

Air Pollution and Ischemic Stroke Among Young Adults

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Background and Purpose—Studies have demonstrated consistent associations between cardiovascular illness and particulate matter (PM) <10 and <2.5 μm in diameter, but stroke received less attention. We hypothesized that air pollution, an inflammation progenitor, can be associated with stroke incidence in young patients in whom the usual risk factors for stroke are less prevalent. We aimed to evaluate the association between stroke incidence and exposure to PM <10 and <2.5 μm , in a desert area characterized by a wide range of PM.

Methods—We included all members of the largest health maintenance organization in Israel, who were admitted to a local hospital with stroke between 2005 and 2012. Exposure assessment was based on a hybrid model incorporating daily satellite remote sensing data at 1-km spatial resolution. We performed case-crossover analysis, stratified by personal characteristics and distance from main roads.

Results—We identified 4837 stroke cases (89.4% ischemic stroke). Interquartile range of PM <10 and <2.5 μm was 36.3 to 54.7 and 16.7 to 23.3 $\mu\text{g}/\text{m}^3$, respectively. The subjects' average age was 70 years; 53.4% were males. Associations between ischemic stroke and increases of interquartile range average concentrations of particulate matter <10 or <2.5 μm at the day of the event were observed among subjects <55 years (odds ratio [95% confidence interval], 1.11 [1.02–1.20] and 1.10 [1.00–1.21]). Stronger associations were observed in subjects living within 75 m from a main road (1.22 [1.03–1.43] and 1.26 [1.04–1.51]).

Conclusions—We observed higher risk for ischemic stroke associated with PM among young adults. This finding can be explained by the inflammatory mechanism, linking air pollution and stroke. (*Stroke*. 2015;46:3348–3353. DOI: 10.1161/STROKEAHA.115.010992.)

Key Words: air pollution ■ inflammation ■ particulate matter ■ risk factor ■ stroke

Epidemiological studies have demonstrated a consistent increased risk for cardiovascular morbidity and mortality after exposure to air pollution.^{1–4} Stroke, a common cause of death and severe chronic disability,⁵ has received less attention.⁶ Of the studies that examined the association between particulate matter <10 μm in diameter (PM₁₀) or <2.5 μm in diameter (PM_{2.5}) and stroke, several have found positive associations^{5,7–13} predominantly with incidence of the ischemic stroke.^{3,6,8,10,13} Other studies did not find associations between PM and stroke risk.^{14,15} A major limitation of most studies is the exposure assessment that was based mostly on monitoring stations, a method that could have potentially lead to some inaccuracy and biased results.^{16,17}

We have recently presented a new method of assessing spatiotemporal resolved PM_{2.5} and PM₁₀ exposures^{18,19} in the Negev (South Israel)—a semi-arid area, located in the global dust belt, which extends from West Africa to the Arabian Desert.²⁰ Unlike many commonly used exposure models, our model makes use of satellite aerosol optical depth measurements, which allowed us to estimate daily, spatially resolved,

PM₁₀ and PM_{2.5} concentration with the inclusion of populations in rural areas not living nearby monitoring stations.

Stroke in older patients is mostly related to atherosclerosis.²¹ In the young, however, stroke is less common, and the cause is much more diverse and often unexplained.²¹ We hypothesize that PM exposure is positively associated with stroke, especially among young adults.

