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Ambient Air Pollution and the Risk of Acute Ischemic Stroke

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Abstract

Background—The link between daily changes in ambient fine particulate matter air pollution (PM_{2.5}) and cardiovascular morbidity and mortality is well established. Whether PM_{2.5} at levels below current US National Ambient Air Quality Standards also increases the risk of ischemic stroke remains uncertain.

Methods—We reviewed the medical records of 1705 Boston-area patients hospitalized with neurologist-confirmed ischemic stroke and abstracted data on the time of symptom onset and clinical characteristics. PM_{2.5} concentrations were measured at a central monitoring station. We used the time-stratified case-crossover study design to assess the association between the risk of ischemic stroke onset and PM_{2.5} levels in the hours and days preceding each event. We examined whether the association with PM_{2.5} differed by ischemic stroke etiology and patient characteristics.

Results—The estimated odds ratio of ischemic stroke onset was 1.34 (95% confidence interval (CI): 1.13, 1.58; p<0.001) following a 24-hour period classified as “moderate” (PM_{2.5} 15–40 µg/m³) by the US Environmental Protection Agency's (EPA) Air Quality Index compared to a 24-hour period classified as “good” (< 15 µg/m³). Considering PM_{2.5} as a continuous variable, the estimated odds ratio of ischemic stroke onset was 1.11 (95% CI: 1.03, 1.20; p=0.006) per interquartile range increase in PM_{2.5} (6.4 µg/m³). The increase in risk was greatest within 12–14 hours of exposure to PM_{2.5} and was most strongly associated with markers of traffic-related pollution.

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Conclusion—These results suggest that exposure to PM_{2.5} levels considered generally safe by the US EPA increase the risk of ischemic stroke onset within hours of exposure.

Keywords

Stroke; risk factors; air pollution; epidemiology

Daily changes in ambient fine particulate matter (PM_{2.5}) have been associated with higher risk of acute cardiovascular events, excess hospitalizations and deaths.¹ These cardiovascular effects of PM_{2.5} appear to be mediated through a combination of autonomic, hemostatic, inflammatory, and vascular endothelial disturbances with consequent changes in cardiac and vascular function.^{2–7} Based on the current evidence, the US Environmental Protection Agency (EPA) regulates mean daily and annual PM_{2.5} levels. Whether the current regulatory standards are sufficient to protect public health remains controversial.⁸

Although a number of studies have examined the association between other air pollutants and the risk of stroke,^{9–12} relatively fewer studies have evaluated the effects of PM_{2.5} on stroke risk and the results remain equivocal. Specifically, some,^{13–15} but not all,^{16–18} studies suggest that PM_{2.5} may increase the incidence of the combined endpoint of acute cerebrovascular diseases, an etiologically diverse group with multiple underlying pathophysiologic mechanisms. Prior work has suggested that ambient air pollution is more strongly associated with ischemic stroke than intracranial hemorrhage.¹⁹ However, few studies have specifically evaluated the link between PM_{2.5} and ischemic stroke risk,^{14, 20–22} and only one of these studies assessed whether the associations differ by ischemic stroke etiology.²²

We therefore evaluated the association between daily and hourly changes in PM_{2.5} and the risk of ischemic stroke onset among patients residing in the greater Boston area and admitted between 1999 and 2008 to the Beth Israel Deaconess Medical Center (BIDMC). Of note, during the study period PM_{2.5} levels in the Boston area did not exceed current EPA standards.

