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Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series study in Changzhou, China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020425
Article Type:	Research
Date Submitted by the Author:	03-Nov-2017
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Cardiovascular medicine
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, PUBLIC HEALTH

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4 **Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series**
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6 **study in Changzhou, China**
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ABSTRACT

Objective To investigate the acute effect of air pollutants on ischemic stroke (IS) and IS related death.

Setting 5 urban districts in Changzhou, China between January 9, 2015 and December 31, 2016.

Participants 32,840 IS cases and 4,028 IS deaths were enrolled.

Main outcome measures Time- series design, generalized additive model and multivariable regression model were used to examine the percentage change (95% confidence interval [CI]) in daily IS counts and deaths with an interquartile range (IQR) increase in air pollutants levels for different single or multiple lag days in single-pollutant and two-pollutants models.

Results Daily IS counts increased 0.208% (95% [CI]: 0.036%-0.381%) with an IQR increment in levels of NO₂. The estimated risk of NO₂ was more robust in males and cold season. For daily IS counts, the estimated effects of NO₂ and SO₂ were more significant when adjusted for PM_{2.5} and PM₁₀. An IQR increment in the concentration of PM₁₀, SO₂ and NO₂ significantly increased IS deaths with 6 days cumulative effects (0.268%, 95% CI: 0.007%-1.528%; 0.34%, 0.088%-0.592%; 0.263%, 0.004%-0.522%, respectively). Young individuals (< 65) had higher IS mortality risk for PM_{2.5}, PM₁₀, NO₂ and CO. For IS death, the effects estimates of SO₂ in the elderly, female and cold season were more pronounced, statistical significance was also identified for SO₂ when adjusted for CO.

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3 **Conclusions** This study suggested that short term exposure to ambient NO₂ was
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5 associated with increased IS risk. And SO₂ were associated with increased IS onsets
6
7 and deaths.
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10 11 **Article Summary**

12 13 **Strengths and limitations of this study**

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▪ This is the first comprehensive research in China that exploring the short-term effects of air pollutants on the morbidity and mortality of stroke at the same time.
- The statistical power to detect the association was sufficient because of the tremendous numbers of IS cases and IS deaths recorded in our work.
- This time-series study evaluated the association of modifiers between air pollution and daily IS counts or deaths, which may provide clues for the primary prevention of IS and IS related death.
- We could not precisely quantify the air pollutants exposure of individuals using the fixed-site monitoring data.
- This is a single city-based study and the results should be extrapolated with caution.

INTRODUCTION

Air pollution is considered as a primary risk factor for a mounting body of pollution-related diseases and deaths [1]. Moreover, as a modifiable risk factor, air pollution accounts for more than 7 million deaths annually [2]. Studies have extensively explored the association between air pollution and risk of respiratory, reproductive and cardiovascular diseases [3-5]. Epidemiological studies suggested that exposure to air pollutants may increase the risk of cardiovascular diseases in haze days [6-8]. For instance, a study conducted in Stockholm suggested that short-term exposure to PM_{2.5} was associated with out of hospital cardiac arrest. Increments in particulate matters with aerodynamic diameters < 2.5 µm (PM_{2.5}), < 10 µm (PM₁₀), nitrogen dioxide (NO₂), sulfur dioxide (SO₂) and carbon monoxide (CO) were associated with higher risk of heart failure hospitalization and death. A meta-analysis indicated that long-term exposure to PM_{2.5} was related to a dramatic increase in cardiovascular mortality [9].

Stroke is a persistent neurological deficit caused by cerebrovascular damages. It can be classified into ischemic stroke (IS) and hemorrhagic stroke (HS) on the basis of pathophysiologic mechanisms [10-12]. Stroke is one of the most leading causes of death and disability-adjusted life years worldwide [13, 14]. In 2010, the estimated number of individuals suffered from stroke was 50 million and among them, approximately 17 million cases were newly identified that year. China bears enormous stroke burden in the world with the highest stroke prevalence, incidence and mortality among other developing world [15]. As the major subtype of stroke in China, IS

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3 accounts for 43% to 79% of all strokes and provokes growing concerns recently [16].

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6 Given the tremendous disease burden of stroke, risk factors identification and
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8 prevention are critical and effective public health strategies [17]. However, in terms of
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10 stroke, the effect of air pollutants remains a matter of debate, which might be, at least
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12 in part, explained by the heterogeneity in different stroke subtypes [18, 19]. Thus, it is
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14 a pressing need to synthetically explore the association between air pollutants and
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16 specific subtype of stroke related incidence and mortality.
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20 Changzhou stands on the southern bank of the Yangtze River. The city serves as
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22 part of the Suzhou-Wuxi-Changzhou metropolitan area and by the year of 2010, there
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24 were about 4 million residents in five urban districts (Tianning district, Wujin district,
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26 Jintan district, Xinbei district and Liyang city) [20]. Moreover, with the rapid
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28 industrialization and economic development in the past years, Changzhou is now
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30 experiencing severe air pollution. The concentrations of several air pollutants (such as
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32 PM_{2.5}, PM₁₀, SO₂ and NO₂) were equal or higher than the national ambient air quality
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34 in the recent years [21, 22]. Therefore, Changzhou was chosen as a suitable place to
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36 study the effect of air pollution on incidence and mortality of IS. In this study, a
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38 comprehensive time-series study was conducted in Changzhou to examine the
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40 association between main air pollutants and daily IS counts and deaths. To explore the
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42 effect modification, the association of modifiers between air pollution and daily IS
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44 counts and deaths was also evaluated. This work will help provide insights into the
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46 relationship between stroke and air pollutants and have implication for prevention of
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48 IS and IS related deaths.
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MATERIALS AND METHODS

Data collection

Air pollution data, including daily 24-hour average levels of PM_{2.5}, PM₁₀, NO₂, SO₂ and CO between January 9, 2015 and December 31, 2016 were obtained from ten air quality monitoring stations run by Changzhou Environmental Monitoring Center. The daily mean levels for air pollutants were averaged from all the stations and approximately all the cases recorded in this study resided less than 40 km from the nearest monitoring station. Thus, the monitoring data could be used as an appropriate proxy for personal exposure. Daily meteorological data on temperature (°C) and relative humidity (%) were collected from Changzhou Meteorological Bureau.

Daily IS and IS mortality data from January 9, 2015 to December 31, 2016 were obtained from the database of Changzhou Center for Disease Control and Prevention (CDC). This database belonged to the government -controlled network reporting system for chronic diseases, which was established in Changzhou, 2012.

Cardiovascular physicians were responsible for the diagnosis of IS according to the cerebrovascular ICD-10 codes for IS (I63). Demographic data were collected from Changzhou Municipal Bureau of Statistics. Daily IS counts and deaths were also stratified into groups by gender (male and female) and age group (<65 and ≥65 year-old) to explore the effect modification of individual characteristics.

Statistical analysis

Daily IS counts, daily IS death counts, air pollutants levels and weather data were linked by date for the subsequent time-series study, which was applied to analyze the

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3 effects of each air pollutant on IS counts and death. After evaluating the distribution
4 patterns of daily IS counts and deaths, Poisson distributions were identified. Poisson
5 regression was used in generalized additive model (GAM) to calculate the data.
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10 Multivariable regression model was used to detect the air pollutants related
11 associations and control the potential confounding factors, such as calendar time, day
12 of week (DOW), daily average relative humidity and temperature. The five degree of
13 freedom (df) was used to adjust for all the confounding factors mentioned above
14 except for DOW (df= 7). Furthermore, to explore the potential modification, data
15 were stratified by sex, age (<65 as young individuals and ≥ 65 as the elderly) and
16 season (warm season as 1 May to 31 October and cold season as 1 November to 30
17 April). Associations between air pollutants and IS and IS related death were
18 separately examined according to the following equation:
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$$\text{Log}[E(T/D_n)] = \text{intercept} + \beta_1 \text{AirPollution}_{n-i} + \beta_2 \text{DOW} + \text{ps}(\text{calendar time, df= 7}) + \text{ps}(\text{Temp}_{n-i}, \text{df= 5}) + \text{ps}(\text{Relative Humidity}_{n-i}, \text{df= 5})$$

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35 $E(T/D_n)$ represents the estimated numbers of IS onsets or deaths on day n;

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38 $\text{AirPollution}_{n-i}$ represented the average levels of different air pollutants on day n and i
39 is the day lag; β was vector of the coefficients; DOW was the day of week; ps ()
40 presented penalized spline function; Temp_{n-i} and $\text{Relative Humidity}_{n-i}$ represented
41 average temperature and relative humidity on day n and i is the day lag.
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48 In addition, for both daily IS counts and deaths, single-pollutant models were
49 fitted with different single lag days (lag0, lag1, lag3 and lag5) to detect the effects of
50 air pollution on IS. As underestimation may occur in single-day models, multiple-day
51 lag models (lag0-1, lag0-3 and lag0-5) were also applied in this study. Smoothing
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function was used in the analysis of the exposure-response relationship between the log-relative risk of daily IS counts or deaths and air pollutants concentrations using a 5 df in single-pollutant model.

Statistical software R (version 3.2.3, R Foundation for Statistical Computing, Austria) was used for data analysis and result output. The baseline data was presented as mean \pm standard deviation (SD) for continuous variables. All tests were two-sided, and $P < 0.05$ was considered as statistically significant.

RESULTS

Descriptive Analysis

During this study period, there were 32,840 IS cases and 4,028 IS deaths recorded, respectively. For IS, on average, 45.4 cases were identified each day (Table S1). Of these, 52.2% were males and 81.3% were the elderly (≥ 65). And for IS related death, there were 5.6 deaths recorded on average each day (Table S1). Of these, 48.2% were males and 96.4% were the elderly.