Methods

Study Population

We included all Clalit Health Services members with available geocoded addresses in Southern Israel, admitted to Soroka University Medical Center (SUMC) with hemorrhagic (*International Classification of Diseases Ninth Revision* [ICD9] 430–432) or ischemic stroke (ICD9 432–435) between the years 2005 and 2012. SUMC is the only medical center providing acute neurological care in the area, serving a population of ≈ 1 million residents; therefore, all the patients with stroke are referred to SUMC. Clalit Health Service is the largest health care provider in the area, covering $\approx 70\%$ of the population. To avoid within subject correlation among recurrent events, we used only the first stroke event, within the study period, for each subject.²²

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Clinical and Demographic Characteristics

Demographic, clinical, laboratory, and medication prescription data were available for all subjects. Clalit Health Service uses electronic medical records system with subjects identified by the national ID, and thus, the following data were fully available: age, sex, ethnicity, comorbidities, body mass index, smoking status, medications purchase, and socioeconomic status. Socioeconomic status was defined based on home addresses and according to the definitions of the Israel Central Bureau of Statistics assigning socioeconomic status level in a scale of 1 to 10, based on the population residing in the same statistical zone.²³

Air Pollution and Meteorologic Data

Exposure assessment was based on a hybrid satellite-based model incorporating daily satellite remote sensing data at spatial resolution of 1×1 km.¹⁹ Briefly, we make use of a new algorithm developed by National Aeronautics and Space Administration –Multi-Angle Implementation to Atmospheric Correction,²⁴ which provides aerosol optical depth data in a high resolution. Using mixed models, we regressed daily PM₁₀ and PM_{2.5} mass concentration from the Ministry of Environmental Protection against aerosol optical depth, traditional land use regression temporal predictors (obtained from the Technion Center of Excellence in Exposure Science and Environmental Health air pollution monitoring database) and spatial predictors (obtained through the Israeli Central Bureau of Statistics and Survey Bureau mapping service). When aerosol optical depth was not available, we fitted a generalized additive model with a thin plate spline term of latitude and longitude to interpolate the estimates. Good model performance was achieved, with out-of-sample cross validation R^2 of 0.79 and 0.72 for PM₁₀ and PM_{2.5}, respectively. Both model predictions had little bias, with cross-validated slopes (predicted versus observed) of 0.99. More in-depth details can be found in Kloog et al.¹⁹ The daily average concentrations of the pollutants, estimated throughout the studied region, were assigned for each patient based on proximity to his geocoded home address.

Daily data on air temperature and relative humidity for the study period were obtained from a central monitoring site located in the center of the largest city of the region.

Statistical Analysis

Results are presented by mean±SD and interquartile range (IQR) continuous variables and as percentages for categorical data. Continuous variables were compared using independent *t* test or ANOVA. Mann–Whitney test or Kruskal Wallis test were used if parametric assumptions could not be satisfied. Pearson χ^2 test was used to compare categorical variables.

Air Pollution Exposure

We examined the association between stroke and PM₁₀ or PM_{2.5} using a case-crossover design²⁵; in which we sample only cases and compared the subject's exposure in the case day to that subject's exposure in other time periods. Because each subject serves as their own control, all measured or unmeasured characteristics that do not vary over time are matched by design and therefore cannot confound the association with air pollution. To avoid confounding by seasonal patterns, we used Navidi bidirectional approach and matched control days on day of the week from the same month of the same year.²⁶ Case period was defined as the hospitalization day. One- to 4-day legged exposures were tested as well. Associations with PM₁₀ and PM_{2.5} were tested separately and were adjusted for daily average temperature and relative humidity. PM values higher than the 99th percentile were considered as outliers and were excluded from the analyses.

Stratified Analyses

In a stratified analysis by age, sex, comorbidities, medications use, seasons, smoking, and distance from main roads, we assessed whether the effect was modified by specific diagnoses and personal characteristics. In the latter, patients were grouped by the quartiles of distance from main

roads (in meters). We have a priori defined young adults as subjects <55 years.²⁷ Others were grouped into 2 age groups (55–65 and >65 years).

We further explored the associations with PM in groups in which we observed significant associations with PM, using penalized splines to allow the detection of nonlinear associations with the pollutants. Odds ratio (OR) and 95% confidence intervals (CI) were then obtained from the regression predicted values and were calculated for IQR increases in selected concentrations across the range of the pollutants.

