemental Table S2), however hazard ratios did not differ statistically significantly by
253 cerebrovascular outcome.
254
255 There were also strong associations between both PM_{10} and NO_2 and cerebrovascular outcomes
256 (Figure 2). The HR for all cerebrovascular events was 1.17 (95% CI: 1.03, 1.32) comparing the
257 top versus bottom quartiles of PM_{10}, or 1.04 (95% CI: 1.01, 1.07) per interquartile range shift in
258 PM_{10} (Figure 1,Supplemental Table S2). The hazard ratio for an IQR shift in NO_2 ranged from
259 1.02 (95% CI: 0.93, 1.11) to 1.16 (95% CI: 1.06, 1.27) depending on event type, with NO_2
260 having the strongest association with unclassified stroke hospitalizations (Supplemental Table
261 S3), however differences across stroke type were not statistically significant. In contrast, there
262 was little evidence of an association between geocoded participant address-specific PM_{coarse} and
263 incident cerebrovascular events (Supplemental Table S4).
264

We evaluated whether the association between particulate matter, specifically $PM_{2.5}$ and PM_{10}, and the hazard of all cerebrovascular events varied by the presence of key stroke risk factors. We found no evidence of statistically significant heterogeneity by age, race, education, hypertension, diabetes, BMI, smoking history, or neighborhood socioeconomic status (Supplemental Table S6).

DISCUSSION

In this national cohort of post-menopausal women, we found long-term geocoded participant address-specific concentrations of $PM_{2.5}$, PM_{10}, and NO_2 to be associated with higher risk of cerebrovascular events, with the strength of association remaining relatively consistent across event types. A linear association was most apparent and statistically significant between $PM_{2.5}$ and PM_{10} and all stroke hospitalizations, ischemic stroke hospitalizations, unclassified stroke hospitalizations, and all cerebrovascular events. Associations were weaker and not statistically significant between PM_{10} and hemorrhagic stroke hospitalizations. In contrast, there were no significant associations between PM_{coarse} and cerebrovascular events.

An earlier study done in the WHI-OS cohort with approximately 6 years of follow-up for cardiovascular events found a HR of 1.28 (95% CI:1.02-1.61) for time to first ever all-cause stroke event per 10 $\mu g/m^3$ increase in $PM_{2.5}$.[9] Our study provided updated evidence to the prior research by extending the follow-up time to an average of 15 years, examining several exposures metrics of ambient air pollution ($PM_{2.5}$, PM_{10}, $PM_{coarse,}$ and NO_2), and investigating differences in associations by stroke event types. However, the pattern of results found in the Miller et al.

288 study[9] and the current analysis are similar and support the existence of an association between air
289 pollution and cerebrovascular events.
290
291 The inclusion of stroke sub-type in our study builds on the existing research supporting an
292 association between long-term exposure to ambient air pollution and incident stroke. Prior
293 studies of long-term exposure to PM and incident all-cause stroke have generally suggested a
294 positive association.[8–14,36] However, in many other studies, the estimates of association were
295 either null or report positive associations that have not reached statistical significance[10,15–20,37–41]
296 Similar to the aforementioned WHI study, in the international PURE study, the largest
297 prospective cohort study on this topic to date, the authors found a HR for incident stroke of 1.07
298 (95% confidence interval [CI]: 1.05, 1.10) per 10 μg/m^3 increase in ambient fine particles
299 ($PM_{2.5}$).[36] The European ESCAPE study of 22 pooled cohorts, found increased risk of
300 cerebrovascular disease deaths with exposure to higher levels of $PM_{2.5}$, PM_{10}, and coarse PM. [15]
301 While this study and others have found associations between long-term exposure to pollutants
302 and cerebrovascular mortality. [42,43] several studies have only found associations among specific
303 subgroups of participants such as women[16], those with specific ischemic stroke subtypes[22], or
304 other subsets of the study population.[16–18,21]
305
306 While pathophysiologic mechanisms behind the effect of ambient air pollution on stroke remain
307 largely unknown, research demonstrates that long-term exposure to air pollution may cause
308 systemic inflammation leading to vascular inflammation, altered sympathovagal balance causing
309 sympathetic nervous system dominance, and altered hemostatic balance instigating a
310 prothrombotic inflammatory state.[44–48] Each mechanisms may play a different role on stroke