Methods

This study was approved by the Committee on Clinical Investigations at BIDMC. We identified 1763 consecutive patients 21 years old admitted to the BIDMC between April 1, 1999, and October 31, 2008, with neurologist-confirmed ischemic stroke, excluding patients with in-hospital strokes or transient ischemic attacks. BIDMC is a 650-bed teaching hospital of Harvard Medical School and designated as a Primary Stroke Service Hospital by the state. The Stroke Service consists of 5 Vascular Neurologists who see ~550 stroke patients annually. As in previous studies,²³ we excluded patients residing >40 km from the Harvard ambient monitoring station to reduce exposure misclassification. Patients potentially eligible for this study were identified by reviewing daily emergency department admission logs, stroke service admission logs, stroke service consult logs, and hospital electronic discharge records. For patients meeting eligibility criteria, we abstracted data on demographics, presenting symptoms, medical history (including history of prior stroke) and imaging results from each patient's medical record. We classified stroke etiology as due to: 1) large artery atherosclerosis, 2) small vessel occlusion, 3) cardioembolism, 4) other determined etiology or undetermined etiology according to the approach developed for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST).²⁴ Time of stroke symptom onset or time last seen normal as documented by the attending stroke neurologist at the time of hospital presentation was classified as “exact”, “estimated” or “unknown”.²² Given the documented morning peak in ischemic stroke incidence,²⁵ we assumed stroke onset occurred at 9am for

221 (13%) patients where the date of stroke symptom onset was documented but not the time. We excluded 58 (3%) patients for whom neither the date nor time of stroke onset were documented, leaving 1705 patients available for analysis.

PM_{2.5} and black carbon concentrations were measured continuously and sulfate particles (SO₄²⁻) were measured daily (9am–9am) at the Harvard ambient monitoring station, as previously described.²³ Hourly measures of nitrogen dioxide (NO₂), carbon monoxide (CO), and ozone (O₃) were obtained from local monitoring sites operated by the Massachusetts Department of Environmental Protection and averaged. We obtained hourly meteorological data from the National Weather Service station at Boston's Logan Airport and calculated apparent temperature, an index of thermal comfort, as previously described.²⁶ In a secondary analysis, we estimated exposure to black carbon at each subject's home as a marker of traffic pollution using a validated temporal-spatial model.²⁷ Briefly, black carbon predictions are based on over 6,000 black carbon measurements at 82 locations in the greater Boston area, meteorological and other characteristics of a given day, and measures of land use (e.g. traffic and population density) at a given location.

We used the time-stratified case-crossover study design²⁸ to assess the association between the risk of ischemic stroke onset and PM_{2.5} concentrations in the hours and days preceding each event. In this design, each subject's exposure prior to a case-defining event (case period) is compared with his or her own exposure experience during one or more control periods when the subject did not become a case (control period). Control periods were chosen such that exposures during the case period were compared to exposures occurring on other days of the same month falling on the same day of the week and time of day as the case period. The use of control periods from both before and after the index event is appropriate in this setting because individual events do not affect the distribution of future exposure in the overall study population.²⁹ This approach effectively controls for seasonality, time-trends, and chronic and slowly-varying potential confounders because the exposure information for cases and controls within the same stratum come from the same calendar month.³⁰

We performed conditional logistic regression, stratifying on each hospitalization, to obtain estimates of odds ratios associated with PM_{2.5} and corresponding 95 percent confidence intervals (CI). In all analyses, we controlled for ambient temperature and dew point temperature using natural cubic splines (3 degrees of freedom each) and barometric pressure modeled as a linear continuous variable. We first considered 2 categories of PM_{2.5} levels defined *a priori* by the EPA's Air Quality Index as either "good" (15 µg/m³) or "moderate" (15–40 µg/m³), excluding 11 (0.3%) days where PM_{2.5} levels exceeded 40 µg/m³. Next we considered 5 *a priori* categories of PM_{2.5} levels (breakpoints at 5, 10, 15, and 20 µg/m³). Finally, we considered PM_{2.5} as a continuous variable.

