


BMJ Open Short-term associations between ambient air pollution and stroke hospitalisations: time-series study in Shenzhen, China

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ABSTRACT

Objective To investigate the association between ambient air pollution and stroke morbidity in different subgroups and seasons.

Methods We performed a time-series analysis based on generalised linear models to study the short-term exposure–response relationships between air pollution and stroke hospitalisations, and conducted subgroup analyses to identify possible sensitive populations.

Results For every 10 µg/m³ increase in the concentration of air pollutants, across lag 0–3 days, the relative risk of stroke hospitalisation was 1.029 (95% CI 1.013 to 1.045) for PM_{2.5}, 1.054 (95% CI 1.031 to 1.077) for NO₂ and 1.012 (95% CI 1.002 to 1.022) for O₃. Subgroup analyses showed that statistically significant associations were found in both men and women, middle-aged and older populations, and both cerebral infarction and intracerebral haemorrhage. The seasonal analyses showed that statistically significant associations were found only in the winter.

Conclusions Our study indicates that short-term exposure to PM_{2.5}, NO₂ and O₃ may induce stroke morbidity, and the government should take actions to mitigate air pollution and protect sensitive populations.

INTRODUCTION

Stroke is one of the leading causes of disability-adjusted life years (DALYs) and mortality, accounting for approximately 132 million DALYs and 6.2 million deaths globally in 2017.^{1 2} It is also the leading cause of long-term adult disability and the leading cause of death in China; 20.19% of total deaths were caused by stroke in 2017,^{3 4} and the age-standardised incidence and mortality rates were 246.8 and 114.8 per 100 000 person-years, respectively.⁵ Well-known risk factors of stroke include history of hypertension, current smoking status and alcohol intake.⁶

With the deterioration of global air quality, concerns have been raised about the relationship between ambient air pollution and stroke. According to the Global Burden

Strengths and limitations of this study

- This study investigated the association between air pollution and subtypes of stroke morbidity.
- This study included more than 67 000 cases, ensuring high statistical power.
- The modification effects of different demographic characteristics and seasons were explored.
- Being a single-city study limited the generalisation of the findings.
- Associations between air pollution and stroke hospitalisations did not prove causality.

of Disease, approximately 12.75% of stroke cases in China in 2017 were linked to air pollution.³ Possible mechanisms linking ambient air pollution to stroke include inflammation, oxidative stress, atherosclerosis and autonomic dysregulation.⁷ To date, most of the relevant epidemiological studies have focused on stroke mortality instead of morbidity,^{8 9} but it should be noted that morbidity is more indicative of the early stages of stroke; early prevention of stroke has an important public health significance. Studies that examined the relationship between ambient air pollution and stroke morbidity obtained inconsistent results, and most of them studied the association over a full year but failed to consider the seasonal differences in pollutant concentration and their health effects.^{10–12}

In this study, a time-series analysis was conducted to investigate the association between ambient air pollution and stroke morbidity in different seasons; we also researched possible sensitive populations by conducting subgroup analyses by sex, age group, education level and stroke subtypes.

Table 1 Summary statistics of stroke hospitalisations in Shenzhen

Variables	Number	Percentage (%)
Stroke cases	67 078	100.0
Sex		
Male	41 546	61.9
Female	25 526	38.1
Age (years)		
<40	4051	6.0
40–64	33 053	49.3
≥65	29 968	44.7
Education		
Primary school or below	18 558	27.7
Junior high school	26 686	39.8
High school or above	21 792	32.5
Stroke subtypes		
Cerebral infarction	52 168	77.8
Intracerebral haemorrhage	11 415	17.0
Subarachnoid haemorrhage	2369	3.5
Stroke not specified as haemorrhage or infarction	219	0.3
Other non-traumatic intracranial haemorrhage	783	1.2

MATERIALS AND METHODS

Study area

Shenzhen is located within the Pearl River Delta, China, is 1 degree south of the Tropic of Cancer and has a permanent population of approximately 12.5 million people.¹³ Because of the Siberian anticyclone, it has a warm and humid subtropical climate. Six kinds of air pollutants, including ozone (O₃), fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), inhalable particulate matter (PM₁₀), sulfur dioxide (SO₂) and carbon monoxide, are monitored in Shenzhen, and the main ambient air pollutants are O₃, PM_{2.5} and NO₂.

