# Epidemiological evidence on association between ambient air pollution and stroke mortality

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## ABSTRACT

**Background** Inconsistent results have been found on the association between air pollution and stroke mortality. Additionally, evidence on people who are potentially sensitive to air pollution-associated stroke mortality is limited.

**Methods** Daily stroke mortality of adults aged over 65 between 2003 and 2008 in Shanghai, China were collected. The time-stratified case-crossover approach was used to assess the association between daily concentrations of air pollutants including particles with size <10 μm, sulfur dioxide ($SO_2$) and nitrogen dioxide ($NO_2$) and stroke mortality.

**Results** Both total-stroke and ischaemic-stroke mortalities were found to be significantly associated with all three air pollutants. Haemorrhagic stroke was significantly associated with $SO_2$ and $NO_2$ only. Substantial differences were observed for effect estimates of ischaemic-stroke mortality in relation to $NO_2$ among people with cardiac diseases compared with those without; for an increase of 10 μg/m$^3$ in $NO_2$, the increase in ischaemic-stroke mortality was 7.05% (95% CI 1.92% to 12.17%) for people with comorbid cardiac diseases versus 0.60% (95% CI −0.49% to 1.68%) for those without. We did not find evidence of effect modification by hypertension and diabetes.

**Conclusions** This study provides new evidence for the association between exposure to ambient air pollution and stroke mortality. Our results also suggest that underlying cardiac disorder may increase the risk for ischaemic-stroke mortality in relation to air pollution exposure, especially $NO_2$.

## INTRODUCTION

High concentrations of particulate air pollution have been found to be associated with higher rates of cardiac and respiratory mortality in studies conducted throughout the world.[1–6] In addition, several secondary diagnoses of cardiorespiratory disorders have been identified as effect modifiers for such associations.[7–10] Although the relative increase in risk for persons with these comorbid conditions is sometimes small, given that there are a large number of people exposed to these conditions, even a small relative risk may be of significant public-health interest.

The association between air pollution and stroke mortality has also been hypothesised. In the past decade, an increasing body of literature has provided compelling evidence to link outdoor air pollution with stroke morbidity and mortality. Positive and significant associations have been observed not only for total stroke, but also for the subtype of stroke, such as ischaemic stroke and haemorrhagic stroke.[11–15] However, there are also studies suggesting that stroke mortality is not significantly associated with common air pollutants.[16] Such controversial results were also observed for the associations between stroke admissions and air pollution.[17–22] Apparently, the results for the existing studies have been inconsistent. Moreover, little information can be found in these studies regarding whether there are populations particularly susceptible to stroke mortality associated with air pollution.

In Shanghai, the largest city in China, stroke has become one of the leading causes of death. The relatively high stroke death rate also gives us enough power to examine the outcome. The objective of the present study was to investigate the association between air pollution and stroke mortality of adults aged above 65 over a 6-year period (2003–2008) in Shanghai, China. The identification of potentially sensitive groups of stroke mortality in relation to air pollution was also the focus of our study.

## METHODS

### Materials

Our target population includes all permanent residents living in Shanghai—around 13.8 million in 2008. In the target population, the male/female ratio was 100.2%, and the elderly (>65 years of age) accounted for 15.3% of the total population. In Shanghai, there are about 0.1 million total deaths each year, among which the proportions of stroke and cardiovascular mortality are about 12.8% and 34.4%, respectively.

Daily mortality data from 1 January 2003 to 31 December 2008 were collected from the database of the Shanghai Municipal Center for Disease Control and Prevention. Death certificates in Shanghai are completed either by community doctors for deaths at home or by hospital doctors for deaths in hospitals. The information on the certificates was coded according to the International Classification of Diseases, Revision 10 (WHO 1993). Deaths with codes I60–I61 and I63–I64 as the underlying cause of death were considered as fatal strokes; code I61 was considered as s fatal-haemorrhagic stroke and I63 was considered as a fatal-ischaemic stroke. The data were classified by sex and age (65–75, ≥75). To examine the modifying effect of comorbid health conditions, hypertension (codes I10), diabetes (codes E10–E14) and cardiac diseases (codes I01, I02.0, I05–I09, I11, I13, I20–I25, I27 and I30–I52) were also defined.