In all analyses, PM_{2.5} exposure was assessed relative to the time of stroke symptom onset. We separately evaluated the association between the risk of ischemic stroke onset and PM_{2.5} levels averaged 0 to <24, 24 to <48, 48 to <72, and 72 to <96 hours prior to stroke symptom onset. Results were subsequently confirmed using unconstrained distributed lag models such that pollutant levels at each time point were considered jointly in a single model. To explore associations with shorter exposures in more detail, we additionally evaluated the association between risk of stroke onset and PM_{2.5} levels averaged 0 to <2, 2 to <4, 4 to <6, ... 36 to <38 hours prior to stroke symptom onset. We repeated these analyses for black carbon, NO₂, CO, O₃ and SO₄.

We evaluated whether the associations with PM_{2.5} differed by ischemic stroke etiology or according to the presence of major stroke risk factors including diabetes mellitus, atrial

fibrillation, hypertension, and past history of stroke or transient ischemic attack using fully stratified models. We used the Chi-squared test for homogeneity³¹ to evaluate whether associations differ significantly across subgroups. A two-sided p value of <0.05 was considered statistically significant. Analyses were performed using SAS V9.2 (SAS Institute Inc., Cary, NC) and the R statistical package (R v 2.8.1).

Results

The 1705 patients were predominantly white women with a mean age of 73.1 (SD: 14.5) years (Table 1). Small vessel strokes (26%) were the most common determined stroke etiology, followed by strokes due to cardioembolism (25%) and large artery atherosclerosis (20%). The median delay time from stroke symptom onset to hospital presentation was 10 hours (25th percentile: 3 hours, 75th percentile: 26 hours). In-hospital mortality was 5.8%. The majority (87%) of patients resided <20 km from the Boston/Harvard ambient monitoring site (eTable 1).

During the study period 2888 (83%) days were classified as “good” according to the EPA’s Air Quality Index for PM_{2.5} (with the accompanying statement: “air pollution poses little or no risk”), and 572 (16%) days were classified as “moderate” (“air quality is acceptable; however, there may be a moderate health concern for a very small number of people”).

The odds ratio of ischemic stroke onset was 1.34 (95% CI: 1.13, 1.58; p<0.001) following a 24-hour period classified by the EPA as “moderate” compared to a period classified as “good”. The association between PM_{2.5} and risk of ischemic stroke onset was approximately linear (Fig. 1). Considering PM_{2.5} as a continuous variable, the odds ratio of stroke onset was 1.11 (95% CI: 1.03, 1.20; p=0.006) comparing the 75th to 25th percentile of PM_{2.5} (6.4 μg/m³) over the previous 24 hours. PM_{2.5} levels preceding stroke onset by more than 24 hours were not associated with higher risk.

The results were not materially different when we excluded from analyses patients living >20 km from the monitoring site; those where we imputed time of symptom onset; those presenting more than 48 hours after symptom onset; or after statistical adjustment for apparent temperature or ozone (eTable 2). The results from an unconstrained distributed lag model were also similar.

Figure 2 shows that the odds ratio of stroke onset was elevated immediately, peaked in association with mean PM_{2.5} levels 12 to <14 hours earlier (odds ratio comparing the 75th to 25th percentile of PM_{2.5}: 1.10, 95% CI: 1.04, 1.17; p=0.001), and decreased thereafter.

We examined whether the association between PM_{2.5} and stroke onset varied across subgroups of patients with specific clinical characteristics (Table 3). PM_{2.5} was associated with stroke onset among patients with ischemic stroke classified as due to large artery atherosclerosis and small vessel disease, but not cardioembolism. There was no evidence suggesting that the association varied according to the presence of comorbid diabetes mellitus, atrial fibrillation or hypertension, past history of stroke or transient ischemic attack, or age.

We considered the association between the risk of stroke onset and other pollutants (Table 2). Results for black carbon (measured at either the Harvard ambient monitoring site or estimated at each patient’s home address) and NO₂ were similar to those for PM_{2.5}, while results for CO, O₃, and SO₄²⁻ were not statistically significant.