Daily average meteorological data were 17.0°C for temperature and 75% for relative humidity. The daily average levels were 51.8 $\mu\text{g}/\text{m}^3$ for PM_{2.5}, 85.3 $\mu\text{g}/\text{m}^3$ for PM₁₀, 22.3 $\mu\text{g}/\text{m}^3$ for SO₂, 38.7 $\mu\text{g}/\text{m}^3$ for NO₂ and 1 mg/ m³ for CO (Table 2).

According to the WHO air quality guidelines (25 $\mu\text{g}/\text{m}^3$ for PM_{2.5}, 50 $\mu\text{g}/\text{m}^3$ for PM₁₀ and 20 $\mu\text{g}/\text{m}^3$ for SO₂), the corresponding average levels of PM_{2.5}, PM₁₀ and SO₂ in Changzhou were far beyond the WHO standard.

Estimated Effects of Air Pollutants

Fig. 1 summarizes the percentage change (95% CI) in daily IS counts and deaths with

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3 an interquartile range (IQR) increase in air pollutants levels for different single or
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5 multiple lag days in single-pollutant models. For daily IS counts, statistically positive
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7 association was observed only in IQR increment of NO₂ levels and this association
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9 was the more significant at multi-day exposure than single day exposure. A highest
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11 association was observed for lag 0-5 (0.208%, 0.036%-0.381%) and was used in the
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13 subsequent study. For daily IS deaths, statistically positive associations were observed
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15 in different IQRs increments of PM₁₀, SO₂ and NO₂. All the associations were the
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17 most significant at lag5 (0.268%, 0.007%-0.528% for PM₁₀; 0.34%, 0.088%-0.592%
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19 for SO₂; 0.263%, 0.004%-0.522% for NO₂) than other days and was thus used in the
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21 subsequent analysis.
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28 Concentration-response relationships of air pollutants with daily IS counts or
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30 deaths were conducted in Fig. 2. For IS counts, the curve of NO₂ was linear positive
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32 and flat at higher concentrations. For daily IS deaths, the concentration-response
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34 curves of PM₁₀ and SO₂ were similar, flat at low levels and dramatically linear
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36 positive at high levels, whereas the curve for NO₂ suggest a linear rise in daily IS
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38 deaths.
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43 The effect of NO₂ on the increase of daily IS counts was more significant among
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45 males than that of females and the effects of NO₂ and SO₂ on daily IS counts were
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47 significant in the cold season, but not in the warm season. No significant association
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49 was observed when modifying by age (Table 3). As for daily IS deaths, the estimated
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51 effect of PM₁₀ was more pronounced among males, whereas the effects of NO₂ and
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53 SO₂ were more robust among females. Moreover, PM_{2.5}, PM₁₀, NO₂ and CO were
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3 found to have greater deleterious effects among young individuals and SO₂ showed
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5 more risk in the elderly. And when modifying by seasons, statistical significance was
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7 identified only for SO₂ in the cold season (Table 3).
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11 Table 4 shows the percent increases in daily IS counts and daily IS deaths with
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13 each IQR increment in air pollutants levels in two-pollutants models. For daily IS
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15 counts, the estimated effects of NO₂ and SO₂ were more significant when adjusted for
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17 PM_{2.5} and PM₁₀. For daily IS deaths, statistical significance was identified for SO₂
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19 when adjusted for CO.
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24 **DISCUSSION**

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26 In this population-based time-series study, a total of 32,840 IS cases and 4,028 IS
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28 death were identified in Changzhou from 2015 to 2016. Significant association of
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30 NO₂ with daily IS counts was observed even when adjusted by PM_{2.5} and PM₁₀. The
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32 estimated IS risk of NO₂ was more robust in the elderly and the cold season. In
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34 addition, PM₁₀, SO₂ and NO₂ were positively associated with daily IS deaths. The
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36 young individuals had higher IS mortality risk for PM_{2.5}, PM₁₀, NO₂ and CO. And IS
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38 mortality risk of SO₂ was more robust in the elderly, female and cold season,
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40 statistical significance was also identified for SO₂ when adjusted for CO. To the best
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42 of our knowledge, in China, this is the first comprehensive study to explore the acute
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44 effect of air pollutants on the morbidity and mortality of stroke at the same time.
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51 PM₁₀ could cause endothelial dysfunction, inflammatory response and
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53 neuro-functional impairment and subsequently induce ischemia-like injuries in the
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55 brain [23]. In the current study, an IQR increment in PM₁₀ concentrations was
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3 associated with 0.268% increment in daily IS deaths, which was in consistent with the
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5 previous investigations [24, 25]. Moreover, the function curve for PM₁₀/ daily IS
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7 deaths was flat at <150 µg/m³ and became dramatically sharp at high levels. Previous
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9 multicity time-series study indicated an acute, deleterious and significant effect of
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11 PM₁₀ on IS mortality and the estimated rate ratios were 1.016 [26]. Long-term
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13 exposure to PM₁₀ was also demonstrated to positively associate with IS relate death
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15 and the estimated relative risk was 1.37 [27]. Moreover, in this study, greater
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17 estimated IS mortality risk was observed among males and young individuals. It is
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19 plausible that males and young individuals spent more time outdoors and exposed to
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21 higher levels of PM₁₀ than females and the elderly [28].
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28 NO₂, a representative pollutant of vehicle exhaust, was found to induce
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30 excitotoxicity, endothelial and inflammatory responses and damage synaptic plasticity
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32 in the brain [29],[30, 31]. In China, a multicity case-crossover study demonstrated that
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34 an IQR increase (25.4 µg/m³) in NO₂ was corresponded to 2.6% increment in IS
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36 admissions. Stroke mortality was also positively associated with ambient NO₂ levels
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38 [32]. In the present study, we indicated that IQR increments in NO₂ (12 µg/m³) was
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40 associated with 0.208% and 0.263% increases in daily IS counts and IS deaths,
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42 respectively. An approximately linear concentration-response relationship was
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44 identified for NO₂ and daily IS counts or daily IS deaths, which was consistent with
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46 the previous report [33, 34]. The positive association for NO₂ and daily IS counts
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48 could be observed even below the National Ambient Air Quality Standards of China
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50 (80 µg/m³). For daily IS counts, the effects of NO₂ were statistically positive and
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3 stronger when adjusted for other pollutants except for SO₂ (no statistical but stronger
4 association was observed), suggesting that the adverse effect of NO₂ on IS onsets was
5 stable an NO₂ contributed most to the increased risk of IS. Moreover, the effects of
6 NO₂ were more significant in cold season and males. For IS deaths, young females
7 were found to be experienced higher risk. The underlying reasons may be that the
8 exposed levels of NO₂ were much higher at these conditions, which was similar to
9 that of PM₁₀. The risk factors for stroke, such as hypertension, atrial fibrillation and
10 diabetes mellitus are more frequent and the estimated effects are stronger among
11 females [35]. Females are considered to be more sensitive to stroke onsets and deaths.
12 Thus, our findings regarding the higher risk of IS deaths observed among females
13 were reasonable.
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30 SO₂ was considered as a strong irritant ambient gaseous pollutant, and could
31 elevate the expression of vasoregulatory pathways and proinflammatory enzymes
32 such as ET-1, iNOS, COX-2, ICAM-1 and TNF- α [36]. And its exposure was
33 demonstrated to contribute to the development and progression of IS [18]. In the
34 present study, SO₂ was significantly associated with daily IS counts when adjusted by
35 PM_{2.5} or PM₁₀. In addition, exposure to SO₂ also had statistical associations with daily
36 IS deaths (the percentage increase was 0.34%), which was in agreement with previous
37 studies [19, 37]. The function curve for SO₂/ daily IS deaths was flat at <35 $\mu\text{g}/\text{m}^3$ and
38 became dramatically sharp at high levels, suggesting that acute and robust increments
39 of SO₂ might result in exacerbating IS death. Furthermore, the associations were more
40 pronounced among females, suggesting that females are more susceptible to IS related
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3 deaths when exposed to gaseous pollutants (NO₂ and SO₂). In addition, SO₂ exhibited
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5 higher risk of IS deaths in the elderly [38]. And it can be deduced that the elderly are
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7 more likely to bear preexisting respiratory or cardiovascular burdens and the
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9 vulnerable condition could influence the effect of SO₂ on stroke [39]. We also found
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11 that exposure to SO₂ had more significant effects on both IS onsets and deaths in cold
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13 season than in warm season.
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18 In conclusion, our results suggested that short term exposure to ambient NO₂ was
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20 associated with increased IS risk. And SO₂ were associated with increased IS counts
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22 and deaths. These findings may have significant public health implications for
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24 prevention of IS and IS related death. Further studies are recommended to validate our
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26 research.
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33 **Contributors** The study was conceived and designed by Huibin Dong, Yan Lu and Zhan
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35 Zhang, and overall study management was by Xingjuan Yao, Shou-Lin Wang and Zhan
36
37 Zhang. Zhiyong Chen, Guiying Li and Yao Yao contributed to data collection and
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39 processing. Shen Yao performed the statistical analysis, Huibin Dong, Yao Yao and Yan
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41 Lu helped manuscript preparation and interpret the results. All authors contributed to the
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43 revision of the manuscript and reviewed and approved the final version.
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47 **Funding** This work was supported by the Natural Science Foundation of China (81502801), a
48
49 project funded by the Priority Academic Program Development of Jiangsu Higher Education
50
51 Institutions (2014), a collegiate Natural Science Foundations of Jiangsu province
52
53 (16KJB330005), the science and technology support program funded by Changzhou
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3 Municipal Science and Technology Bureau (CE20145046) and the Science and Technique
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6 Foundation for Youths by Health and Family Planning Commission of Changzhou
7
8 (QN201603).
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10 **Disclaimer** The funding sponsors had no role in the design of the study, in the collection,
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12 analysis or interpretation of data, in the writing of the manuscript or in the decision to publish
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14 the research results.
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18 **Ethical approval** The present study was approved by the Institutional Review Board of
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20 Changzhou Center for Disease Control and Prevention, and all procedures were in accordance
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22 with prevailing ethical principles.
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25 **Competing interests** None.
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28 **Patient consent** Not needed.
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30 **Provenance and peer review** Not commissioned; externally peer reviewed.
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33 **Data sharing statement** No additional data are available.
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Figure legends

Figure 1 The percentage change in daily ischemic stroke (IS) counts and daily IS deaths with an interquartile range increase in air pollutants levels on different lag days in single-pollutant models in Changzhou, 2015-2016. The data was expressed as mean with 95% confidence interval.