Data collection

Stroke data containing 67 078 cases from 1 January 2014 to 31 December 2016 were collected from the Shenzhen Centre for Chronic Disease Control. Sixty-nine hospitals from 10 administrative districts reported their stroke case information (including patient age and sex, clinical diagnosis and classification, onset date, diagnosis date and major risk factors) to the Shenzhen Centre for Chronic Disease Control. All the cases were coded according to the WHO's International Classification of Diseases, 10th Revision, ranging from I60 to I64: (1) subarachnoid haemorrhage, which was coded as I60; (2) intracerebral haemorrhage (ICH), which was coded as I61; (3) other non-traumatic intracranial haemorrhage, which was coded as I62; (4) cerebral infarction (CBI), which was coded as I63; and (5) stroke not specified

as haemorrhage or infarction, which was coded as I64. All cases were diagnosed in the hospital with CT, MRI or neurological examination. In the subgroup analysis for stroke subtypes, we focused on ICH and CBI, which accounted for 94.8% of all stroke cases.

Hourly concentrations of O₃, PM_{2.5} and NO₂ were obtained from the National Urban Air Quality Real-time Publishing Platform (<http://106.37.208.233:20035/>). The daily mean concentrations for each air pollutant were averaged from all the 11 fixed-site air pollution monitoring stations in Shenzhen.¹⁴ Daily meteorological data were obtained from the National Meteorological Data Sharing Platform (<http://data.cma.cn/>), including the daily mean, maximum and minimum temperatures, the mean relative humidity, the mean wind speed and the mean atmospheric pressure.

Statistical modelling

This time-series analysis adopted generalised linear Poisson models to estimate the association between air pollutants and stroke hospitalisations.¹⁵ The daily mean concentrations of air pollutant (PM_{2.5}, NO₂ or O₃) were the independent variables, and the number of daily hospital admissions for stroke was the dependent variable. Meteorological variables (ie, temperature, relative humidity and air pressure), long-term trends and seasonal patterns, as well as day of the week, were used as adjustment variables. The influence of other pollutants was examined in two-pollutant models.

Considering the possible delayed and/or cumulative effects of air pollution on stroke morbidity, we created cross-basis matrix for air pollutants, within the framework of distributed lag linear model.¹⁶ The selection of lag days was justified by the polynomial lag models.

The model to represent the relationship between the daily mean concentration of air pollutants and hospital admissions for stroke is as follows:

$$\log [E(Y_t)] = \alpha + \beta POL_{t,t} + ns(TEM_t, df=3) + ns(RH_t, df=3) + ns(PRE_t, df=3) + ns(TIME_t, df=7/year * No. of years) + \gamma DOW_t$$

Here, E(Y_t) indicates the expected number of hospital admissions for stroke on day t; POL_{t,t} is the cross-basis matrix of the air pollutants (PM_{2.5}, NO₂ or O₃), with β as the corresponding vector of coefficients; and ns() is the natural cubic spline function. DOW_t is a dummy variable for the day of week. We used 7 df per year for the time trend (TIME_t), 3 df for the previous 14 days' moving average temperature (TEM_t),^{17 18} and 3 df for both the relative humidity (RH_t) and the air pressure (PRE_t) on day t; the choice of df for each variable was based on the Akaike Information Criterion for quasi-Poisson models.

Subgroup analyses were conducted for different sexes, age groups (<40, 40–64 and ≥65 years), education levels (primary school or below, junior high school, high school or above) and stroke subtypes (CBI and ICH).