Discussion

In this Boston-area study conducted while the region was in attainment of EPA regulatory standards, we found that ischemic stroke risk was 34% (95% CI: 13, 58%; $p < 0.001$) higher on days with “moderate” $PM_{2.5}$ levels as compared to days with “good” levels according to the EPA’s air quality index. The relationship between higher $PM_{2.5}$ and increased risk of stroke onset was linear, strongest within 12 hours of $PM_{2.5}$ exposure, and observed among patients presenting with strokes classified as due to large artery atherosclerosis or small vessel occlusion, but not cardioembolism. Stroke risk was more strongly associated with black carbon and NO_2 , markers of traffic pollution, than with components linked to non-traffic sources.

From a public health perspective, it is noteworthy that we observed an association between $PM_{2.5}$ levels and ischemic stroke onset in an area in attainment of the US National Ambient Air Quality Standards. Although the observed relative risk is modest, the number of strokes attributable to $PM_{2.5}$ may be high given the high incidence of ischemic stroke and the fact that nearly everyone is exposed to ambient fine particulate matter. If the association observed in this study is causal and assuming a linear dose-response function, a $2 \mu\text{g}/\text{m}^3$ (approximately 20%) reduction in mean $PM_{2.5}$ levels during this time period may have averted approximately 6,100 of the 184,000 stroke hospitalizations observed in the US Northeast region in 2007 alone.³²

An analysis of Medicare beneficiaries in 204 US counties found a 0.4% (95% CI: 0.0, 0.9%) higher risk of admission for the combined endpoint of cerebrovascular disease per $10 \mu\text{g}/\text{m}^3$ increase in same day $PM_{2.5}$.¹³ Smaller studies in Taiwan¹⁴ and Southern California¹⁵ have reported excess relative risks of approximately 2% per $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$, while others have found no evidence of an association.^{16–18} Of four prior studies that have specifically evaluated the association between $PM_{2.5}$ and the risk of ischemic stroke, two Canadian studies found no association,^{20, 22} while studies from Taiwan¹⁴ and Nueces County, Texas²¹ found a 3% (95% CI: –1 to 7%) and 6% (95% CI: –1 to 13%) excess risk per $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$, respectively.

The estimate from the current study scaled to a $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ would be 18% (95% CI: 5, 34%), substantially larger than previous reports. We believe that this difference is attributable, at least in part, to the use in the current study of data on the timing of ischemic stroke onset. Most prior studies have assessed exposure to $PM_{2.5}$ based on the calendar day of hospital admission; an exposure assessment strategy which can bias health effects estimates towards the null by as much as 60%.³³ Our previous study in a quality of care registry in Ontario, Canada²² may have been null partly due to misclassification of stroke onset time for patients presenting beyond the limited time window where they may benefit from thrombolytic therapy. Differences in outcome assessment methods, population and pollutant characteristics, and other aspects of the exposure assessment strategy very likely also contribute to heterogeneity across studies. For example, health effects of $PM_{2.5}$ in North America are known to vary geographically depending on the local pollutant sources and components,³⁴ as well as community characteristics.³⁵

In the current study we were able to estimate the time course of the association between $PM_{2.5}$ and stroke onset in greater detail than has been previously possible. We observed an immediate increase in the odds ratio for stroke onset that peaked 12 hours after $PM_{2.5}$ exposure, and decreased thereafter (Fig. 2). Experimental studies in humans and animals have shown that exposure to concentrated ambient $PM_{2.5}$ can induce increases in blood pressure and heart rate and reductions in heart rate variability within this time frame,^{7, 36} suggesting that altered hemodynamics could play an important role. Other potential

mechanisms include alterations in hemostatic factors, systemic inflammation, endothelial cell injury, and vascular dysfunction.⁴⁻⁶ Although these physiologic intermediates have typically been investigated in association with PM_{2.5} exposures lasting a day or longer, there is some evidence suggesting that these effects may also follow exposures shorter than 24 hours.^{7, 37-39}