Figure 2 The concentration-response relationships of daily ischemic stroke (IS) counts, daily IS deaths with air pollutants on different lag days (lag 0-5 for daily IS counts and lag 5 for daily IS deaths) in single-pollutant models in Changzhou, 2015-2016.

Table 1 The means, medians and interquartile ranges (IQRs) for daily air pollutants and weather conditions variables in Changzhou, 2015-2016

Variables	Mean± SD	Min	25th	Median	75th	Max	IQR
Weather Condition							
Temperature (°C)	17.1±8.9	-6.6	9.4	18.3	24.1	34.6	5.8
Humidity (%)	75.3±14.2	35.0	66.0	76.0	86.0	100.0	10.0
Air Pollutions							
PM _{2.5} (µg/m ³)	51.8±30.6	6.8	29.4	44.4	64.4	181.1	20.0
PM ₁₀ (µg/m ³)	85.3±43.3	10.5	51.5	76.6	108.6	289.1	32.0
NO ₂ (µg/m ³)	38.7±16	10.9	26.5	35.8	47.8	117.3	12.0
SO ₂ (µg/m ³)	22.3±10	6.9	14.7	20.2	27.0	67.8	6.9
CO (mg/m ³)	1±0.3	0.4	0.8	1.0	1.2	2.6	0.2

PM_{2.5}, particulate matter <2.5 mm in diameter; PM₁₀, particulate matter <10 mm in diameter; NO₂, nitrogen dioxide; SO₂, sulfur dioxide; CO, carbon monoxide.

Table 2 The percentage change in daily IS counts and deaths with an interquartile range increase in air pollutants levels modifying by age, gender and seasons in Changzhou, 2015-2016

Variable	Total	Age		Sex		Seasons	
		≤65	>65	Female	Male	Warm	Cold
Daily IS counts*							
PM _{2.5}	-0.063 (-0.215-0.088)	-0.246 (-0.568-0.076)	-0.042 (-0.21-0.127)	-0.097 (-0.311-0.119)	-0.08 (-0.289-0.128)	-0.149 (-0.525-0.228)	-0.098 (-0.267-0.071)
PM ₁₀	-0.053 (-0.22-0.114)	-0.219 (-0.572-0.136)	-0.004 (-0.191-0.184)	-0.086 (-0.324-0.153)	-0.047 (-0.279-0.185)	-0.057 (-0.41-0.297)	-0.088 (-0.282-0.107)
NO ₂	0.208 (0.036-0.381)‡	0.258 (-0.075-0.592)	0.166 (-0.025-0.357)	0.168 (-0.055-0.391)	0.238 (0.002-0.475)‡	-0.136 (-0.481-0.21)	0.382 (0.169-0.596)‡
SO ₂	0.125 (-0.034-0.284)	-0.044 (-0.364-0.277)	0.113 (-0.062-0.289)	0.15 (-0.068-0.369)	0.056 (-0.162-0.275)	-0.309 (-0.651-0.033)	0.298 (0.099-0.498)‡
CO	-0.078 (-0.22-0.064)	-0.213 (-0.511-0.086)	-0.061 (-0.222-0.1)	-0.151 (-0.355-0.053)	-0.007 (-0.206-0.192)	-0.175 (-0.432-0.083)	-0.053 (-0.237-0.131)
Daily IS deaths†							
PM _{2.5}	0.228 (-0.005-0.462)	1.144 (0.329-1.965)‡	0.152 (-0.091-0.395)	0.124 (-0.19-0.439)	0.29 (-0.043-0.625)	-0.199 (-0.77-0.375)	0.184 (-0.088-0.456)
PM ₁₀	0.268 (0.007-0.528)‡	1.52 (0.656-2.391)‡	0.152 (-0.12-0.424)	0.093 (-0.261-0.448)	0.404 (0.03-0.78)‡	-0.012 (-0.53-0.509)	0.247 (-0.075-0.57)
NO ₂	0.263 (0.004-0.522)‡	0.894 (0.058-1.736)‡	0.195 (-0.073-0.463)	0.37 (0.027-0.715)‡	0.132 (-0.247-0.512)	0.275 (-0.222-0.775)	0.198 (-0.13-0.528)
SO ₂	0.34 (0.088-0.592)‡	0.67 (-0.175-1.523)	0.307 (0.045-0.57)‡	0.434 (0.096-0.772)‡	0.215 (-0.15-0.58)	0.017 (-0.493-0.531)	0.388 (0.081-0.696)‡
CO	0.175 (-0.042-0.392)	0.9 (0.166-1.639)‡	0.108 (-0.118-0.335)	0.189 (-0.11-0.49)	0.154 (-0.162-0.471)	0.02 (-0.401-0.443)	0.169 (-0.104-0.443)

*The multivariable regression model fits the pollutants for daily IS counts data at lag 0-5 and

adjusts for calendar time (df=5), DOW (df=7), daily average humidity (df=5) and average

temperature (df=5).

†The multivariable regression model fits the pollutants for daily IS deaths data at lag 5 and adjusts

for calendar time (df=5), DOW (df=7), daily average humidity (df=5) and average temperature

(df=5).

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‡ Statistically positive association between air pollutants and daily IS counts or deaths

The data was expressed as mean with 95% confidence interval.

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Table 3 The percent increases in daily IS counts and deaths with each interquartile range increment in air pollutants levels in two-pollutants models in Changzhou, 2015-2016

Variables	PM _{2.5}	PM ₁₀	NO ₂	SO ₂	CO
Daily IS counts					
PM _{2.5}	-0.063 (-0.215-0.088)	0.25 (-0.314-0.817)	0.497 (0.259-0.735)‡	0.305 (0.083-0.527) ‡	-0.059 (-0.274-0.157)
PM ₁₀	-0.423 (-0.881-0.038)	-0.053 (-0.22-0.114)	0.539 (0.29-0.788)‡	0.262 (0.034-0.491) ‡	-0.065 (-0.293-0.163)
NO ₂	-0.346 (-0.558--0.134)	-0.438 (-0.691--0.185)	0.208 (0.036-0.381)‡	-0.007 (-0.267-0.253)	-0.341 (-0.556--0.124)
SO ₂	-0.24 (-0.46--0.019)	-0.244 (-0.49-0.003)	0.22 (-0.067-0.507)	0.125 (-0.034-0.284)	-0.166 (-0.356-0.023)
CO	-0.089 (-0.314-0.137)	0.029 (-0.223-0.281)	0.45 (0.215-0.685)‡	0.172 (-0.016-0.361)	-0.078 (-0.22-0.064)
Daily IS deaths					
PM _{2.5}	0.228 (-0.005-0.462)	0.436 (-0.36-1.238)	0.22 (-0.127-0.567)	0.28 (-0.071-0.632)	0.065 (-0.314-0.446)
PM ₁₀	0.211 (-0.463-0.89)	0.268 (0.007-0.528)‡	0.218 (-0.135-0.573)	0.295 (-0.055-0.646)	0.137 (-0.23-0.504)
NO ₂	0.106 (-0.201-0.414)	0.149 (-0.21-0.509)	0.263 (0.004-0.522)‡	0.351 (-0.096-0.8)	0.057 (-0.269-0.384)
SO ₂	0.066 (-0.25-0.383)	0.126 (-0.242-0.496)	0.066 (-0.387-0.521)	0.34 (0.088-0.592)‡	0.035 (-0.281-0.351)
CO	0.186 (-0.199-0.571)	0.233 (-0.187-0.656)	0.23 (-0.14-0.601)	0.346 (0.002-0.691)‡	0.175 (-0.042-0.392)

*The multivariable regression model fits the pollutants for daily IS counts data at lag 0-5 and

adjusts for the other pollutants, calendar time (df=5), DOW (df=7), daily average humidity (df=5)

and average temperature (df=5).

†The multivariable regression model fits the pollutants for daily IS deaths data at lag 5 and adjusts

for the other pollutants, calendar time (df=5), DOW (df=7), daily average humidity (df=5) and

average temperature (df=5).

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‡ Statistically positive association between air pollutants and daily IS counts or deaths

The data was expressed as mean with 95% confidence interval.