Table 2 Distribution of daily air pollution concentrations, meteorological factors and stroke hospitalisations in Shenzhen

Variables	Mean	SD	Min	P ₂₅	P ₅₀	P ₇₅	Max
Air pollutants							
PM _{2.5} (µg/m ³)	30.1	16	6.3	16.8	27	39.9	96.1
NO ₂ (µg/m ³)	33.2	11.1	11.3	25	31	39.5	84.8
O ₃ (µg/m ³)	56.9	22.1	16.9	38.8	52.9	71.9	147.8
Meteorological factors							
Temperature (°C)	23.5	5.7	3.5	19.0	25.1	28.2	33.0
Relative humidity (%)	74.7	12.2	19.0	69.0	76.0	83.0	99.0
Air pressure (hPa)	1005.6	6.6	986.8	1000.7	1005.3	1010.6	1027.3
Stroke cases							
All strokes	61.2	15.7	23.0	51.0	59.0	70.0	182.0
Type							
Intracerebral haemorrhage	10.4	4.2	1.0	7.0	10.0	13.0	40.0
Cerebral infarction	47.6	13.1	17.0	39.0	46.0	54.0	143.0
Sex							
Male	37.9	10.2	15.0	31.0	37.0	43.0	113.0
Female	23.3	7.4	7.0	18.0	22.0	27.0	77.0
Age (years)							
<40	3.7	2.1	0.0	2.0	4.0	5.0	12.0
40–64	30.2	8.4	9.0	24.0	30.0	35.0	90.0
≥65	27.3	8.7	9.0	21.0	26.0	32.0	101.0
Education							
Primary school or below	16.9	5.4	3.0	13.0	16.0	20.0	51.0
Junior high school	24.4	7.9	7.0	19.0	23.0	29.0	85.0
High school or above	19.9	7.6	5.0	14.0	19.0	24.0	67.0

NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, fine particulate matter.

When comparing seasonal differences, we defined spring as the period from 1 March to 31 May, summer as the period from 1 June to 31 August, autumn as the period from 1 September to 30 November and winter as the period from 1 December to 28 February of the next year. The differences among the effect estimates between different subgroups were tested via the Z-test.¹⁹ Sensitivity analyses were performed by adjusting the df values of *TIME_i* and *TEM_i*, as well as the number of lags considered for the air pollutant. All results were

reported as relative risks (RRs) and 95% CIs of hospital admissions for stroke for every 10 µg/m³ increase in air pollutant exposure, and two-tailed p<0.05 was considered statistically significant. Main analyses were performed using the ‘dlnm’ and ‘splines’ packages in R V.3.5.1.

Patient and public involvement

This study belongs to ecological research and does not reveal any personal information; patients or the public

Table 3 Spearman’s rank coefficients between daily mean air pollutants and meteorological variables

Variables	PM _{2.5}	NO ₂	O ₃	Temperature	Relative humidity	Air pressure
PM _{2.5}	1.00					
NO ₂	0.55*	1.00				
O ₃	0.56*	0.02	1.00			
Temperature	−0.43*	−0.27*	−0.09*	1.00		
Relative humidity	−0.53*	−0.1*	−0.51*	0.27*	1.00	
Air pressure	0.50*	0.26*	0.21*	−0.85*	−0.45*	1.00

*P<0.05.

NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, fine particulate matter.

Table 4 RRs (95% CI) of stroke hospitalisations for every 10 µg/m³ increase in ambient PM_{2.5}, NO₂ and O₃ in the single-pollutant model, across lag 0–3 days