The observation that PM_{2.5} was more strongly associated with stroke onset in patients with strokes due to large artery atherosclerosis is consistent with a mechanism involving altered hemodynamics and/or vascular dysfunction that results in disruption of a vulnerable atherosclerotic plaque with subsequent thrombosis and/or downstream embolism, as well as with results from a prior study.²² This result is also consistent with a Boston-area study showing a higher risk of acute myocardial infarction within 2 hours of exposure to elevated levels of PM_{2.5}.⁴⁰ The mechanisms underlying the observed association between PM_{2.5} and small vessel stroke are less clear since the pathology of these strokes remains poorly understood. However, evidence suggests that endothelial dysfunction and injury, potentially triggered by PM_{2.5} or its components, may contribute to the distinct non-atherosclerotic arteriopathy which likely underlies many small vessel strokes.⁴¹ We did not find evidence to suggest that the presence of comorbid diabetes, hypertension, atrial fibrillation or a past history of stroke increased patients' vulnerability to PM_{2.5}-related stroke.

Identifying the components or sources of PM_{2.5} responsible for the observed associations is of public health and regulatory interest. We found that the risk of stroke onset was most strongly associated with PM_{2.5}, but also significantly associated with black carbon and NO₂, markers of traffic pollution. This finding is in agreement with past studies suggesting that traffic pollution may trigger ischemic strokes.^{20, 42-43} We did not find any association between risk of stroke onset and ozone, a secondary pollutant formed from the reaction of oxides of nitrogen and volatile organic compounds in the presence of sunlight. This is in agreement with most,^{14, 16-17, 20} but not all,⁴⁴ prior studies. We also did not find any association between risk of stroke onset and SO₄²⁻, consistent with prior studies using administrative data.^{16, 45} In the Northeast, SO₄²⁻ generally represents regional pollution from coal-fired power plants.⁴⁶

Our study has some limitations. First, the use of air quality measures from a single monitoring site is expected to lead to exposure misclassification, increasing the width of our confidence intervals but not otherwise biasing our results.⁴⁷ However, PM_{2.5} levels measured at this monitoring site have been shown to be strong proxies for personal exposure to particles of ambient origin in communities surrounding Boston.⁴⁸ In support of this, our results were not materially different when we restricted the analyses to patients living <20 km from the monitoring site and the results were similar when we evaluated the association between black carbon estimated at patients' homes and ischemic stroke onset. Second, we did not study the association between PM_{2.5} and stroke resulting in death prior to coming to medical attention. Third, in 13% of patients we were able to estimate the day but not the time of stroke symptom onset, likely resulting in some exposure misclassification and biasing our results towards the null hypothesis of no association. Consistent with this notion, the association between PM_{2.5} and ischemic stroke was more pronounced after exclusion of these patients from analysis. Fourth, this study involved patients from a single tertiary care center in Boston. Since the effects of PM_{2.5} likely vary depending on population characteristics, pollution sources, and particle constituents, our results are not necessarily generalizable to other populations or geographic locations.

As in previous studies, important strengths of this study include detailed data on the time of stroke symptom onset²² and patient clinical characteristics.^{22, 43} In particular, our use of

data on the time of stroke symptom onset provides novel insights into the mechanisms by which PM_{2.5} may increase the risk of ischemic stroke onset.