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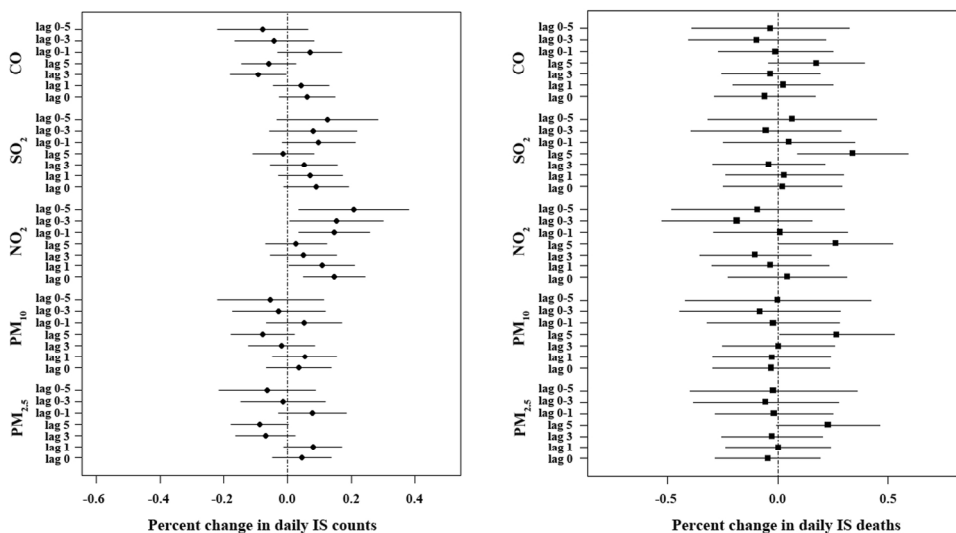


Figure 1 The percentage change in daily ischemic stroke (IS) counts and daily IS deaths with an interquartile range increase in air pollutants levels on different lag days in single-pollutant models in Changzhou, 2015-2016. The data was expressed as mean with 95% confidence interval.

86x48mm (600 x 600 DPI)

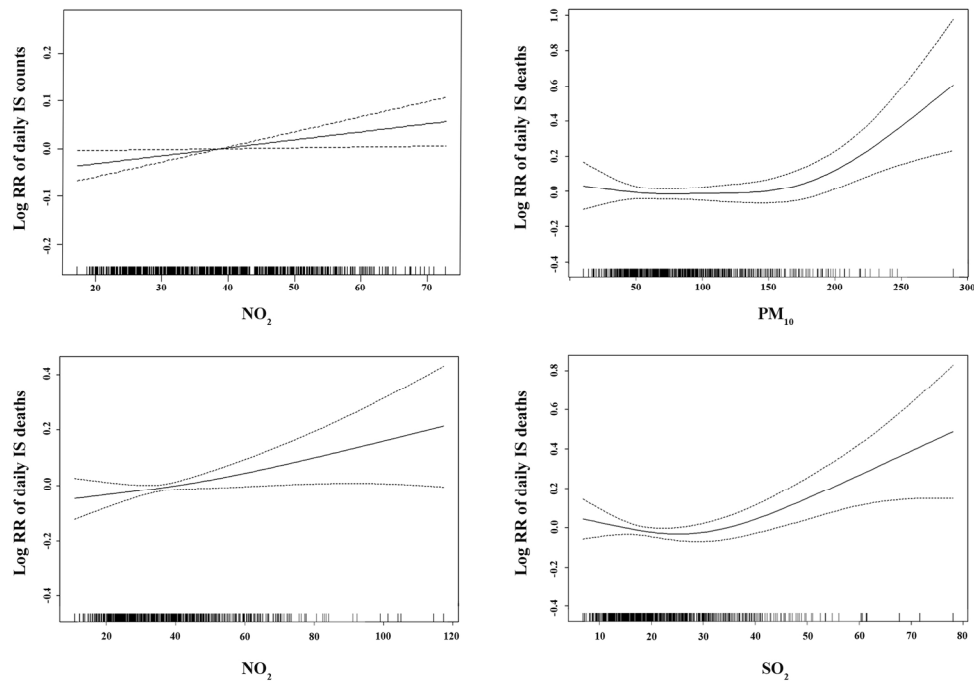


Figure 2 The concentration-response relationships of daily ischemic stroke (IS) counts, daily IS deaths with air pollutants on different lag days (lag 0-5 for daily IS counts and lag 5 for daily IS deaths) in single-pollutant models in Changzhou, 2015-2016.

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4 **Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series**
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6 **study in Changzhou, China**
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10 Hui bin Dong^{1, a}, Yongquan Yu^{2, a}, Shen Yao², Yan Lu³, Zhiyong Chen¹, Guiying Li¹,

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13 Yao Yao¹, Xingjuan Yao¹, Shou-Lin Wang², Zhan Zhang^{4*}
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17 **Supplementary data**
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Table S1 The descriptive statistics for daily ischemic stroke (IS) counts and deaths in Changzhou, 2015-2016*

Variables	Mean± SD	Min	25th	Median	75th	Max
Daily IS counts	45.4±11.2	14.0	38.0	45.0	53.0	99.0
Male	23.7±7	6.0	19.0	23.0	28.0	60.0
Female	21.8±6.1	6.0	18.0	22.0	26.0	48.0
<65	8.5±3.6	0.0	6.0	8.0	11.0	23.0
≥65	36.9±9.2	11.0	31.0	36.0	43.0	80.0
Daily IS deaths	5.6±2.9	0.0	3.0	5.0	7.0	19.0
Male	2.7±1.8	0.0	1.0	3.0	4.0	10.0
Female	2.8±2	0.0	1.0	3.0	4.0	10.0
<65	0.4±0.7	0.0	0.0	0.0	1.0	3.0
≥65	5.1±2.8	0.0	3.0	5.0	7.0	18.0

*A total of 32,840 IS cases and 4,028 IS deaths recorded were recorded during the study period.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1-4	Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series study in Changzhou, China (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	5-6	Explain the scientific background and rationale for the investigation being reported
Objectives	6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	7-9	Present key elements of study design early in the paper
Setting	7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	7	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	7*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	7-8	Describe any efforts to address potential sources of bias
Study size	7	Explain how the study size was arrived at
Quantitative variables	8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	9	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses
Results		
Participants	9*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	9*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest
Outcome data	10-11*	Report numbers of outcome events or summary measures
Main results	10-11	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	10-11	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	11	Summarise key results with reference to study objectives
Limitations	12-13	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	12-13	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	14	Discuss the generalisability (external validity) of the study results
Other information		
Funding	14	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series study in Changzhou, China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020425.R1
Article Type:	Research
Date Submitted by the Author:	08-Mar-2018
Complete List of Authors:	Dong, Huibin; Changzhou Center for Disease Control and Prevention Yu, Yongquan; Nanjing Medical University Yao, Shen; Nanjing Medical University Lu, Yan; The First Affiliated Hospital of Nanjing Medical University Chen, Zhiyong; Changzhou Center for Disease Control and Prevention Li, Guiying; Changzhou Center for Disease Control and Prevention Yao, Yao; Changzhou Center for Disease Control and Prevention Yao, Xingjuan ; Changzhou Center for Disease Control and Prevention Wang, Shoulin; Nanjing Medical University Zhang, Zhan
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Cardiovascular medicine
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, PUBLIC HEALTH

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4 **Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series**
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ABSTRACT

Objective To investigate the acute effect of air pollutants on ischemic stroke (IS) and IS related death.

Setting 5 urban districts in Changzhou, China between January 9, 2015 and December 31, 2016.

Participants 32,840 IS cases and 4,028 IS deaths were enrolled.

Main outcome measures Time- series design, generalized additive model and multivariable regression model were used to examine the percentage change (95% confidence interval [CI]) in daily IS counts and deaths with an interquartile range (IQR) increase in air pollutants levels for different single or multiple lag days in single-pollutant and two-pollutants models.

Results Daily IS counts increased 0.208% (95% [CI]: 0.036%-0.381%) with an IQR increment in levels of NO₂. The estimated risk of NO₂ was more robust in males and cold season. For daily IS counts, the estimated effects of NO₂ and SO₂ were more significant when adjusted for PM_{2.5} and PM₁₀. An IQR increment in the concentration of PM₁₀, SO₂ and NO₂ significantly increased IS deaths with 6 days cumulative effects (0.268%, 95% CI: 0.007%-1.528%; 0.34%, 0.088%-0.592%; 0.263%, 0.004%-0.522%, respectively). Young individuals (< 65) had higher IS mortality risk for PM_{2.5}, PM₁₀, NO₂ and CO. For IS death, the effects estimates of SO₂ in the elderly, female and cold season were more pronounced, statistical significance was also identified for SO₂ when adjusted for CO.

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3 **Conclusions** This study suggested that short term exposure to ambient NO₂ was
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5 associated with increased IS risk. And SO₂ were associated with increased IS onsets
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10 11 12 **Article Summary**

13 14 **Strengths and limitations of this study**

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17 ▪ This is the first comprehensive research in China that exploring the short-term
18 effects of air pollutants on the morbidity and mortality of stroke at the same time.
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21 ▪ The statistical power to detect the association was sufficient because of the
22 tremendous numbers of IS cases and IS deaths recorded in our work.
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25 ▪ This time-series study evaluated the association of modifiers between air
26 pollution and daily IS counts or deaths, which may provide clues for the primary
27 prevention of IS and IS related death.
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30 ▪ The exposures measurement of this study was at the community level, and we
31 could not precisely quantify the air pollutants exposure of individuals using the
32 fixed-site monitoring data, this may lead to exposure measurement error.
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35 ▪ This is a single city-based study and the results should be extrapolated with
36 caution.
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INTRODUCTION

Air pollution is considered as a primary risk factor for a mounting body of pollution-related diseases and deaths [1]. Moreover, as a modifiable risk factor, air pollution accounts for more than 7 million deaths annually [2]. Studies have extensively explored the association between air pollution and risk of respiratory, reproductive and cardiovascular diseases [3-5]. Epidemiological studies suggested that exposure to air pollutants may increase the risk of cardiovascular diseases in haze days [6-8]. For instance, a study conducted in Stockholm suggested that short-term exposure to PM_{2.5} was associated with out of hospital cardiac arrest. Increments in particulate matters with aerodynamic diameters < 2.5 µm (PM_{2.5}), < 10 µm (PM₁₀), nitrogen dioxide (NO₂), sulfur dioxide (SO₂) and carbon monoxide (CO) were associated with higher risk of heart failure hospitalization and death. A meta- analysis indicated that long-terms exposure to PM_{2.5} was related to a dramatic increase in cardiovascular mortality [9].