Daily air pollution data, including particles with size <10 μm ($PM_{10}$), sulfur dioxide ($SO_2$) and

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nitrogen dioxide ($NO_2$), were retrieved from the database of the Shanghai Environmental Monitoring Center, the government agency in charge of collection of air pollution data in Shanghai. The daily concentrations for each pollutant were averaged from the available monitoring results of six fixed-site stations and covered by China National Quality Control. These stations are mandated to be located away from major roads, industrial sources, buildings or residential sources of emissions from the burning of coal, waste or oil; thus, our monitoring results reflect the background urban air pollution level in Shanghai rather than local sources such as traffic or industrial combustion. To allow adjustment for the effect of weather conditions on mortality, we also obtained the daily mean temperature and humidity data from the Shanghai Meteorological Bureau database.

### Statistical analysis

The time-stratified case-crossover approach, which has been shown to be an attractive alternative to the Poisson time-series models, was used to examine the association between air pollution and stroke mortality. The case-crossover approach is a design in which only cases are sampled, and their exposure at the time of their failure is compared with some estimate of their typical level of exposure. This approach only requires exposure data for cases and can be regarded as a special type of case-control study in which case serves his/her referent. The time-stratified referent selection has the ability to avoid some subtle selection bias issues and further result in an unbiased effect estimate using conditional logistic regression models.[23 24] In our analysis, we selected control days matched on the same day of the week in the same month of the same year when a death occurred. Given that the association between weather conditions (temperature and relative humidity) and mortality has been found to be generally non-linear, the temperature and relative humidity on the concurrent day of death was adjusted by us using a natural smooth spline with 3 degrees of freedom.[4] As a sensitivity analysis, we examined the effect of air pollutants with different lag structures (from lag0 to lag3). Lag0 was defined as the current-day pollutant concentration, lag1 referred to the previous-day concentration, and so on. We calculated the 95% CI to test the statistically important significance of differences between effect estimates of the strata divided by potential effect modifiers. The theory of the method was elaborated by Zeka A and we refer to the formula in their work.[25]

We report effect estimates as the percentage change in daily mortality for a 10 $\mu g/m^3$ increase of air-pollutant concentrations. The reported p values are based on two-sided tests at $\alpha=0.05$ level. All the analyses were performed using R, V.2.11.0 (R Development Core Team 2010).

## RESULTS

There were a total of 66 366 stroke deaths for adults above 65 between 1 January 2003 and 31 December 2008. Among them, there were 30 583 cases of ischaemic–stroke deaths and 17 582 cases of haemorrhagic-stroke deaths, accounting for 46.1% and 26.5%, respectively, of total-stroke deaths. The averaged daily stroke deaths during our study period were 30.3 for total-stroke mortality, 14 for ischaemic-stroke mortality, and 8 for haemorrhagic-stroke mortality. Table 1 presents the distribution of air pollutants, meteorological measurements and stroke mortality. The number and percentage of stroke deaths by age and gender groups and in the presence of the secondary diagnoses are shown in table 2. Generally, the number of deaths was similar for different gender groups. However, for each type of stroke mortality, the number of deaths was much larger for people ≥75 when compared with the 65–75 age group. There was a secondary diagnosis of hypertension in 62.8% of total-stroke deaths, 54.5% of ischaemic-stroke deaths and 68.3% of haemorrhagic-stroke deaths.

Positive and statistically significant associations were found between levels of air pollutants and stroke mortality (table 3). An increase of 10 $\mu g/m^3$ in lag0, lag1, lag2 and lag3 concentrations of $SO_2$ corresponds to a 0.43% (95% CI 0.07% to 0.79%), 0.58% (95% CI 0.23% to 0.92%), 0.74% (95% CI 0.41% to 1.07%) and 0.52% (95% CI 0. 18% to 0.85%) increase of total-stroke mortality, respectively. Significant associations were also observed for $PM_{10}$ in lag0 and lag1 and for $NO_2$ in lag0, lag1 and lag2. For ischaemic-stroke mortality, the associations were generally positive, but statistically significant associations were only found for $PM_{10}$ and $NO_2$ in lag0 and for $SO_2$ in lag2 and lag3. For haemorrhagic stroke, an increase of 10 $\mu g/m^3$ in $SO_2$ was associated with a 0.77% (95% CI 0.08% to 1.46%) and 1.01% (95% CI 0.34% to 1.67%) increase in mortality at lag1 and lag2, respectively, and for $NO_2$ at 1.02% (95% CI 0.11% to 1.93%), 1.14% (95% CI 0.25% to 2.03%) and 0.91 (0.02, 1.80) at lag1, lag2 and lag3, respectively.