In conclusion, these results suggest that PM_{2.5} increases the risk of ischemic stroke at levels below those currently considered safe under US regulations. These associations can be observed within hours of exposure and are most strongly associated with pollution from local or transported traffic emissions. If pollution levels decline with regulation, data on timing of stroke onset, patient clinical characteristics, and stroke etiology will be essential for proper evaluation of the clinical benefits of pollution control on stroke risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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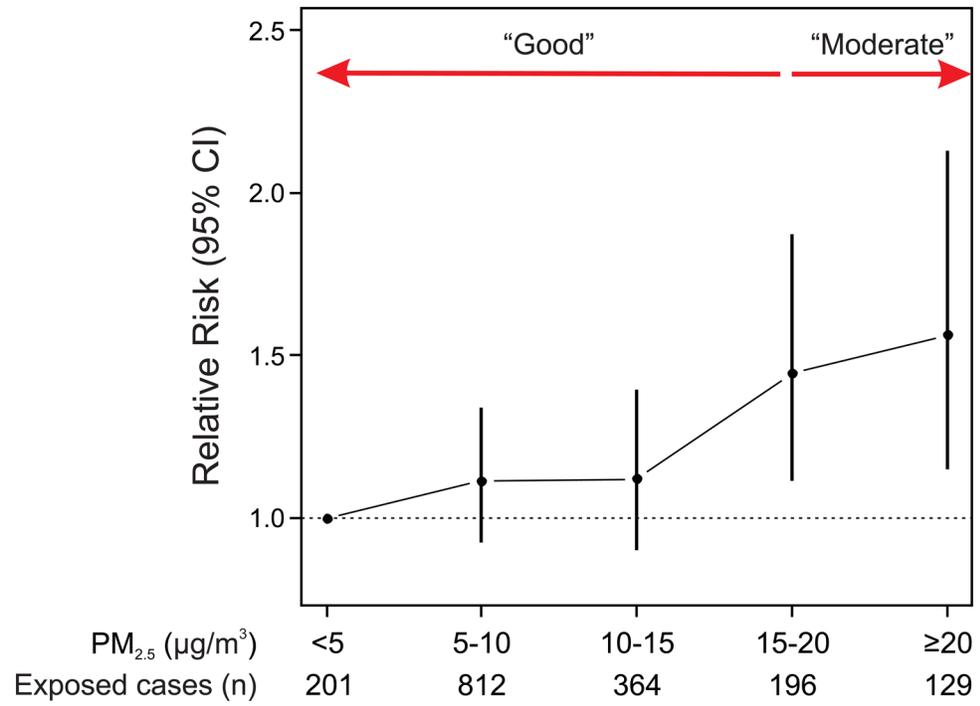


Figure 1. Odds ratio of ischemic stroke onset for categories of mean PM_{2.5} levels in the 24 hrs preceding stroke onset.