311 incidence across stroke types. In our analysis, we found consistent strength of effects when
312 looking across stroke types. These results are consistent with studies assessing the effects of
313 short-term spikes in air pollution on stroke risk where the effects of an acute increase of air
314 pollution were stronger in ischemic strokes compared to hemorrhagic stroke.[49,50] We did see
315 slightly attenuated effects of PM_{10} and NO_2 among hemorrhagic stroke hospitalizations, although
316 the differences between stroke types were not statistically significant in contrast to several earlier
317 studies which saw stronger effects of PM on incident ischemic stroke.[8,11,14] These results support
318 the existing science which states that while all sizes of particulate matter are considered harmful
319 to human health, the smaller particles of $PM_{2.5}$ are more likely to travel deeper into the lungs
320 where they will be trapped and become available to interact with defense mechanisms to trigger
321 systemic inflammation, or pass directly into the circulatory system and be distributed throughout
322 the body.[51,52]
323
324 The current study adds to the growing scientific evidence supporting the importance of exposure
325 to air pollution in cerebrovascular health, although the authors acknowledge the analysis had
326 several important limitations.
327
328 Address histories were collected from participants over the duration of follow-up, there may be
329 potential for misclassification of exposure from inaccurate address information. Additionally,
330 different methods were utilized to assess exposure between 1993-1998 in comparison to 1999-
331 2013.Previous research in this cohort suggest that bias from these types of exposure
332 misclassification will be relatively small in urban areas and potentially larger in suburban and
333 rural areas of residence, but in both instances would bias our results towards the null.[26] A second

limitation is that the geocoded participant address-specific pollution estimates used here do not include data on time spent in locations outside the home. However, time spent indoors averages 19.6 hours/day at ages > 65 years.[53] Moreover, ambient PM exposure-outcome associations are often biased toward the null given that ambient-personal PM correlations are driven by ambient PM concentrations. [54,55] In addition, the measurement of late-life environmental exposures does not necessarily indicate an individual's true lifetime exposure. Lastly, the study was limited to post-menopausal women participating in either the WHI clinical trial or the WHI observational study, potentially limiting the generalizability of our findings to younger individuals, men, or the United States population in general.

Key strengths of this study include the use of a large, well characterized, geographically diverse prospective cohort with detailed clinical adjudication of cerebrovascular events and mortality. In addition, we were able to assess the differing effects of ambient air pollution on stroke type. Lastly, the comprehensive, high-quality WHI covariate data obtained longitudinally at follow-up allowed for rigorous adjustment for confounding.

CONCLUSIONS

Ambient particulate matter air pollution is a leading cause of global death and disability, with 184,000 ischemic stroke deaths and 226,000 hemorrhagic stroke deaths attributed to particulate matter each year. While PM is a well-established risk factor for cardiovascular disease, the evidence supporting an association between long-term exposure to ambient PM and incident stroke remains less clear. Our study showed that long-term exposure to PM is associated with the

incidence of cerebrovascular events among postmenopausal women. The strength of associations did not vary substantially by stroke etiology. These findings speak to the need for future studies to investigate the differential effects of air pollution by stroke type in order to strengthen the evidence surrounding the association between particulate matter and stroke incidence.

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CONFLICTS OF INTEREST/DISCLOSURES

GAW has received consulting income from the Health Effects Institute (Boston, MA) and Google, LLC (Mountain View, CA). All other authors report no disclosures.

Table 1: Characteristics of WHI participants at study enrollment, overall and by quartiles of $PM_{2.5}$.