As shown in table 4, the air pollution effect on stroke mortality varied by gender. For total-stroke mortality, the effect estimates of $PM_{10}$, $SO_2$ and $NO_2$ in men were statistically significant and slightly higher than in women. Similar results were also found for haemorrhagic-stroke mortality. However, for ischaemic-stroke mortality, the effects of air pollutants in women were slightly higher than in men, except that the effect

**Table 1** Summary statistics of daily death numbers, air pollutant concentrations and weather conditions in Shanghai, China, from 2003 to 2008

| Variables | Mean(SD) | Minimum | Q1 | Median | Q3 | Maximum |
|---|---|---|---|---|---|---|
| Daily death counts | | | | | | |
| Stroke | 30.3 (8.5) | 7.0 | 24.0 | 29.0 | 35.0 | 66.0 |
| Ischaemic stroke | 14.0 (4.7) | 2.0 | 11.0 | 13.0 | 17.0 | 35.0 |
| Haemorrhagic stroke | 8.0 (3.3) | 0.0 | 6.0 | 8.0 | 10.0 | 23.0 |
| Meteorology | | | | | | |
| Temperature (°C) | 17.5 (9.1) | −3.1 | 9.7 | 18.5 | 25.1 | 34.1 |
| Humidity (%) | 71.5 (11.9) | 31.0 | 64.0 | 72.0 | 80.0 | 101.0 |
| Pollutants($\mu g/m^3$) | | | | | | |
| $PM_{10}$ | 90.7 (53.9) | 12.0 | 52.0 | 78.0 | 114.0 | 600.0 |
| $SO_2$ | 52.7 (28.9) | 8.0 | 32.0 | 46.0 | 68.0 | 234.5 |
| $NO_2$ | 58.2 (23.1) | 11.2 | 43.2 | 54.4 | 70.4 | 216.0 |

$NO_2$, nitrogen dioxide; $PM_{10}$, particles with size <10 μm; $SO_2$, sulfur dioxide.

**Table 2** Distribution of stroke mortality by age, gender and comorbid conditions in Shanghai, China, 2003–2008

| | | | Primary diagnosis | | | |
|---|---|---|---|---|---|---|
| | Stroke | | Ischaemic stroke | | Haemorrhagic stroke | |
| Variables | N | Per cent | N | Per cent | N | Per cent |
| Age | | | | | | |
| 65–75 | 14 358 | 21.6 | 5482 | 17.9 | 5438 | 30.9 |
| ≥75 | 52008 | 78.4 | 25101 | 82.1 | 12144 | 69.1 |
| Gender | | | | | | |
| Male | 29734 | 44.8 | 13400 | 43.8 | 8906 | 50.7 |
| Female | 36632 | 55.2 | 17183 | 56.2 | 8676 | 49.3 |
| Comorbid condition | | | | | | |
| Hypertension (I10) | 41672 | 62.8 | 16724 | 54.5 | 12007 | 68.3 |
| Diabetes (E10–E14) | 5933 | 8.9 | 3823 | 12.5 | 1192 | 6.8 |
| Chronic rheumatic heart disease (I05–I09) | 118 | 0.2 | 85 | 0.3 | 0 | 0.0 |
| Ischaemic heart disease (I20–I25) | 8907 | 13.4 | 6231 | 20.4 | 1363 | 7.8 |
| Other forms of heart disease (I30–I52) | 2624 | 3.95 | 2021 | 6.6 | 323 | 1.8 |
| Cardiac diseases | 10965 | 16.5 | 7654 | 25.0 | 1692 | 9.6 |

estimates of $PM_{10}$ were insignificant for both men and women. It should be emphasised that none of the above differences were statistically significant for all the pollutants we examined.