Stroke is a persistent neurological deficit caused by cerebrovascular damages and includes ischemic stroke (IS) and hemorrhagic stroke (HS) [10-12]. It is one of the most leading causes of death and disability-adjusted life years worldwide [13, 14]. In 2010, the estimated number of individuals suffered from stroke was 50 million and among them, approximately 17million cases were newly identified. China bears enormous stroke burden in the world with the highest stroke prevalence, incidence and mortality among other developing world [15]. As the major subtype of stroke in China, IS accounts for 43% to 79% of all strokes and provokes growing concerns

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3 recently [16]. Given the tremendous disease burden of stroke, risk factors
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5 identification and prevention are critical and effective public health strategies [17].
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8 However, the effect of air pollutants remains a matter of debate, which might be, at
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10 least in part, explained by the heterogeneity in different stroke subtypes [18, 19]. Thus,
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12 it is a pressing need to synthetically explore the association between air pollutants and
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14 specific subtype of stroke related incidence and mortality.
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18 Changzhou stands on the southern bank of the Yangtze River. The city serves as
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20 part of the Suzhou-Wuxi-Changzhou metropolitan area and by the year of 2010, there
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22 were about 4 million residents in five urban districts (Tianning district, Wujin district,
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24 Jintan district, Xinbei district and Liyang city) [20]. Moreover, with the rapid
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26 industrialization and economic development in the past years, Changzhou is now
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28 experiencing severe air pollution. The concentrations of several air pollutants (such as
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30 $PM_{2.5}$, PM_{10} , SO_2 and NO_2) were equal or higher than the national ambient air quality
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32 in the recent years [21, 22]. Therefore, Changzhou was chosen as a suitable place to
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34 study the effect of air pollution on incidence and mortality of IS. In this study, a
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36 comprehensive time-series study was conducted in Changzhou to examine the
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38 association between main air pollutants and daily IS counts and deaths. To explore the
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40 effect modification, the association of modifiers between air pollution and daily IS
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42 counts and deaths was also evaluated. This work will help provide insights into the
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44 relationship between stroke and air pollutants and have implication for prevention of
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46 IS onset and IS related deaths.
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MATERIALS AND METHODS

Data collection

Air pollution data, including daily 24-hour average levels of PM_{2.5}, PM₁₀, NO₂, SO₂ and CO between January 9, 2015 and December 31, 2016 were obtained from ten air quality monitoring stations run by Changzhou Environmental Monitoring Center. The daily mean levels for air pollutants were averaged from all the stations and approximately all the cases recorded in this study resided less than 40 km from the nearest monitoring station. Thus, the monitoring data could be used as an appropriate proxy for personal exposure [23-25]. Daily meteorological data on temperature (°C) and relative humidity (%) were collected from Changzhou Meteorological Bureau.

Daily IS and IS mortality data from January 9, 2015 to December 31, 2016 were obtained from the database of Changzhou Center for Disease Control and Prevention (CDC). This database belonged to the government- controlled network reporting system for chronic diseases, which was established in Changzhou, 2012.

Cardiovascular physicians were responsible for the diagnosis of IS according to the cerebrovascular ICD-10 codes for IS (I63). Demographic data were collected from Changzhou Municipal Bureau of Statistics. Daily IS counts and deaths were also stratified into groups by gender (male and female) and age group (<65 and ≥65 year-old) to explore the effect modification of individual characteristics.

Statistical analysis

Daily IS counts, daily IS death counts, air pollutants levels and weather data were linked by date for the subsequent time-series study, which was applied to analyze the

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3 effects of each air pollutant on IS counts and death. After evaluating the distribution
4 patterns of daily IS counts and deaths, Poisson distributions were identified. Poisson
5 regression was used in generalized additive model (GAM) to calculate the data.
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10 Multivariable regression model was used to detect the air pollutants related
11 associations and control the potential confounding factors, such as calendar time, day
12 of week (DOW), daily average relative humidity and temperature. The five degree of
13 freedom (df) was used to adjust for all the confounding factors mentioned above
14 except for DOW (df= 7). Furthermore, to explore the potential modification, data
15 were stratified by sex, age (<65 as young individuals and ≥ 65 as the elderly) and
16 season (warm season as 1 May to 31 October and cold season as 1 November to 30
17 April). Associations between air pollutants and IS and IS related death were
18 separately examined according to the following equation:
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$$\text{Log}[E(T/D_n)] = \text{intercept} + \beta_1 \text{AirPollution}_{n-i} + \beta_2 \text{DOW} + \text{ps}(\text{calendar time, df= 7}) + \text{ps}(\text{Temp}_{n-i}, \text{df= 5}) + \text{ps}(\text{Relative Humidity}_{n-i}, \text{df= 5})$$

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35 $E(T/D_n)$ represents the estimated numbers of IS onsets or deaths on day n;

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38 $\text{AirPollution}_{n-i}$ represented the average levels of different air pollutants on day n and i
39 is the day lag; β was vector of the coefficients; DOW was the day of week; ps ()
40 presented penalized spline function; Temp_{n-i} and $\text{Relative Humidity}_{n-i}$ represented
41 average temperature and relative humidity on day n and i is the day lag.
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48 In addition, for both daily IS counts and deaths, single-pollutant models were
49 fitted with different single lag days (lag0, lag1, lag3 and lag5) to detect the effects of
50 air pollution on IS. As underestimation may occur in single-day models, multiple-day
51 lag models (lag0-1, lag0-3 and lag0-5) were also applied in this study. Smoothing
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3 function was used in the analysis of the exposure-response relationship between the
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6 log-relative risk of daily IS counts or deaths and air pollutants concentrations using a
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9 5 df in single-pollutant model.

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11 Statistical software R (version 3.2.3, R Foundation for Statistical Computing,
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13 Austria) was used for data analysis and result output. The baseline data was presented
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15 as mean \pm standard deviation (SD) for continuous variables. All tests were two-sided,
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17 and $P < 0.05$ was considered as statistically significant.
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20 21 **Public and patient involvement**

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23 Public and patient involvement (PPI) was central and integral in the present study.
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25 The PPI group consisted of three male and four female representative patients who
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27 were recruited and chaired by HB. D. The members of the existing group were
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29 involved throughout all stages of this research to make contributions. At the outset,
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31 they helped researchers with topics choosing and study designing by providing
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33 constructive suggestions. Furthermore, they took part in the conference presentations
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35 and group discussions to help filter and interpret data collected from database
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37 mentioned above. They also contributed to discussion about the implications of the
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39 results by using their experiences. These findings have been disseminated to all the
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45 PPI members at the end of the study.
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50 51 **RESULTS**

52 53 **Descriptive Analysis**

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55 During this study period, there were 32,840 IS cases and 4,028 IS deaths recorded,
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3 respectively. For IS, on average, 45.4 cases were identified each day (Table S1). Of
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5 these, 52.2% were males and 81.3% were the elderly (≥ 65). And for IS related death,
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7 there were 5.6 deaths recorded on average each day (Table S1). Of these, 48.2% were
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9 males and 96.4% were the elderly.
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13 Daily average meteorological data were 17.0°C for temperature and 75% for
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15 relative humidity. The daily average levels were 51.8 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 85.3 $\mu\text{g}/\text{m}^3$ for
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17 PM_{10} , 22.3 $\mu\text{g}/\text{m}^3$ for SO_2 , 38.7 $\mu\text{g}/\text{m}^3$ for NO_2 and 1 mg/m^3 for CO (Table 1).
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20 According to the WHO air quality guidelines (25 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 50 $\mu\text{g}/\text{m}^3$ for PM_{10}
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22 and 20 $\mu\text{g}/\text{m}^3$ for SO_2), the corresponding average levels of $\text{PM}_{2.5}$, PM_{10} and SO_2 in
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24 Changzhou were far beyond the WHO standard.
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27 28 **Estimated Effects of Air Pollutants**