These data were analyzed using a conditional logistic regression (coxph, R statistical software, version 3.1.1). Results are presented as OR and 95% CI for an IQR increase of the pollutants daily average concentration.

Results

Population

We identified 4837 subjects admitted to SUMC with stroke between the years 2005 and 2012, of which 4325 were cases of ischemic stroke. Figure 1 shows the study region. Half of the subjects were males, and the mean age was 70 years. Diagnoses of ischemic stroke and history of cardiovascular diseases were less frequent in younger patients. The purchase of aspirin, lipid-modifying agents, and antidiabetic medications were similar in all groups (Table 1).

Pollution and Meteorology

The IQR of PM₁₀ ranged between 36.3 and 54.7 $\mu\text{g}/\text{m}^3$, reaching a maximal value of 235.2 $\mu\text{g}/\text{m}^3$. The IQR of PM_{2.5} ranged between 16.7 and 23.3 $\mu\text{g}/\text{m}^3$, reaching a maximal value of 75 $\mu\text{g}/\text{m}^3$. Daily PM_{2.5} and PM₁₀ concentrations were higher than the threshold, defined by the World Health Organization guidelines, in 19% and 35% of the days, respectively.²⁸

The climate in the study region is relatively hot and dry, reaching a maximal temperature of 33.5°C in the summer (Table 2).

Short-Term Exposure Effect

Using a case-crossover design, we examined the association between stroke and short-term exposure to PM₁₀ and PM_{2.5}. Positive significant associations between ischemic stroke and PM₁₀ or PM_{2.5} concentrations in the day of the event were observed among subjects <55 years (OR [95% CI], 1.11 [1.02–1.20] and 1.10 [1.00–1.21], respectively).

No associations were found with hemorrhagic stroke (1.05 [0.96–1.14] and 1.04 [0.93–1.15] for an IQR elevation in PM₁₀ and PM_{2.5}, respectively) or all available cases of ischemic stroke (Table 3).

In a stratified analysis by season, associations with PM₁₀ and PM_{2.5} were observed only among subjects admitted in the spring season (1.08 [1.01–1.15] and 1.077 [0.99–1.15], respectively). Sex, comorbidities, socioeconomic status, smoking, ethnicity, and medications use did not modify the associations.

Exposure Range and Distance From Main Roads

Among subjects <55 years, we found stronger associations with ischemic stroke within the lower ranges of PM. For instance, an increase of IQR concentration of PM₁₀ from 30 to 48 $\mu\text{g}/\text{m}^3$ was associated with an OR of 1.16 (95% CI: 1.09–1.23), compared with an OR of 1.10 (95% CI: 1.01–1.20) associated with IQR elevation of PM₁₀ between 160 and 178 $\mu\text{g}/\text{m}^3$. Similar associations were observed with PM_{2.5} (Fig. 2).