The effect estimates of air pollutants for the 65–75 age group were generally higher than for the ≥75 age group for total stroke and ischaemic-stroke mortality, although the difference of effect estimates was insignificant (table 4). We did not find a statistically significant association for both the 65–75 and ≥75 age groups for haemorrhagic-stroke mortality.

Results from analysis examining different types of stroke mortality with comorbid diagnosis are presented in table 5. Generally, for total-stroke, ischaemic-stroke and haemorrhagic-stroke mortalities, the estimated effects for examined air pollutants were insignificant among patients with comorbid hypertension or diabetes and the difference of estimated effects for strata divided by both of them were statistically insignificant. In contrast, for patients with a secondary diagnosis of cardiac diseases, the estimated associations of different stroke types, in relation to $PM_{10}$, $SO_2$ and $NO_2$, were much higher than for those without comorbid cardiac diseases. The strongest associations among patients with cardiac diseases were observed for ischaemic-stroke mortality in relation to $NO_2$; an increase of 10 $\mu g/m^3$ in $NO_2$ was associated with a 7.05% (95% CI 1.92% to 12.17%) increase in mortality, which was markedly stronger than that among patients without cardiac diseases.

## DISCUSSION

In a time-stratified case-crossover design, our study summarises the relationship between air pollution and stroke mortality in Shanghai, China over a 6-year interval. We found that a transient increase in ambient air pollution was associated with an increased risk of mortality for total stroke, ischaemic stroke and haemorrhagic stroke, respectively. Interestingly, we observed a substantial difference of effect estimates for ischaemic-stroke mortality in relation to $NO_2$ among people with cardiac diseases compared with those without. In comparison, no significant

**Table 3** Per cent increase of daily mortality associated with 10 $\mu g/m^3$ increase of pollutant concentrations in Shanghai, China, 2003–2008 (mean and 95% CI)

| | $PM_{10}$ | $SO_2$ | $NO_2$ |
|---|---|---|---|
| Stroke | | | |
| Lag0 | 0.22 (0.04 to 0.39)* | 0.43 (0.07 to 0.79)* | 0.84 (0.39 to 1.29)* |
| Lag1 | 0.19 (0.02 to 0.37)* | 0.58 (0.23 to 0.92)* | 0.83 (0.38 to 1.28)* |
| Lag2 | 0.15 (−0.02 to 0.32) | 0.74 (0.41 to 1.07)* | 0.62 (0.17 to 1.07)* |
| Lag3 | 0.16 (−0.01 to 0.33) | 0.52 (0.18 to 0.85)* | 0.40 (−0.04 to 0.84) |
| Ischaemic stroke | | | |
| Lag0 | 0.28 (0.02 to 0.53)* | 0.41 (−0.12 to 0.94) | 0.91 (0.24 to 1.58)* |
| Lag1 | 0.12 (−0.14 to 0.37) | 0.37 (−0.15 to 0.88) | 0.62 (−0.06 to 1.30) |
| Lag2 | 0.17 (−0.08 to 0.42) | 0.80 (0.31 to 1.29)* | 0.62 (−0.04 to 1.28) |
| Lag3 | 0.20 (−0.05 to 0.45) | 0.54 (0.05 to 1.03)* | 0.42 (−0.24 to 1.08) |
| Haemorrhagic stroke | | | |
| Lag0 | −0.03 (−0.38 to 0.32) | 0.58 (−0.15 to 1.31) | 0.69 (−0.21 to 1.60) |
| Lag1 | 0.13 (−0.21 to 0.47) | 0.77 (0.08 to 1.46)* | 1.02 (0.11 to 1.93)* |
| Lag2 | 0.31 (−0.02 to 0.64) | 1.01 (0.34 to 1.67)* | 1.14 (0.25 to 2.03)* |
| Lag3 | 0.20 (−0.14 to 0.53) | 0.62 (−0.05 to 1.29) | 0.91 (0.02 to 1.80)* |

*$p<0.05$.
$NO_2$, nitrogen dioxide; $PM_{10}$, particles with size <10 μm; $SO_2$, sulfur dioxide.