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30 Fig. 1 summarizes the percentage change (95% CI) in daily IS counts and deaths with
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32 an interquartile range (IQR) increase in air pollutants levels for different single or
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34 multiple lag days in single-pollutant models. For daily IS counts, statistically positive
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36 association was observed only in IQR increment of NO_2 levels and this association
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38 was the more significant at multi-day exposure than single day exposure. A highest
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40 association was observed for lag 0-5 (0.208%, 0.036%-0.381%) and was used in the
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42 subsequent study. For daily IS deaths, statistically positive associations were observed
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44 in different IQRs increments of PM_{10} , SO_2 and NO_2 . All the associations were the
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46 most significant at lag5 (0.268%, 0.007%-0.528% for PM_{10} ; 0.34%, 0.088%-0.592%
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48 for SO_2 ; 0.263%, 0.004%-0.522% for NO_2) than other days and was thus used in the
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50 subsequent analysis.
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4 Concentration-response relationships of air pollutants with daily IS counts or
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6 deaths were conducted in Fig. 2. For IS counts, the curve of NO₂ was linear positive
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8 and flat at higher concentrations. For daily IS deaths, the concentration-response
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10 curves of PM₁₀ and SO₂ were similar, flat at low levels and dramatically linear
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12 positive at high levels, whereas the curve for NO₂ suggest a linear rise in daily IS
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14 deaths.
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18 The effect of NO₂ on the increase of daily IS counts was more pronounced
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20 among males than that of females and the effects of NO₂ and SO₂ on daily IS counts
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22 were more serious in the cold season, but not in the warm season. No significant
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24 association was observed when modifying by age (Table 2). As for daily IS deaths, the
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26 estimated effect of PM₁₀ was more pronounced among males, whereas the effects of
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28 NO₂ and SO₂ were more robust among females. Moreover, PM_{2.5}, PM₁₀, NO₂ and CO
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30 were found to have greater deleterious effects among young individuals and SO₂
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32 showed more risk in the elderly. And when modifying by seasons, statistical
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34 significance was identified only for SO₂ in the cold season (Table 2).
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40 Table 3 shows the percent increases in daily IS counts and daily IS deaths with
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42 each IQR increment in air pollutants levels in two-pollutants models. For daily IS
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44 counts, the estimated effects of NO₂ and SO₂ were more serious when adjusted for
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46 PM_{2.5} and PM₁₀. For daily IS deaths, statistical significance was identified for SO₂
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48 when adjusted for CO.
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52 53 **DISCUSSION**

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56 In this population-based time-series study, a total of 32,840 IS cases and 4,028 IS
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3 death were identified in Changzhou from 2015 to 2016. Significant association of
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5 NO₂ with daily IS counts was observed even when adjusted by PM_{2.5} and PM₁₀. The
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7 estimated IS risk of NO₂ was more robust in the elderly and the cold season. In
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10 addition, PM₁₀, SO₂ and NO₂ were positively associated with daily IS deaths. The
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12 young individuals had higher IS mortality risk for PM_{2.5}, PM₁₀, NO₂ and CO. And IS
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14 mortality risk of SO₂ was more robust in the elderly, female and cold season,
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16 statistical significance was also identified for SO₂ when adjusted for CO. To the best
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18 of our knowledge, in China, this is the first comprehensive study to explore the acute
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20 effect of air pollutants on the morbidity and mortality of stroke at the same time.
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25 PM₁₀ could cause endothelial dysfunction, inflammatory response and
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27 neuro-functional impairment and subsequently induce ischemia-like injuries in the
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29 brain [26]. In the current study, an IQR increment in PM₁₀ concentrations was
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31 associated with 0.268% increment in daily IS deaths, which was in consistent with the
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33 previous investigations [27, 28]. Moreover, the function curve for PM₁₀/ daily IS
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35 deaths was flat at <150 µg/m³ and became dramatically sharp at high levels. Previous
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37 multicity time-series study indicated an acute, deleterious and significant effect of
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39 PM₁₀ on IS mortality and the estimated rate ratios were 1.016 [29]. Long-term
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41 exposure to PM₁₀ was positively associated with IS relate death and the estimated
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43 relative risk was 1.37 [30]. Moreover, in this study, greater estimated IS mortality risk
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45 was observed among males and young individuals. It is plausible that males and
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47 young individuals spent more time outdoors and exposed to higher levels of PM₁₀
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49 than females and the elderly [31].
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4 NO₂, a representative pollutant of vehicle exhaust, was found to induce
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6 excitotoxicity, endothelial and inflammatory responses and damage synaptic plasticity
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8 in the brain [32-34]. In China, a multicity case-crossover study demonstrated that an
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10 IQR increase (25.4 µg/m³) in NO₂ was corresponded to 2.6% increment in IS
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12 admissions. Stroke mortality was also positively associated with ambient NO₂ levels
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14 [35]. In the present study, we indicated that IQR increments in NO₂ (12 µg/m³) was
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16 associated with 0.208% and 0.263% increases in daily IS counts and IS deaths,
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18 respectively. An approximately linear concentration-response relationship was
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20 identified for NO₂ and daily IS counts or daily IS deaths, which was consistent with
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22 the previous studies [36, 37]. The positive association for NO₂ and daily IS counts
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24 could be observed even below the National Ambient Air Quality Standards of China
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26 (80 µg/m³). For daily IS counts, the effects of NO₂ were statistically positive and
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28 stronger when adjusted for other pollutants except for SO₂ (no statistical but stronger
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30 association was observed), suggesting that the adverse effect of NO₂ on IS onsets was
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32 stable and NO₂ contributed most to the increased risk of IS. Moreover, the effects of
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34 NO₂ were more serious in cold season and males. For IS deaths, young females were
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36 found to be experienced higher risk. The underlying reasons may be that the exposed
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38 levels of NO₂ were much higher at these conditions, which was similar to that of PM₁₀.
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40 The risk factors for stroke, such as hypertension, atrial fibrillation and diabetes
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42 mellitus are more frequent and the estimated effects are stronger among females [38].
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44 Females are considered to be more sensitive to stroke onsets and deaths. Thus, our
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46 findings regarding the higher risk of IS deaths observed among females were
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3 reasonable.

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6 SO_2 was considered as a strong irritant ambient gaseous pollutant, and could
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8 elevate the expression of vasoregulatory pathways and proinflammatory enzymes
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10 such as ET-1, iNOS, COX-2, ICAM-1 and TNF- α [39]. And its exposure was
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12 demonstrated to contribute to the development and progression of IS [18]. In the
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14 present study, SO_2 was significantly associated with daily IS counts when adjusted by
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16 $\text{PM}_{2.5}$ or PM_{10} . In addition, exposure to SO_2 also had statistical associations with daily
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18 IS deaths (the percentage increase was 0.34%), which was in agreement with previous
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20 studies [19, 40]. The function curve for SO_2 and daily IS deaths was flat at $<35 \mu\text{g}/\text{m}^3$
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22 and became dramatically sharp at high levels, suggesting that acute and robust
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24 increments of SO_2 might result in exacerbating IS death. Furthermore, the
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26 associations were more pronounced among females, suggesting that females are more
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28 susceptible to IS related deaths when exposed to gaseous pollutants (NO_2 and SO_2). In
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30 addition, SO_2 exhibited higher risk of IS deaths in the elderly [41]. And it can be
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32 deduced that the elderly are more likely to bear preexisting respiratory or
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34 cardiovascular burdens and the vulnerable condition could influence the effect of SO_2
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36 on stroke [42]. We also found that exposure to SO_2 had more serious effects on both
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38 IS onsets and deaths in cold season than in warm season.
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47 In conclusion, our results suggested that short term exposure to ambient NO_2 was
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49 associated with increased IS risk. And SO_2 were associated with increased IS counts
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51 and deaths. These findings may have significant public health implications for
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53 prevention of IS and IS related death. Further studies are recommended to validate our
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4 research.

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8 **Acknowledgements** The authors are grateful to the PPI group chaired by HB. D who support
9
10 the wider programme of work of which the qualitative interviews are a part, to patient
11
12 representative and to other members of the study advisory group.
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15
16 **Contributors** The study was conceived and designed by HB. D, Y. L and Z. Z, and overall
17
18 study management was by XJ. Y, SL. W and Z. Z. ZY. C, GY. L and Y. Y contributed to
19
20 data collection and processing. S. Y performed the statistical analysis, HB. D, Y. Y and Y.
21
22 L helped manuscript preparation and interpret the results. All authors contributed to the
23
24 revision of the manuscript and reviewed and approved the final version.
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27
28 **Funding** This work was supported by the Natural Science Foundation of China (81502801), a
29
30 project funded by the Priority Academic Program Development of Jiangsu Higher Education
31
32 Institutions (2014), a collegiate Natural Science Foundations of Jiangsu province
33
34 (16KJB330005), the science and technology support program funded by Changzhou
35
36 Municipal Science and Technology Bureau (CE20145046) and the Science and Technique
37
38 Foundation for Youths by Health and Family Planning Commission of Changzhou
39
40 (QN201603).
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45 **Disclaimer** The funding sponsors had no role in the design of the study, in the collection,
46
47 analysis or interpretation of data, in the writing of the manuscript or in the decision to publish
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49 the research results.
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Ethical approval The present study was approved by the Institutional Review Board of Changzhou Center for Disease Control and Prevention, and all procedures were in accordance with prevailing ethical principles.

Competing interests None declared.

Patient consent Not needed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Figure legends

Figure 1 The percentage change in daily ischemic stroke (IS) counts and daily IS deaths with an interquartile range increase in air pollutants levels on different lag days in single-pollutant models in Changzhou, 2015-2016. The data was expressed as mean with 95% confidence interval.

Figure 2 The concentration-response relationships of daily ischemic stroke (IS) counts, daily IS deaths with air pollutants on different lag days (lag 0-5 for daily IS counts and lag 5 for daily IS deaths) in single-pollutant models in Changzhou, 2015-2016.

Table 1 The means, medians and interquartile ranges (IQRs) for daily air pollutants and weather conditions variables in Changzhou, 2015-2016

Variables	Mean± SD	Min	25th	Median	75th	Max	IQR
Weather Condition							
Temperature (°C)	17.1±8.9	-6.6	9.4	18.3	24.1	34.6	5.8
Humidity (%)	75.3±14.2	35.0	66.0	76.0	86.0	100.0	10.0
Air Pollutions							
PM _{2.5} (µg/m ³)	51.8±30.6	6.8	29.4	44.4	64.4	181.1	20.0
PM ₁₀ (µg/m ³)	85.3±43.3	10.5	51.5	76.6	108.6	289.1	32.0
NO ₂ (µg/m ³)	38.7±16	10.9	26.5	35.8	47.8	117.3	12.0
SO ₂ (µg/m ³)	22.3±10	6.9	14.7	20.2	27.0	67.8	6.9
CO (mg/m ³)	1±0.3	0.4	0.8	1.0	1.2	2.6	0.2

PM_{2.5}, particulate matter <2.5 mm in diameter; PM₁₀, particulate matter <10 mm in diameter; NO₂, nitrogen dioxide; SO₂, sulfur dioxide; CO, carbon monoxide.