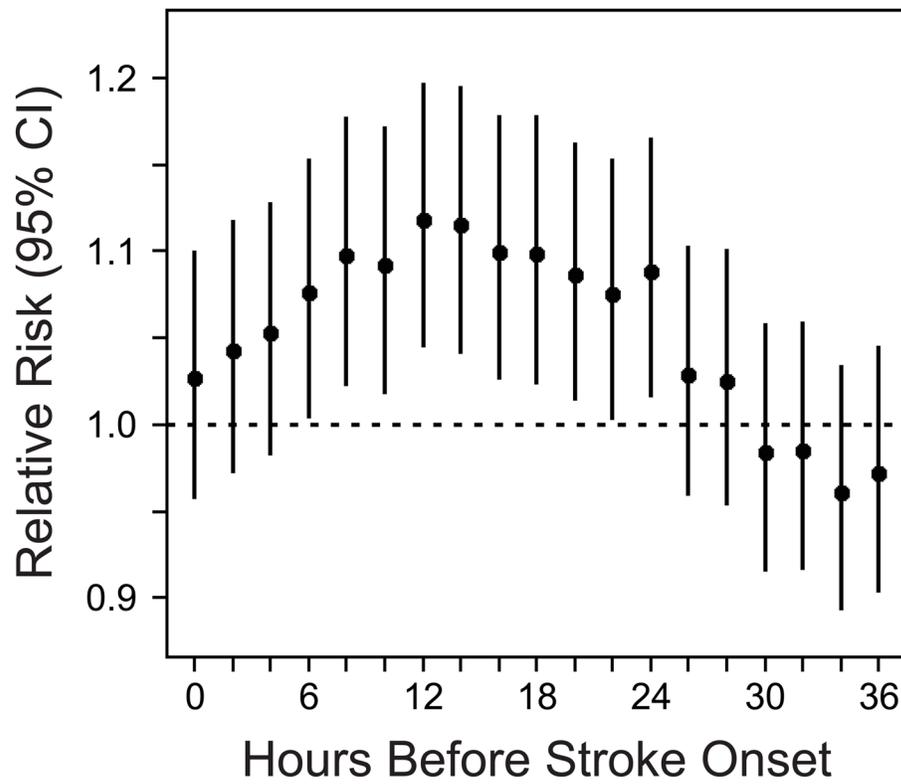


Figure 2. Odds ratio of ischemic stroke onset per interquartile range increase in $PM_{2.5}$ ($6.4 \mu\text{g}/\text{m}^3$) in the hours preceding stroke onset.

Table 1

Characteristics of 1705 patients hospitalized with acute ischemic stroke and residing in the Boston metropolitan area, 1999–2008.

	n (%) or mean \pm SD
Age, y (mean \pm SD)	73.1 \pm 14.5
Female, n (%)	931 (54.6)
White, n (%)	1165 (68.3)
Past Medical History, n (%)	
Stroke or TIA	482 (28.3)
Atrial Fibrillation	424 (24.9)
Hypertension	1216 (71.3)
Coronary Artery Disease	432 (25.3)
Heart Failure	221 (13.0)
Diabetes Mellitus	495 (29.0)
Chronic Obstructive Pulmonary Disease	105 (6.2)
Smoking History, n (%)	
Current	236 (13.8)
Former	457 (26.8)
Presumed Stroke Etiology, n (%)	
Large Artery Atherosclerosis	339 (19.9)
Small Vessel Occlusion	450 (26.4)
Cardioembolism	427 (25.0)
Other or Undetermined	489 (28.7)

Table 2

Odds ratio of ischemic stroke onset comparing the 75th to 25th percentile (interquartile range) of each pollutant in the 24 hours preceding stroke onset.

Pollutant	Interquartile Range	Odds Ratio (95% CI)	p
PM _{2.5} [†]	6.4 µg/m ³	1.11 (1.03, 1.20)	0.006
Black Carbon [‡]	0.5 µg/m ³	1.10 (1.02, 1.19)	0.017
Estimated Residential Black Carbon [‡]	0.6 µg/m ³	1.08 (1.01, 1.16)	0.018
NO ₂	8.1 ppb	1.12 (1.03, 1.22)	0.009
CO	0.3 ppm	1.07 (0.96, 1.19)	0.24
O ₃	15.2 ppb	0.97 (0.87, 1.09)	0.65
SO ₄ ²⁻ [†]	2.1 µg/m ³	1.06 (0.99, 1.13)	0.12

[†] Measured at the Boston/Harvard Ambient Monitoring Station;

[‡] Mean daily black carbon levels estimated at each patient's address using a validated spatial-temporal land use regression model.

Table 3

Odds ratio of ischemic stroke onset per interquartile range increase in PM_{2.5} levels 0–24 hours prior to stroke symptom onset among subgroups of patients.

Subgroup		OR (95% CI)	P _h
Presumed Stroke Etiology	Large Artery	1.24 (1.04,1.48)	0.19
	Small Vessel	1.19 (1.02,1.37)	
	Cardioembolic	1.09 (0.93,1.27)	
	Other/Undetermined	0.99 (0.85,1.15)	
History of Diabetes	Yes	1.10 (1.00,1.21)	0.67
	No	1.14 (0.99,1.31)	
History of Atrial Fibrillation	Yes	1.11 (1.02,1.22)	0.92
	No	1.13 (0.96,1.32)	
History of Hypertension	Yes	1.10 (0.96,1.27)	0.86
	No	1.12 (1.02,1.23)	
History of Stroke	Yes	1.12 (1.02,1.23)	0.80
	No	1.09 (0.95,1.26)	
Age	≥75 years	1.17 (1.05, 1.31)	0.23
	<75 years	1.06 (0.96, 1.19)	