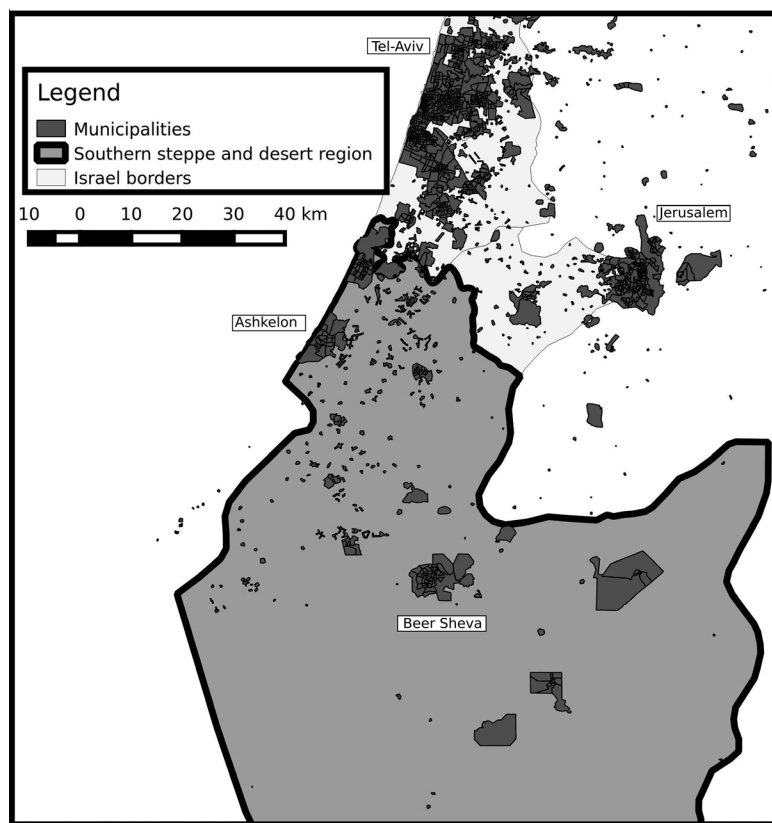


Figure 1. A map of the studied region.

Of the young subjects (<55 years), 25% lived <75 m from a main road, 50% lived 150 m from a main road, and 75% lived 250 m from a main road. When stratifying these cases by the quartiles of distance from the nearest main road, we found higher and significant risk for ischemic stroke only among subjects living within 75 m from a main road (OR [95% CI], 1.22 [1.03–1.43] and 1.26 [1.04–1.51] for IQR increase of PM_{10} and $PM_{2.5}$, respectively). The risk estimates in all other distance groups were similar and were, therefore, combined into 1 group: no associations were observed among subjects living in further locations (OR [95% CI], 1.07 [0.97–1.18] and 1.04 [0.93–1.17] for IQR increase of PM_{10} and $PM_{2.5}$, respectively; Table I in the online-only Data Supplement).

No associations were found with PM_{10} or $PM_{2.5}$ concentrations 1 to 4 days before the hospitalization day.

Discussion

In this large-scale case-crossover study, we found higher risk of ischemic stroke associated with daily average PM_{10} and $PM_{2.5}$ concentration on the day of the event, among young subjects. The associations were more pronounced in the lower range of the pollutants, where particles most likely originate from traffic,²⁹ and among subjects who reside in proximity to main roads.

Biological Mechanism

Inflammation is a known casual factor for several central nervous system diseases.³⁰ Among the environmental exposures that may induce inflammation and oxidative stress leading to central nervous system pathology, air pollution may be considered as the most prevalent source.³¹ The 2 possible pathways in which PM

can affect neurocognitive function are (1) oxidative stress induced by respiratory intake of PM and the penetration of the inflammatory compounds into the blood–brain barrier³²; (2) direct entry of PM into the central nervous system through the olfactory bulb.³³

Stroke in the Young

Unlike other studies that found higher risks for air pollution-related stroke in older patients,^{5,13} we observed significant increased risk among subjects <55 years and found no associations in other age groups.

Stroke is less common and the cause is much more diverse in young adults than in old patients.²¹ In older patients, atherosclerosis is the main cause of ischemic stroke.²¹

Similarly, Ruidavets et al³⁴ found that acute myocardial infarction in patients with no vascular risk factors may be related to air pollution. Their suggested explanation for this finding was reactive increased vascular resistance in patients who are not chronically treated with statins and vasodilators (as the older population with chronic vascular risk factors).³⁴ Another possible explanation is that atherosclerosis makes the vessels less reactive,³⁵ which actually protects the vessels air pollution effects in older patients.