Characteristics	All (N=155,410)	Quartiles of PM2.5 ($\mu g/m^3$) at Enrollment			
		Q1 ≤ 9.9	Q2 (9.9,11.8]	Q3 (11.8, 13.6]	Q4 >13.6
Age, years, mean ± SD†	63.2 (7.2)	63.4 (7.1)	63.4 (7.1)	63.0 (7.2)	63.0 (7.4)
Race, %					
White	84.1	88.5	91.0	81.6	75.2
African American or Black	9.0	2.1	3.8	12.7	17.8
Hispanic or Latina	4.0	6.9	2.6	2.8	3.6
Asian or Pacific Islander	1.2	0.8	1.1	1.3	1.7
Other	1.4	1.6	1.3	1.4	1.4
Education, %					
< College degree	59.8	64.8	59.4	57.1	57.8
College graduate	39.4	34.4	40.0	42.1	41.5
Married or living with partner, %	62.1	67.5	66.0	60.1	54.6
Household income, %					
<$20,000	15.5	16.7	12.7	14.5	17.9
$20,000-<$50,000	42.0	44.7	42.1	40.1	40.8
≥ $50,000	35.9	31.8	38.7	38.6	34.7
Body mass index, %					
≤ 25 kg/m^2	34.7	34.2	35.6	34.5	34.3
25-<30 kg/m^2	34.5	35.6	34.7	34.0	33.7
≥ 30 kg/m^2	30.0	29.5	28.8	30.5	31.2
Alcohol drinks/week, %					
None or < 1	62.0	60.4	59.7	62.7	65.3
1-6	25.9	26.5	27.6	25.7	23.7
≥ 7	11.8	12.6	12.4	11.4	10.7
Ever Smoker, %					
Never	50.2	51.4	50.6	49.3	41.5
Past	41.7	40.9	42.1	42.3	49.2
Current	6.8	6.3	6.1	7.1	7.8
Currently working, %	34.9	32.4	35.6	36.6	35.2
Health insurance, %	94.4	93.0	95.9	95.0	93.9
Physical activity, %					
<3.00 MET† hr/wk	26.4	26.4	25.9	26.7	26.6
3.00 - <11.75 MET hr/wk	30.8	30.8	30.9	30.7	30.9
≥ 11.75 MET hr/wk	38.1	39.5	39.2	37.8	35.8
Diabetes ever, %	5.7	5.6	5.1	5.8	6.4
High cholesterol ever, %	13.0	12.8	12.8	13.0	13.3

Hypertension ever, %	33.0	32.2	32.0	33.6	34.3
WHI Study Region, %					
Northeast	23.4	20.6	30.2	24.6	18.3
South	26.4	23.0	23.8	28.1	30.7
Midwest	22.4	15.1	24.8	28.3	21.9
West	27.8	41.3	21.2	19.0	29.2

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Table 2: Exposure distribution at participant study enrollment							
Pollutant (units)	Mean (SD)	Minimum	25^{th} Percentile	50^{th} Percentile	75^{th} Percentile	Maximum	IQR
$PM_{2.5}$ ($\mu g/m^3$)	14.2 (2.8)	3.0	12.5	14.3	15.9	25.2	3.5
PM_{10} ($\mu g/m^3$)	23.9 (5.5)	7.8	20.3	23.1	26.5	56.9	6.2
PM_{coarse} ($\mu g/m^3$)	9.7 (4.5)	-0.6	6.6	8.8	11.7	42.2	5.1
NO_2 (ppb)	17.7 (7.2)	0.9	12.4	17.3	21.9	48.4	9.5