Table 2 The percentage change in daily IS counts and deaths with an interquartile range increase in air pollutants levels modifying by age, gender and seasons in Changzhou, 2015-2016

Variable	Total	Age		Sex		Seasons	
		≤65	>65	Female	Male	Warm	Cold
Daily IS counts*							
PM _{2.5}	-0.063 (-0.215-0.088)	-0.246 (-0.568-0.076)	-0.042 (-0.21-0.127)	-0.097 (-0.311-0.119)	-0.08 (-0.289-0.128)	-0.149 (-0.525-0.228)	-0.098 (-0.267-0.071)
PM ₁₀	-0.053 (-0.22-0.114)	-0.219 (-0.572-0.136)	-0.004 (-0.191-0.184)	-0.086 (-0.324-0.153)	-0.047 (-0.279-0.185)	-0.057 (-0.41-0.297)	-0.088 (-0.282-0.107)
NO ₂	0.208 (0.036-0.381)‡	0.258 (-0.075-0.592)	0.166 (-0.025-0.357)	0.168 (-0.055-0.391)	0.238 (0.002-0.475)‡	-0.136 (-0.481-0.21)	0.382 (0.169-0.596)‡
SO ₂	0.125 (-0.034-0.284)	-0.044 (-0.364-0.277)	0.113 (-0.062-0.289)	0.15 (-0.068-0.369)	0.056 (-0.162-0.275)	-0.309 (-0.651-0.033)	0.298 (0.099-0.498)‡
CO	-0.078 (-0.22-0.064)	-0.213 (-0.511-0.086)	-0.061 (-0.222-0.1)	-0.151 (-0.355-0.053)	-0.007 (-0.206-0.192)	-0.175 (-0.432-0.083)	-0.053 (-0.237-0.131)
Daily IS deaths†							
PM _{2.5}	0.228 (-0.005-0.462)	1.144 (0.329-1.965)‡	0.152 (-0.091-0.395)	0.124 (-0.19-0.439)	0.29 (-0.043-0.625)	-0.199 (-0.77-0.375)	0.184 (-0.088-0.456)
PM ₁₀	0.268 (0.007-0.528)‡	1.52 (0.656-2.391)‡	0.152 (-0.12-0.424)	0.093 (-0.261-0.448)	0.404 (0.03-0.78)‡	-0.012 (-0.53-0.509)	0.247 (-0.075-0.57)
NO ₂	0.263 (0.004-0.522)‡	0.894 (0.058-1.736)‡	0.195 (-0.073-0.463)	0.37 (0.027-0.715)‡	0.132 (-0.247-0.512)	0.275 (-0.222-0.775)	0.198 (-0.13-0.528)
SO ₂	0.34 (0.088-0.592)‡	0.67 (-0.175-1.523)	0.307 (0.045-0.57)‡	0.434 (0.096-0.772)‡	0.215 (-0.15-0.58)	0.017 (-0.493-0.531)	0.388 (0.081-0.696)‡
CO	0.175 (-0.042-0.392)	0.9 (0.166-1.639)‡	0.108 (-0.118-0.335)	0.189 (-0.11-0.49)	0.154 (-0.162-0.471)	0.02 (-0.401-0.443)	0.169 (-0.104-0.443)

*The multivariable regression model fits the pollutants for daily IS counts data at lag 0-5 and

adjusts for calendar time (df=5), DOW (df=7), daily average humidity (df=5) and average

temperature (df=5).

†The multivariable regression model fits the pollutants for daily IS deaths data at lag 5 and adjusts

for calendar time (df=5), DOW (df=7), daily average humidity (df=5) and average temperature

(df=5).

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3 ‡ Statistically positive association between air pollutants and daily IS counts or deaths
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Table 3 The percent increases in daily IS counts and deaths with each interquartile range increment in air pollutants levels in two-pollutants models in Changzhou, 2015-2016

Variables	PM _{2.5}	PM ₁₀	NO ₂	SO ₂	CO
Daily IS counts					
PM _{2.5}	-0.063 (-0.215-0.088)	0.25 (-0.314-0.817)	0.497 (0.259-0.735)‡	0.305 (0.083-0.527) ‡	-0.059 (-0.274-0.157)
PM ₁₀	-0.423 (-0.881-0.038)	-0.053 (-0.22-0.114)	0.539 (0.29-0.788)‡	0.262 (0.034-0.491) ‡	-0.065 (-0.293-0.163)
NO ₂	-0.346 (-0.558--0.134)	-0.438 (-0.691--0.185)	0.208 (0.036-0.381)‡	-0.007 (-0.267-0.253)	-0.341 (-0.556--0.124)
SO ₂	-0.24 (-0.46--0.019)	-0.244 (-0.49-0.003)	0.22 (-0.067-0.507)	0.125 (-0.034-0.284)	-0.166 (-0.356-0.023)
CO	-0.089 (-0.314-0.137)	0.029 (-0.223-0.281)	0.45 (0.215-0.685)‡	0.172 (-0.016-0.361)	-0.078 (-0.22-0.064)
Daily IS deaths					
PM _{2.5}	0.228 (-0.005-0.462)	0.436 (-0.36-1.238)	0.22 (-0.127-0.567)	0.28 (-0.071-0.632)	0.065 (-0.314-0.446)
PM ₁₀	0.211 (-0.463-0.89)	0.268 (0.007-0.528)‡	0.218 (-0.135-0.573)	0.295 (-0.055-0.646)	0.137 (-0.23-0.504)
NO ₂	0.106 (-0.201-0.414)	0.149 (-0.21-0.509)	0.263 (0.004-0.522)‡	0.351 (-0.096-0.8)	0.057 (-0.269-0.384)
SO ₂	0.066 (-0.25-0.383)	0.126 (-0.242-0.496)	0.066 (-0.387-0.521)	0.34 (0.088-0.592)‡	0.035 (-0.281-0.351)
CO	0.186 (-0.199-0.571)	0.233 (-0.187-0.656)	0.23 (-0.14-0.601)	0.346 (0.002-0.691)‡	0.175 (-0.042-0.392)

*The multivariable regression model fits the pollutants for daily IS counts data at lag 0-5 and

adjusts for the other pollutants, calendar time (df=5), DOW (df=7), daily average humidity (df=5)

and average temperature (df=5).

†The multivariable regression model fits the pollutants for daily IS deaths data at lag 5 and adjusts

for the other pollutants, calendar time (df=5), DOW (df=7), daily average humidity (df=5) and

average temperature (df=5).

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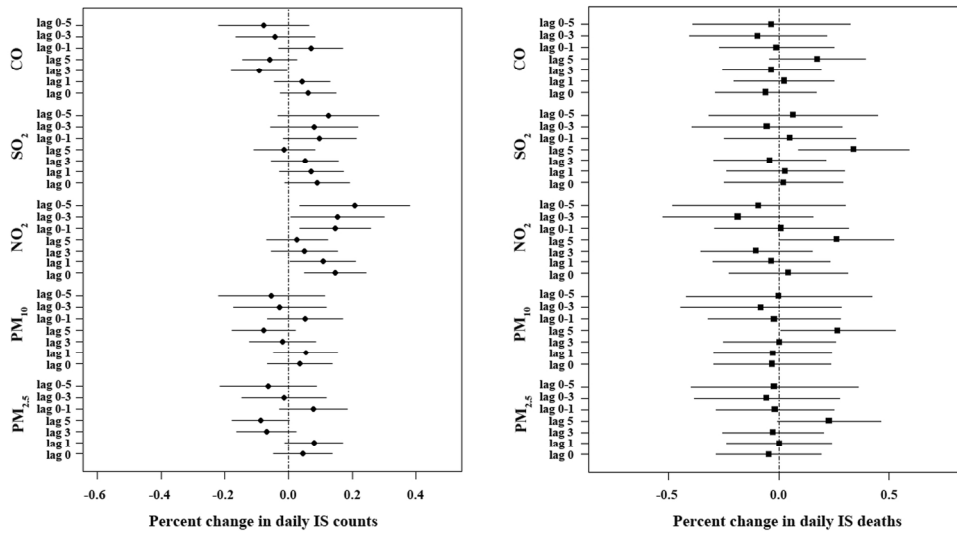


Figure 1 The percentage change in daily ischemic stroke (IS) counts and daily IS deaths with an interquartile range increase in air pollutants levels on different lag days in single-pollutant models in Changzhou, 2015-2016. The data was expressed as mean with 95% confidence interval.