Subgroups	RR (95% CI)		
	PM _{2.5}	NO ₂	O ₃
All strokes	1.029 (1.013 to 1.045)	1.054 (1.031 to 1.077)	1.012 (1.002 to 1.022)
Sex			
Male	1.029 (1.011 to 1.046)	1.056 (1.032 to 1.080)	1.011 (0.999 to 1.022)
Female	1.030 (1.009 to 1.052)	1.050 (1.020 to 1.080)	1.013 (1.000 to 1.027)
Age			
<40	1.030 (0.990 to 1.070)	1.084 (1.027 to 1.145)	0.998 (0.974 to 1.023)
40–64	1.025 (1.008 to 1.044)	1.058 (1.033 to 1.084)	1.013 (1.002 to 1.024)
>65	1.033 (1.012 to 1.055)	1.046 (1.017 to 1.076)	1.012 (0.999 to 1.025)
Education			
Primary and below	1.013 (0.991 to 1.036)	1.050 (1.019 to 1.081)	1.007 (0.993 to 1.021)
Junior high school	1.043 (1.021 to 1.065)	1.072 (1.041 to 1.104)	1.023 (1.009 to 1.037)
Senior high school and above	1.028 (1.006 to 1.049)	1.036 (1.007 to 1.066)	1.003 (0.990 to 1.016)
Stroke subtype			
Intracerebral haemorrhage	1.021 (0.995 to 1.048)	1.058 (1.021 to 1.096)	1.008 (0.991 to 1.025)
Cerebral infarction	1.029 (1.011 to 1.047)	1.050 (1.026 to 1.075)	1.012 (1.001 to 1.023)
Season			
Spring	1.031 (0.989 to 1.076)	1.034 (0.989 to 1.081)	1.012 (0.989 to 1.035)
Summer	1.031 (0.989 to 1.075)	0.992 (0.944 to 1.044)	1.015 (0.990 to 1.041)
Autumn	1.021 (0.993 to 1.050)	1.040 (0.994 to 1.089)	1.009 (0.992 to 1.025)
Winter	1.073 (1.022 to 1.126)	1.095 (1.024 to 1.170)	1.033 (0.983 to 1.086)

NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, fine particulate matter; RR, relative risk.

were not involved in the design, conduct, reporting or dissemination of our research. Therefore, patients did not have to be asked for informed consent.

RESULTS

Data description

In total, during 2014–2016, 67 078 hospital admissions for stroke were recorded, of which 77.8% were first-time cases, and 61.9% were men. Patients aged 40–64 years accounted for 49.3% of the total, and 44.7% were older (age ≥65 years old). In total, 27.7% of the cases had an education level of primary school or below; 39.8% completed junior high school; and 32.5% had a high

school education or higher. Among the subtypes of stroke, CBI and ICH accounted for 52 168 (77.8%) and 11 415 (17.0%), respectively. The other three subtypes accounted for approximately 5% of the total (table 1).

On average, there were approximately 61 hospital admissions for stroke per day during our study period, and the 24 hours mean concentrations of PM_{2.5}, NO₂ and O₃ were 30.1, 33.2 and 56.9 µg/m³, respectively. The daily mean temperature was 23.5°C; the mean relative humidity was 74.7%; and the daily mean air pressure was 1005.7 hPa (table 2). In general, the pollutant concentrations of PM_{2.5} and NO₂ were higher in winter than in other seasons (online supplementary table S1). Correlations between air pollutants and meteorological factors are in table 3.

Regression analysis

When the lag length was set as 7 days, the results showed that the lag effect mainly lasted for 3 days (online supplementary figure S1). Therefore, we used 3 days as the lag length in later analyses. Positive associations and lag effects were observed between stroke morbidity and air pollution. The cumulative effect of a 10 µg/m³ increase in PM_{2.5} concentrations across lag 0–3 days corresponded to a 2.9% (95% CI 1.3% to 4.5%) increase in daily stroke hospitalisations; it was a 5.4% (95% CI 3.1% to 7.7%) increase in the case of NO₂, and a 1.2% (95% CI 0.2% to 2.2%) increase for O₃.

Table 4 showed that, for PM_{2.5}, an association was found in both men and women, populations older than 40 years old and people with education levels of junior high school and above, and the CBI stroke subtype. For NO₂, the association was consistently significant in both men and women, populations in all age groups and all education levels, and subtypes CBI and ICH. For O₃, the association was significant in women, the middle-aged population, populations with an education level of junior high school and the CBI stroke subtype. The associations occurred mainly in the winter. Comparing the effect estimates between different subgroups, we found none of the differences to be statistically significant.