In younger adults, atherosclerosis remains an important risk factor, but cardiometabolic cause is more common.³⁶ Among other components, the cardiometabolic syndrome can be associated with hypercoagulability and mediated by inflammatory response and interferences in the coagulation process, which may contribute to increased risk for cardiovascular events.³⁷

Atrial fibrillation, a common cause for cerebral emboli³⁸ is believed to be under diagnosed in patients with stroke of undetermined cause. Presentation of this common arrhythmia was

Table 1. Population Characteristics

Population Characteristics	<55 y (n=545)	55–65 y (n=914)	>65 y (3378)	P Value
Personal characteristics				
Male sex, % (n)	59.3 (323)	64.0 (585)	49.7 (1678)	<0.001
Bedouin, % (n)	8.9 (47)	6.8 (62)	3.5 (119)	<0.001
SES, median (min–max)	4 (0–10)	4 (0–10)	3 (0–10)	0.343
BMI, mean±SD	29.29±6.45	29.47±5.56	29.01±5.91	0.127
Smoking, % (n)				
No	56.1 (235)	58.5 (432)	76.9 (2016)	
Current smoker	8.1 (34)	10.9 (81)	9.7 (256)	
Past smoker	35.8 (150)	30.5 (225)	13.3 (349)	<0.001
Stroke, % (n)				
Hemorrhagic	14.4 (78)	10.8 (99)	9.9 (335)	
Ischemic	85.6 (467)	89.2 (815)	90.1 (3043)	0.008
Comorbidities, % (n)				
HTN	73.0 (309)	89.2 (815)	94.6 (3196)	<0.001
IHD	24.8 (135)	39.8 (364)	48.9 (1653)	<0.001
Dyslipidemia	85.1 (464)	92.3 (844)	85.3 (2882)	<0.001
Diabetes mellitus	39.1 (213)	58.1 (531)	55.7 (1881)	<0.001
Impaired fasting glucose	11.6 (63)	12.4 (113)	14.3 (483)	0.104
Medications, % (n)				
Aspirin	13.4 (73)	12.7 (116)	11.4 (385)	0.283
Lipids-modifying agents	11.2 (61)	12.1 (111)	10.1 (340)	0.171
Antidiabetic medications	5.7 (31)	6.6 (60)	4.8 (163)	0.099

BMI indicates body mass index; HTN, hypertension; IHD, ischemic heart disease; Max, maximum; Min, minimum; and SES, socioeconomic status.

found³⁹ to be associated with exposure to air pollution in young adults. This yet unexplained association may contribute to the association between stroke and air pollutants in young adults.

Exposure to PM was associated with elevated levels of C-reactive protein, fibrinogen, white blood cells, and several inflammatory factors.⁴ Considering the underlying mechanism in which air pollution may be related to ischemic stroke is based on inflammatory response, it is possible that air pollution-induced stroke is more pronounced in younger patients, where cardiometabolic-related stroke is more common.

Similar to previous studies, PM exposure in our study was associated with ischemic but not with hemorrhagic stroke.^{3,6,8,10,13} Oudin et al,⁸ for instance, found a 13% increase in hospital admissions for ischemic stroke associated with PM₁₀ 30 µg/m³ compared with PM₁₀ <15 µg/m³; and Wellenius et al¹³ found an estimated OR of 1.11 (95% CI: 1.03–1.20) for ischemic stroke comparing the 25th and 75th percentiles of the daily average PM_{2.5} concentration.

Although we observed no association with PM in all available ischemic stroke cases, the associations observed among specific subgroups were higher than most association reported to date.^{3,5,7,13} Commonly used methods for exposure assessment in many of the studies rely on ground monitoring data and are therefore prone to exposure misclassification, which may dilute air pollution-associated health effects.¹⁶ Using our PM prediction models, we were able to include patients reside both in urban and in rural places and to obtain spatially resolved PM estimates, which allowed us to reduce this misclassification.