**Table 4** Per cent increase of daily mortality associated with 10 μg/m$^3$ increase of pollutant concentrations (average of pollution levels lagged 0, 1, 2 and 3 days) by gender and age groups in Shanghai, China, 2003–2008 (mean and 95% CI)

| | | Gender | | Age | |
|---|---|---|---|---|---|
| Primary diagnosis | Pollutant | Male | Female | 65 to 75 | ≥75 |
| Stroke | $PM_{10}$ | 0.52 (0.15 to 0.88) | 0.14 (−0.19 to 0.48) | 0.60 (0.05 to 1.14) | 0.26 (−0.02 to 0.54) |
| | $SO_2$ | 1.29 (0.58 to 2.00) | 0.87 (0.22 to 1.51) | 1.27 (0.20 to 2.33) | 1.10 (0.56 to 1.64) |
| | $NO_2$ | 1.53 (0.60 to 2.46) | 0.94 (0.09 to 1.79) | 1.47 (0.09 to 2.85) | 1.21 (0.50 to 1.92) |
| Ischaemic stroke | $PM_{10}$ | 0.45 (−0.14 to 1.05) | 0.36 (−0.15 to 0.87) | 1.25 (−0.61 to 3.10) | 0.25 (−0.15 to 0.66) |
| | $SO_2$ | 0.81 (−0.35 to 1.98) | 1.59 (0.61 to 2.57) | 4.93 (0.60 to 9.27) | 1.01 (0.23 to 1.79) |
| | $NO_2$ | 1.12 (−0.40 to 2.65) | 1.70 (0.40 to 3.00) | 4.36 (−0.42 to 9.13) | 1.21 (0.18 to 2.25) |
| Haemorrhagic stroke | $PM_{10}$ | 1.58 (0.12 to 3.04) | −0.01 (−1.47 to 1.46) | 0.12 (−2.58 to 2.83) | −1.96 (−2.70 to −1.22) |
| | $SO_2$ | 4.31 (1.02 to 7.60) | 2.66 (−0.61 to 5.92) | −0.29 (−7.22 to 6.65) | −1.91 (−3.37 to 0.45) |
| | $NO_2$ | 7.76 (4.03 to 11.50) | 5.21 (1.58 to 8.83) | −3.52 (−11.13 to 4.09) | 0.09 (−1.79 to 1.97) |

Mean and 95% CI.
$NO_2$, nitrogen dioxide; $PM_{10}$, particles with size <10 μm; $SO_2$, sulfur dioxide.

evidence of effect modification by comorbid hypertension and diabetes was found.

Case-crossover design has been widely used in air pollution epidemiology for its ability to study the effects of varying short-term air pollution exposure on health outcomes with an abrupt onset. The strength of this design is that the effect estimates are not confounded by age, gender, smoking, underlying chronic diseases or other individual-level characteristics. Also, by choosing the control period within a few weeks of death, this approach reduced any potential confounding role of the long-term time trends, seasonality and day of week. Furthermore, the time-stratified referent selection used in our analysis was able to avoid some subtle selection bias issues and result in an unbiased effect estimate using conditional logistic regression models.[26]

Consistent with previous studies, our study found that both total-stroke and ischaemic-stroke mortalities were significantly associated with air pollution. Additionally, significant positive associations were also found between levels of $SO_2$ and $NO_2$ and haemorrhagic stroke, although the influences of air pollutants on different stroke types differed in terms of effect size and lag patterns. These results indicate that different stroke types are likely to be affected by air pollution through different biological mechanisms and may have different critical periods of exposure. However, to the best of our knowledge, few significant results were found on association between air pollution and haemorrhagic-stroke mortality. In view of the high-case death rates of this stroke type, the association pattern we found will contribute to the literature and additional studies on this topic are also warranted.[27]