For the two-pollutant model (figure 1), the results did not vary substantially compared with those in the single-pollutant models, especially for NO₂. The results were stable after adjusting the df values of *TIME_t* and *TEM_t*, as well as the number of lags considered for the air pollutant in the model, indicating the stability of the estimated effects (online supplementary tables S2 and S3).

DISCUSSION

In this study, a positive association was found between the daily stroke hospitalisations and the concentration of ambient PM_{2.5}. Previous studies showed inconsistent results when exploring the short-term associations between PM_{2.5} and stroke morbidity. Some studies observed a non-significant association, while other studies found a significant positive association.^{10 20} For example, a 2014 meta-analysis of nonfatal strokes found an RR of 0.7%–0.8% for short-term

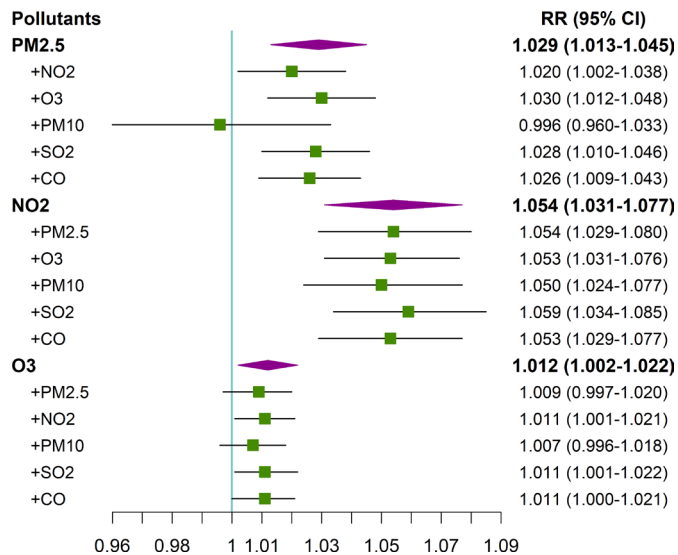


Figure 1 RRs (95% CI) of stroke hospitalisations for every 10 µg/m³ increase in ambient PM_{2.5}, NO₂ and O₃ in the two-pollutant model, across lag 0–3 days. CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM₁₀, inhalable particulate matter; PM_{2.5}, fine particulate matter; RR, relative risk; SO₂, sulfur dioxide.

effects per 10 µg/m³ PM_{2.5}.²¹ Exposure to particulate matter increases inflammation, antioxidant activity and circulating blood platelet activation, and decreases vascular endothelial functions and enzyme activity, the latter of which may increase peripheral thrombosis and blood clotting.^{22–24} Furthermore, compared with PM₁₀, PM_{2.5} has a smaller size and larger surface area and can carry more harmful substances and penetrate deep into the human body,²⁵ finally inducing a stroke.

We found that daily stroke hospitalisations increased by 5.4% for every 10 µg/m³ increase of NO₂. These results are similar to those of previous studies, but some of the previous studies obtained different effect estimates.^{26–28} For example, a study in Wuhan, China, showed a 2.9% increase in stroke hospitalisations per 10 µg/m³ increase in NO₂ in the cold season, which was smaller than the result (9.5%) from our study.²⁹ Evidence has shown that NO₂ is related to plasma fibrinogen³⁰ and is also correlated with PM_{2.5}, which leads to increased coagulability through the release of cytokines.²⁸ Gaseous NO₂ can also be mixed with water to form acid aerosols after inhalation, which damages health through a series of oxidation mechanisms.³¹

The study found that the RR of stroke associated with an increase in the level of air pollution from the first to the third quartile was slightly higher for NO₂ than for PM_{2.5}. Previous studies showed similar results^{14,32}; gaseous pollutants appeared to have a stronger effect on stroke mortality,^{33,34} and some studies indicated that, after adjusting for other pollutants, only NO₂ showed consistent results with a single-pollutant model.^{35,36} Concern has been raised that the observed health effects associated with NO₂ might be a result of exposure to traffic-related emissions or fine particles.³⁷