Traffic- Versus Natural-Related Air Pollution

Given the natural and anthropogenic sources of PM in the Negev area, the range of PM is wide, with different compositions that characterize the pollutants.⁴⁰ Krasnov et al²⁹ assessed the constant anthropogenic contribution of PM₁₀ as an average value of 34 µg/m³. Values >71 µg/m³ were found to be associated with dust events.²⁹ In its lower range, PM originates mostly from traffic emissions.⁴¹ Higher levels of PM, recorded

Table 2. Summary Statistics of Air Pollution and Meteorology Between the Years 2005 and 2012

Population Characteristics	Winter	Spring	Summer	Fall
PM ₁₀ , µg/m ³				
IQR	36–61.7	37.6–63.2	36.3–47.7	35.5–55.8
Mean±SD	55.7±34.5	54.8±27.6	43.1±11.9	48.4±20.5
PM _{2.5} , µg/m ³				
IQR	16.0–24.0	16.6–24.2	17.6–22.7	16.0–22.9
Mean±SD	21.9±9.9	21.6±8.4	20.4±4.1	20.2±6.2
Temperature				
IQR	11.4–15.0	17.5–22.4	24.7–26.9	16.5–23.0
Mean±SD	13.4±3.2	20.2±3.6	25.8±1.9	19.8±4.0
Relative humidity				
IQR	55.0–79.0	51.8–71.0	63.3–73.0	59.0–75.0
Mean±SD	66.1±17.7	59.5±16.1	67.0±10.6	65.5±15.0

IQR indicates Interquartile range; PM₁₀, particulate matter <10 µm; and PM_{2.5}, particulate matter <2.5 µm.

Table 3. Association Between PM₁₀, PM_{2.5}, and Ischemic Stroke: Case-Crossover Results

	PM ₁₀ , OR (95% CI)	P Value	PM _{2.5} , OR (95% CI)	P Value
All available cases	1.00 (0.97–1.03)	0.641	1.01 (0.97–1.04)	0.460
By age, y				
<55	1.11 (1.02–1.20)*	0.010	1.10 (1.00–1.21)*	0.037
55–65	0.97 (0.90–1.04)	0.467	0.99 (0.90–1.04)	0.877
>65	0.99 (0.96–1.03)	0.910	1.00 (0.96–1.03)	0.942

The results of single pollutant models of the association between stroke and daily average concentrations of PM₁₀ or PM_{2.5} at the day of the event, among all available cases and stratified by age are given in this table. Each association with PM was adjusted for average temperature and average relative humidity at the day of the event. Results are presented as OR and 95% CI for IQR increase in PM₁₀ (18.4 μg/m³) or PM_{2.5} (6.6 μg/m³). CI indicates confidence intervals; IQR, interquartile range; OR, odds ratio; PM₁₀, particulate matter <10 μm; and PM_{2.5}, particulate matter <2.5 μm.

*P<0.05.

during dust events, are mostly of natural origin and have different mineral and chemical compositions.^{29,40}

Studies that evaluated the toxicity of PM by its source, size, and composition have found particles with industrial and traffic components to be highly toxic.^{42,43} Although we did not examine the speciation of PM, we did find stronger associations with PM within its lower range and among subjects who reside in proximity to main roads, emphasizing the role of PM composition in addition to its mass.

Limitations

Our study had several limitations. First, we did not have information on the exact onset of stroke symptoms, which may have caused misclassification in the definition of a case day. However, because stroke events require urgent care and hospitalizations and because SUMC is the only available hospital in the region, we think that the misclassification will be minor. Second, we were not able to adjust the effect for traffic noise and gaseous air pollutants in our models and therefore cannot rule out the contribution of these factors to the higher stroke risks found among subjects residing in proximity to major roads.⁴⁴ In addition, we did not have information about smoking history and therefore could not fully assess the modification by smoking status. Finally, the use of 1×1 km model could also be improved as higher resolution satellite data become available. As satellite remote sensing evolves and progresses, finer resolution data should enable us to assess more precise estimated daily individual exposure as they relate to different locations such as residence and work place for data sets where individual addresses are available.

Conclusions

We observed higher risk for ischemic stroke associated with PM in the day of the event, among young adults. This finding can be explained by the inflammatory mechanism, linking air pollution and stroke. Our findings suggest stronger effect of traffic pollution and not pollution of natural sources.