The identification of susceptible subgroups is critically important for scientific and public-health purposes, as it may provide information regarding mechanisms and target certain subgroups that need to reduce exposure during episodes of high levels of air pollution.[28] Our research examined comorbid-health conditions including hypertension, diabetes and cardiac diseases, which may modify the effects of air pollution. Among them, the presence of hypertension and diabetes has been reported to modify the association between air pollution and cardiovascular outcomes.[29 30 5] Contrary to expectations, in the present study, we found that the effects of air pollution on mortality of different stroke types were mostly insignificant among patients with a secondary diagnosis of hypertension or diabetes and no evidence of effect modification was found by both of them. This could partly be explained by the fact that for the residents with chronic diseases such as hypertension and diabetes in Shanghai, all of them will receive periodical surveillance and medical service by community doctors. As a result, the health conditions for most of these patients are well controlled. Another explanation for our results is that patients with a rapid fluctuation of blood pressure rather than hypertension are at increased risk of stroke mortality.[31] In any case, our results for the above comorbid conditions still need to be further validated by other studies.

Cardiac diseases such as rheumatic heart diseases and atrial fibrillation have been reported to be risk factors for stroke mortality.[32] However, whether patients with these cardiac diseases will be at even greater risks of stroke mortality when they were exposed to air pollution is still unknown. In our study, there were low numbers of stroke deaths from the above heart diseases, resulting in unstable models; therefore, these diseases were combined as cardiac diseases and included in our analysis. Our results demonstrated that these underlying cardiac diseases may increase the risk for ischaemic-stroke mortality, in relation to increased air pollution levels, particularly $NO_2$. We believe that this is biologically plausible since air pollutants have been found to be able to raise the heart rate, alter the heart rate variability and further increase the risks of stroke mortality.[33 34] We suspect that such abilities of air pollutants may particularly increase the susceptibility of individuals who have already suffered from cardiac disease. In addition, air pollutants were recently proved to be associated with the increase of atherosclerosis in animals.[35] As atherosclerosis is the most common cause of ischaemic stroke, such mechanisms may help explain the modifying effect of cardiac disease for this specific type of stroke but not haemorrhagic stroke in case of ambient air pollution.

In fact, many mechanisms have been hypothesised for air pollution-associated stroke mortality besides causing changes in cardiac rhythm and automatic function. First, exposure to ambient air pollution is supposed to be able to provoke alveolar inflammation, which may in turn release harmful cytokines that may increase blood coagulation and promote thrombus formation.[36] Particulate exposure was also supposed to have the ability to induce an acute systemic inflammatory response with an increased number of circulating neutrophils and increased levels of C reactive protein.[37] Other postulated mechanisms for the biological plausibility of air pollution associated mortality including causing myocardial infarction as well as initiation of life-threatening arrhythmias.[38] All of these mechanisms provide possible pathways in which air pollution may increase the risk of cardiovascular and, by extension, cerebrovascular events. However,

**Table 5** Per cent increase of stroke mortality associated with 10 μg/m$^3$ increase in air pollutant concentrations (average of pollution levels lagged 0, 1, 2 and 3 days) by secondary diagnosis in Shanghai, China, 2003–2008 (mean and 95% CI)*