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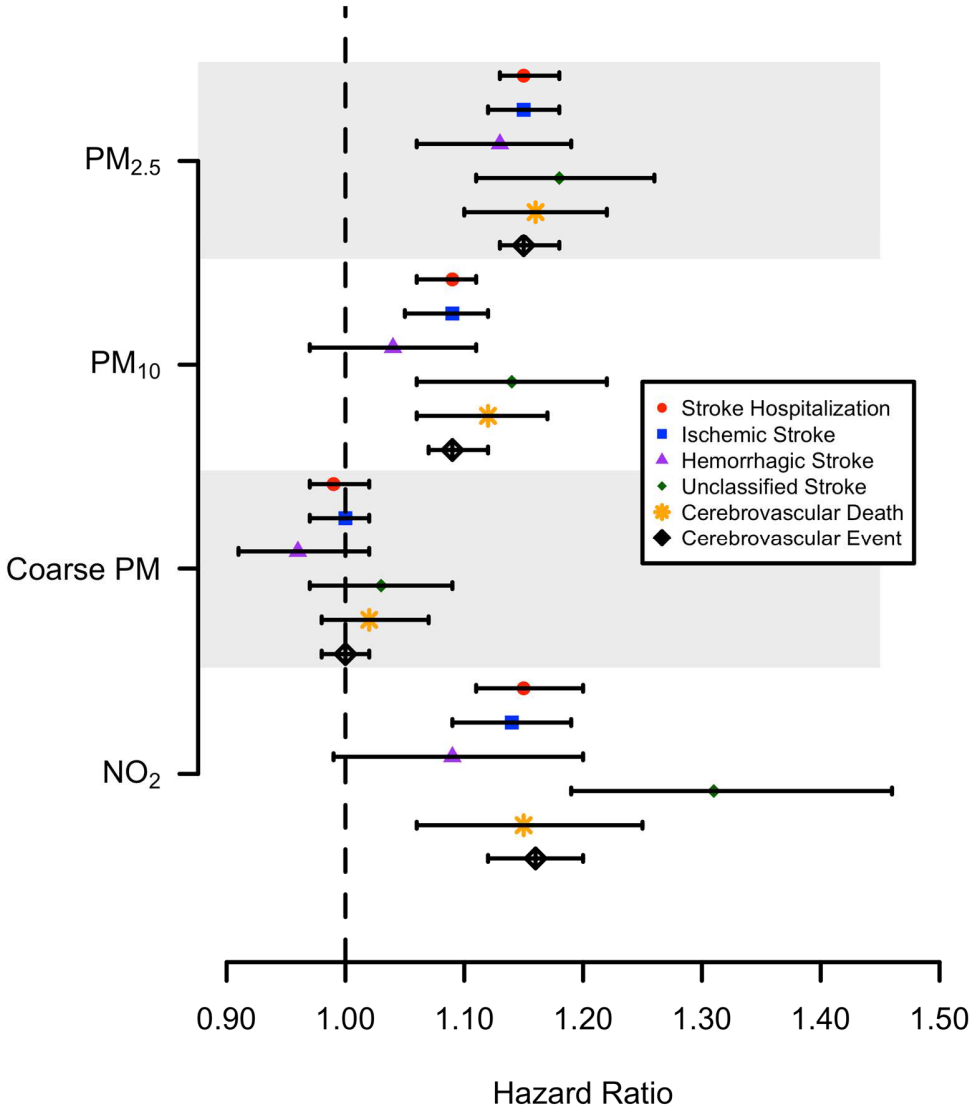
Table 3: Hazard ratios (95% confidence intervals) of the association between time-varying $PM_{2.5}$ and incident stroke.

Outcome*	Number of Events	Quartiles of $PM_{2.5}$				P_{trend}	Per IQR increase in $PM_{2.5}$
		Q1 ≤ 9.9	Q2 (9.9, 11.8]	Q3 (11.8, 13.6]	Q4 >13.6		
All Stroke hospitalization	4217	1.0 (Ref.)	1.37 (1.24, 1.52)	1.75 (1.55, 1.97)	2.15 (1.88, 2.47)	<10^-16	1.15 (1.13 1.18)
Ischemic Stroke	2946	1.0 (Ref.)	1.42 (1.26, 1.61)	1.70 (1.47, 1.97)	2.20 (1.87, 2.59)	<10^-16	1.15 (1.12, 1.18)
Hemorrhagic Stroke	666	1.0 (Ref.)	1.24 (0.94, 1.64)	1.95 (1.45, 2.62)	1.83 (1.30, 2.58)	0.0001	1.13 (1.06, 1.19)
Unclassified Stroke	605	1.0 (Ref.)	1.29 (0.98, 1.68)	1.70 (1.25, 2.32)	2.26 (1.60, 3.20)	<10^-5	1.18 (1.11, 1.26)
Cerebrovascular Death	946	1.0 (Ref.)	1.20 (0.97, 1.49)	1.42 (1.10, 1.83)	1.92 (1.44, 2.55)	<10^-5	1.16 (1.10, 1.22)
Cerebrovascular Event	4556	1.0 (Ref.)	1.36 (1.23, 1.50)	1.71 (1.52, 1.92)	2.14 (1.87, 2.44)	<10^-16	1.15 (1.13, 1.18)

*Stroke hospitalization includes hospitalization for ischemic stroke, hemorrhagic stroke, and other/unclassified stroke. Cerebrovascular events include cerebrovascular death and any type of stroke hospitalization. All models adjusted for age, race, smoking, education, income, marital status, employment status, BMI, high cholesterol, family history of stroke, alcohol consumption, physical activity, WHI study component, neighborhood SES, diabetes and hypertension at enrollment, and WHI center.

FIGURES

Figure 1 – Hazard ratios for association between an IQR increase in ambient air pollutants and incident cerebrovascular events.



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