Subjects younger than 55 years

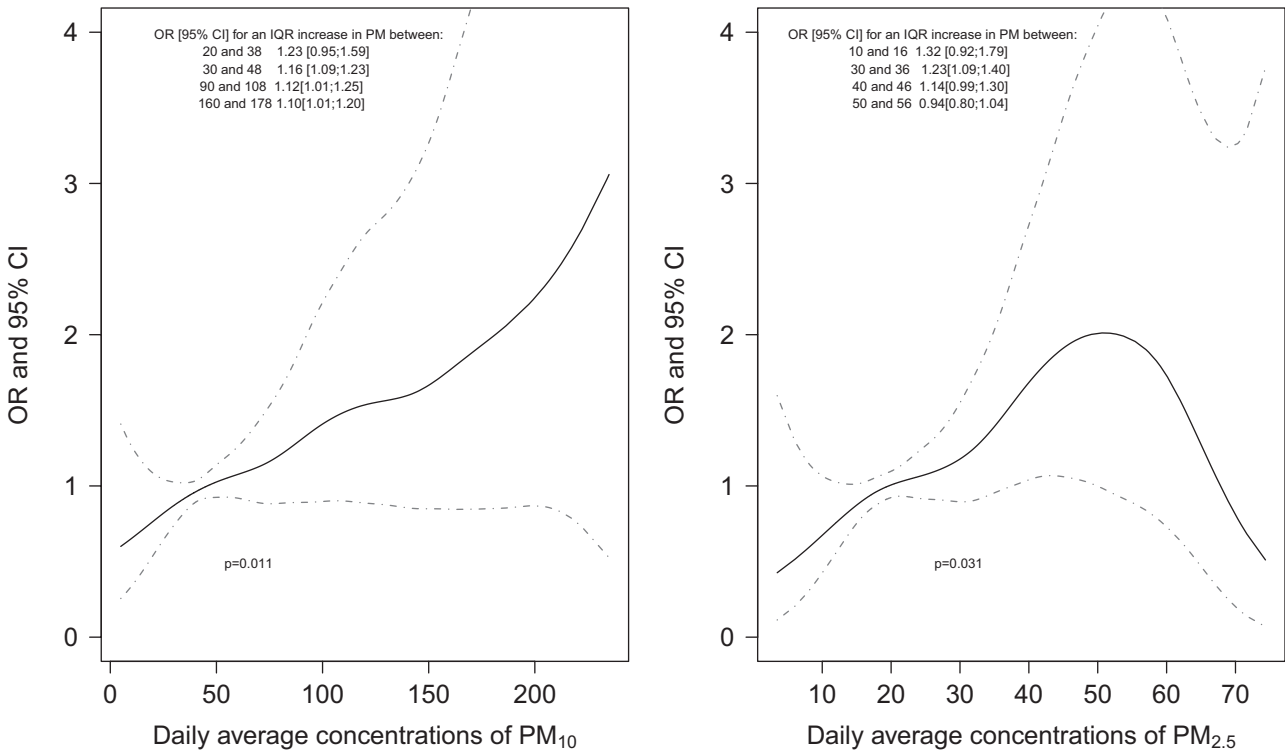


Figure 2. The association between ischemic stroke and daily average concentrations of particulate matter <10 μm (PM₁₀) or particulate matter <2.5 μm (PM_{2.5}) in the day of the event, among patients <55 years. The line represents odds ratio (OR) and 95% confidence intervals (CI) obtained from a penalized spline function of the pollutants. This figure shows the estimated risk for ischemic stroke associated with interquartile range (IQR) elevation in daily average concentrations of PM₁₀ (18 μg/m³) and PM_{2.5} (6 μg/m³), calculated from increments of the penalized spline functions in selected places of the distribution.

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Disclosures

None.

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