| | | Comorbid condition | | | | | |
|---|---|---|---|---|---|---|---|
| | | Hypertension | | Diabetes | | Cardiac diseases | |
| Primary diagnosis | Pollutant | With | Without | With | Without | With | Without |
| Stroke | $PM_{10}$ | 0.17 (−0.15 to 0.48) | 0.56 (0.16 to 0.96) | 0.52 (−0.30 to 1.35) | 0.29 (0.03 to 0.55) | 0.56 (−0.06 to 1.17) | 0.27 (−0.01 to 0.54) |
| | $SO_2$ | 0.78 (0.18 to 1.39) | 1.51 (0.73 to 2.29) | 1.49 (−0.10 to 3.07) | 1.01 (0.51 to 1.51) | 2.04 (0.87 to 3.22) | 0.87 (0.35 to 1.39) |
| | $NO_2$ | 0.84 (0.05 to 1.64) | 1.82 (0.80 to 2.85) | 2.26 (0.17 to 4.36) | 1.10 (0.44 to 1.76) | 2.63 (1.08 to 4.17) | 0.94 (0.25 to 1.62) |
| Ischaemic stroke | $PM_{10}$ | 0.31 (−0.21 to 0.84) | 0.74 (0.18 to 1.30) | 3.08 (−1.90 to 8.06) | 0.40 (0.01 to 0.80) | 1.80 (−0.20 to 3.81) | 0.17 (−0.25 to 0.60) |
| | $SO_2$ | 0.79 (−0.22 to 1.80) | 1.78 (0.70 to 2.87) | 5.21 (−7.69 to 18.11) | 1.03 (0.25 to 1.80) | 5.19 (0.54 to 9.84) | 0.67 (−0.15 to 1.49) |
| | $NO_2$ | 0.91 (−0.42 to 2.24) | 2.48 (1.05 to 3.91) | 12.15 (−2.82 to 27.11) | 1.27 (0.25 to 2.29) | 7.05 (1.92 to 12.17)* | 0.60 (−0.49 to 1.68)* |
| Haemorrhagic stroke | $PM_{10}$ | −1.87 (−2.61 to −1.14) | 0.32 (−2.46 to 3.10) | 0.10 (−1.66 to 1.86) | 0.04 (−0.47 to 0.55) | 5.27 (−4.11 to 14.66) | 0.11 (−0.41 to 0.64) |
| | $SO_2$ | −2.23 (−3.68 to −0.78) | 2.41 (−4.67 to 9.49) | 1.52 (−1.81 to 4.86) | 0.78 (−0.21 to 1.77) | 18.35 (−6.80 to 43.50) | 0.77 (−0.25 to 1.79) |
| | $NO_2$ | −0.25 (−2.10 to 1.60) | −0.38 (−8.06 to 7.31) | 2.00 (−2.50 to 6.50) | 1.45 (0.14 to 2.75) | 18.44 (−10.22 to 47.10) | 1.61 (0.27 to 2.95) |

*p<0.05.
$NO_2$, nitrogen dioxide; $PM_{10}$, particles with size <10 μm; $SO_2$, sulfur dioxide.

more specific biological mechanisms for the observed effects of air pollutants on human health still need to be further explored.

There are some limitations that should be considered in our study. First, we used ambient air pollution levels from fixed outdoor air monitoring sites to represent individual exposure, which may not perfectly reflect variations in personal exposure. Such a measurement error may introduce bias to our analysis results, although we could not quantify such a bias due to lack of available information on personal exposure. Second, among our research population, 78.4% of stroke mortality occurred in people aged above 75. Given that many people in this age group are simultaneously suffering from other diseases and may spend most of their time indoors, there is the possibility that they will suffer from larger risks of stroke mortality than we found when they were sufficiently exposed to air pollution. Third, the cardiac diseases comprised many different forms of heart disease in our analysis, and we need to identify the specific role for each of them in the case of effect modification in future studies. Finally, the results in our research are based on the time-stratified case-crossover method, given its strengths in studying the effects of short-term exposure on health outcomes as well as its wide use in air pollution epidemiology. Other approaches, such as Poisson time series models or the GAM model, are also needed since the findings in the short-term health impact of any air pollutant are dependent on the statistical methods used.

In summary, ambient air pollution was found to be significantly associated with mortality of total stroke, ischaemic stroke and haemorrhagic stroke in Shanghai. We also provide evidence that the underlying cardiac diseases may increase the risk for ischaemic-stroke mortality, in relation to increased $NO_2$ levels. These findings provide new information on the relationship between daily-stroke mortality and air pollution and may have implications for local environmental and social policies. Further toxicological studies are needed to elucidate the biological mechanisms and to confirm or refute our findings.

### What is already known on this subject?

- Ambient air pollution has been found to be associated with higher rates of cardiovascular disease mortality. Populations particularly susceptible to cardiovascular disease mortality associated with air pollution have also been identified. Conclusions on effects of air pollutants on stroke mortality, however, have been controversial. Information on people who are potentially sensitive to air pollution-associated stroke mortality is also limited.

### What this study adds?

- Ambient air pollution is significantly associated with mortality of total stroke, ischaemic stroke and haemorrhagic stroke. Patients with underlying cardiac disorder may suffer greater risks of ischaemic-stroke mortality in relation to increased $NO_2$ levels.

**Contributors** YQ, HK and CW were responsible for the study design and data analysis; MZ and BC were responsible for conducting the pilot study, data collection;

verification are completed by QY and GS; WJ and MH complete the writing and editing of the manuscript.

**Competing interests** None.

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