A weak positive association between O₃ and hospital admissions for stroke was found in our study. Previous studies exploring this relationship showed different results. For example, a 10-year study conducted in France showed a significant positive relationship between O₃ exposure and ischaemic stroke in men over 40 years of age, and the result was observed for a 1-day lag (OR 1.133, 95% CI 1.052 to 1.220).³⁸ In the USA, where air pollution levels are low, the incidence of CBI/transient ischaemic attack was also associated with O₃ exposure.³⁹ However, there was no statistically significant association found between O₃ pollution and the incidence of stroke in South Carolina and Nueces County, Texas.^{40,41} Some studies even showed a significant or non-significant negative association between O₃ and CBI.^{42,43} The mechanisms linking O₃ and stroke need to be further studied.

The associations were found in both men and women; no clear trends were found across age groups and education levels. We found that the associations between air pollution and stroke morbidity had no statistically significant differences between different age groups. Similar results have been found in some previous studies.^{14,44} Elderly people may spend more time indoors, and they are likely to wear masks when air pollution is severe; thus, their individual exposure may be less.⁴⁵ On the other hand, Tian *et al* found that the associations between air pollution and stroke morbidity were stronger in the elderly.³² Therefore, the modification effect of age on the associations between air pollution and stroke morbidity needs further study. In addition, vascular risk factors, such as hypertension and hyperlipidaemia, may also modify these associations, which needs to be addressed in future research.

The seasonal analyses showed that statistically significant associations between ambient air pollutant concentrations and hospital admissions for stroke were only found in the winter; Dong *et al* also found that the harmful effects of NO₂ and SO₂ were more robust in the cold season.¹⁴ One possible reason for this result is that the air pollution concentrations in Shenzhen are higher in winter than in summer (online supplementary table S1). The substances carried by particles may vary between seasons, which would influence the effect.

Our study found that PM_{2.5}, NO₂ and O₃ were related to hospitalisations for CBI but found different results for ICH. Similarly, previous studies showed consistent associations between CBI and air pollution, while the association between ICH was more variable and had a higher imprecision.⁴⁶ One reason is that the prevalence of ICH was much lower than CBI. In our study, 77.8% of stroke hospitalisations were for CBI, and ICH only accounted for 17.0% of stroke hospitalisations. Therefore, the risk estimates for ICH were more imprecise, and the CI of the RR for ICH was wider. Another reason may be the differential mechanisms linking air pollution exposure to CBI and ICH. PM_{2.5} exposure is conducive to atherosclerosis and the oxidative stress of the heart. These conditions may upregulate visfatin, reduce heart rate variability and induce CD36-dependent 7-ketocholesterol, which



accumulate in macrophages.^{47–50} All of these factors are more likely to induce CBI than ICH.

There are several limitations in this study. First, the air pollution data from fixed-site monitoring stations may not be representative of average population exposure. For example, the air pollution concentrations near the main roads with heavy traffic were often higher than those near the parks with few vehicles, and the air pollution monitoring stations were usually located far away from the main roads with heavy traffic. Second, it is difficult to completely eliminate the possibility of ecological fallacy in time-series studies, and we cannot provide absolute risks in this study. Moreover, the associations observed in the present study cannot prove causality.

CONCLUSIONS

PM_{2.5}, NO₂ and O₃ may induce stroke morbidity, especially in the winter. All three air pollutants were associated with higher risks of hospital admission due to CBI, the most prevalent stroke subtype in the study location. The government should take actions to address air pollution issues and develop warning systems for sensitive populations during high-risk periods.

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Contributors The study was conceived and designed by JB, JP and YG; XX and YG conducted statistical analysis and drafted the manuscript; LL, HZ, and SD contributed to data collection and processing; YX and ZL helped in study management and the interpretation of the results; JB, JP and CH reviewed the manuscript for important intellectual content. All authors read and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The institutional review board at the School of Public Health, Sun Yat-sen University, approved the study protocol (number 2019-029) with a waiver of informed consent. Data were analysed at the aggregate level. All patients were anonymous, and no patient privacy were revealed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No additional data are available.

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