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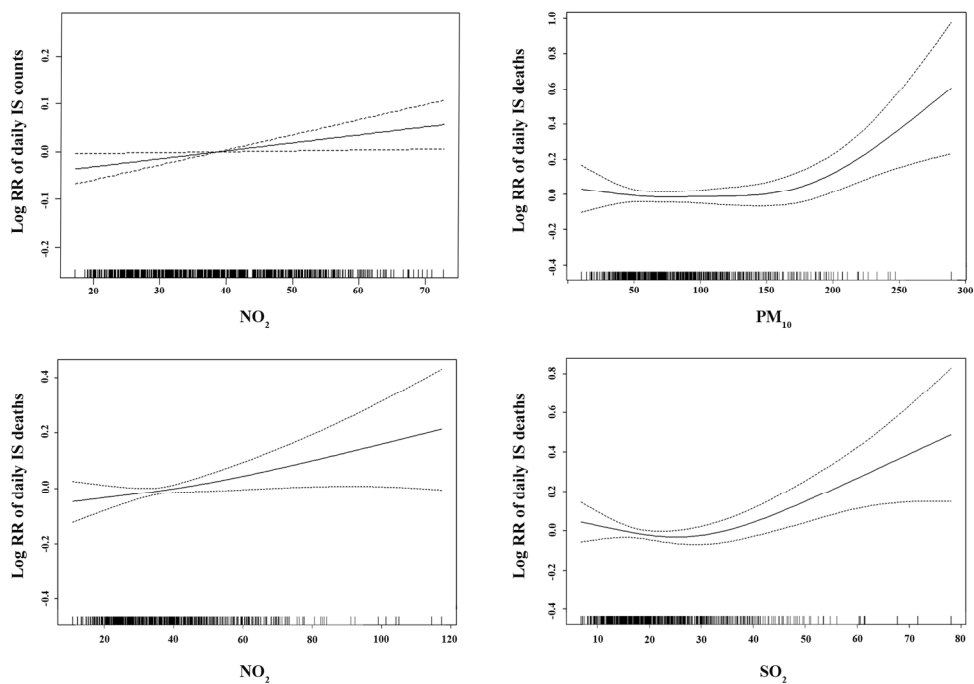


Figure 2 The concentration-response relationships of daily ischemic stroke (IS) counts, daily IS deaths with air pollutants on different lag days (lag 0-5 for daily IS counts and lag 5 for daily IS deaths) in single-pollutant models in Changzhou, 2015-2016.

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4 **Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series**
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12 Huibin Dong^{1, a}, Yongquan Yu^{2, a}, Shen Yao², Yan Lu³, Zhiyong Chen¹, Guiying Li¹,

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14 Yao Yao¹, Xingjuan Yao¹, Shou-Lin Wang², Zhan Zhang^{4*}
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19 **Supplementary data**
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Table S1 The descriptive statistics for daily ischemic stroke (IS) counts and deaths in Changzhou, 2015-2016*

Variables	Mean± SD	Min	25th	Median	75th	Max
Daily IS counts	45.4±11.2	14.0	38.0	45.0	53.0	99.0
Male	23.7±7	6.0	19.0	23.0	28.0	60.0
Female	21.8±6.1	6.0	18.0	22.0	26.0	48.0
<65	8.5±3.6	0.0	6.0	8.0	11.0	23.0
≥65	36.9±9.2	11.0	31.0	36.0	43.0	80.0
Daily IS deaths	5.6±2.9	0.0	3.0	5.0	7.0	19.0
Male	2.7±1.8	0.0	1.0	3.0	4.0	10.0
Female	2.8±2	0.0	1.0	3.0	4.0	10.0
<65	0.4±0.7	0.0	0.0	0.0	1.0	3.0
≥65	5.1±2.8	0.0	3.0	5.0	7.0	18.0

*A total of 32,840 IS cases and 4,028 IS deaths recorded were recorded during the study period.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1-4	Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series study in Changzhou, China (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	5-6	Explain the scientific background and rationale for the investigation being reported
Objectives	6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	7-9	Present key elements of study design early in the paper
Setting	7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	7	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	7*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	7-8	Describe any efforts to address potential sources of bias
Study size	7	Explain how the study size was arrived at
Quantitative variables	8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	9	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses
Results		
Participants	9*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	9*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest
Outcome data	10-11*	Report numbers of outcome events or summary measures
Main results	10-11	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	10-11	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	11	Summarise key results with reference to study objectives
Limitations	12-13	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	12-13	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	14	Discuss the generalisability (external validity) of the study results
Other information		
Funding	14	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Acute effects of air pollution on ischaemic stroke onset and deaths: A time-series study in Changzhou, China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020425.R2
Article Type:	Research
Date Submitted by the Author:	10-May-2018
Complete List of Authors:	Dong, Huibin; Changzhou Center for Disease Control and Prevention Yu, Yongquan; Nanjing Medical University Yao, Shen; Nanjing Medical University Lu, Yan; The First Affiliated Hospital of Nanjing Medical University Chen, Zhiyong; Changzhou Center for Disease Control and Prevention Li, Guiying; Changzhou Center for Disease Control and Prevention Yao, Yao; Changzhou Center for Disease Control and Prevention Yao, Xingjuan ; Changzhou Center for Disease Control and Prevention Wang, Shoulin; Nanjing Medical University Zhang, Zhan
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Cardiovascular medicine
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, PUBLIC HEALTH

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4 **Acute effects of air pollution on ischaemic stroke onset and deaths: A time-series**
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ABSTRACT

Objective To investigate the acute effect of air pollutants on ischaemic stroke (IS) and IS-related death.

Setting Five urban districts in Changzhou, China, between 9 January 2015 and 31 December 2016.

Participants A total of 32,840 IS cases and 4,028 IS deaths were enrolled.

Main outcome measures A time-series design, generalized additive model and multivariable regression model were used to examine the percentage change (95% confidence interval [CI]) in daily IS counts and deaths with an interquartile range (IQR) increase in air pollutant levels for different single or multiple lag days in single-pollutant and two-pollutant models.

Results Daily IS counts increased 0.208% (95% [CI]: 0.036%-0.381%) with an IQR increment in levels of NO₂. The estimated risk of NO₂ was more robust in males and in the cold season. For daily IS counts, the estimated effects of NO₂ and SO₂ were more significant when adjusted for PM_{2.5} and PM₁₀. An IQR increment in the concentration of PM₁₀, SO₂ and NO₂ significantly increased IS deaths with 6 days of cumulative effects (0.268%, 95% CI: 0.007%-1.528%; 0.34%, 0.088%-0.592%; and 0.263%, 0.004%-0.522%, respectively). Young individuals (< 65 years old) had a higher IS mortality risk for PM_{2.5}, PM₁₀, NO₂ and CO. For IS death, the effect estimates of SO₂ in the elderly, females and the cold season were more pronounced; statistical significance was also identified for SO₂ when adjusted for CO.

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3 **Conclusions** This study suggested that short-term exposure to ambient NO₂ was
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5 associated with increased IS risk. In addition, SO₂ was associated with increased IS
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7 onset and death.
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10 11 12 **Article Summary**

13 14 **Strengths and limitations of this study**

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17 ■ This is the first comprehensive research in China that explores the short-term
18 effects of air pollutants on the morbidity and mortality of stroke concurrently.
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21 ■ The statistical power to detect the association was sufficient because of the
22 substantial numbers of IS cases and IS deaths recorded in our work.
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25 ■ This time-series study evaluated the association of modifiers between air
26 pollution and daily IS counts or deaths, which may provide clues for the primary
27 prevention of IS and IS-related death.
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30 ■ The exposure measurement of this study was performed at the community level,
31 and we could not precisely quantify the exposure of individuals to air pollutants
32 using the fixed-site monitoring data; this may lead to exposure measurement
33 error.
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36 ■ This study considers a single city, and the results should be extrapolated with
37 caution.
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INTRODUCTION

Air pollution is considered a primary risk factor for a mounting total of pollution-related diseases and deaths [1]. Moreover, as a modifiable risk factor, air pollution accounts for more than 7 million deaths annually [2]. Studies have extensively explored the association between air pollution and the risk of respiratory, reproductive and cardiovascular diseases [3-5]. Epidemiological studies have suggested that exposure to air pollutants on hazy days may increase the risk of cardiovascular diseases [6-8]. For instance, a study conducted in Stockholm suggested that short-term exposure to particulate matter with aerodynamic diameters $< 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) was associated with out-of-hospital cardiac arrest. Increments in $\text{PM}_{2.5}$, PM_{10} , nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and carbon monoxide (CO) were associated with higher risk of heart failure hospitalizations and death. A study conducted in Stockholm suggested that short-term exposure to $\text{PM}_{2.5}$ was associated with out-of-hospital cardiac arrest. A meta-analysis indicated that long-term exposure to $\text{PM}_{2.5}$ was related to a dramatic increase in cardiovascular mortality [9].

Stroke is a persistent neurological deficit caused by cerebrovascular damage and includes ischaemic stroke (IS) and haemorrhagic stroke (HS) [10-12]. Stroke is one of the leading causes of death and disability-adjusted life years worldwide [13, 14]. In 2010, the estimated number of individuals who suffered from stroke was 50 million, and among them, approximately 17 million cases were newly identified. China bears an enormous stroke burden in the world, having the highest stroke prevalence, incidence and mortality among developing countries worldwide [15]. As the major

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3 subtype of stroke in China, IS accounts for 43% to 79% of all strokes and has recently
4 prompted growing concerns [16]. Given the tremendous disease burden of stroke, the
5 identification and prevention of risk factors are critical and effective public health
6 strategies [17]. However, the effect of air pollutants remains a matter of debate, which
7 might be, at least in part, explained by the heterogeneity of different stroke subtypes
8 [18, 19]. Thus, there is a pressing need to systematically explore the association
9 between air pollutants and specific subtypes of stroke-related incidence and mortality.
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20 Changzhou stands on the southern bank of the Yangtze River. The city is as part
21 of the Suzhou-Wuxi-Changzhou metropolitan area, and by the year of 2010, there
22 were approximately 4 million residents in five urban districts (Tianning district, Wujin
23 district, Jintan district, Xinbei district and Liyang city) [20]. Moreover, because of the
24 rapid industrialization and economic development of the past years, Changzhou is
25 now experiencing severe air pollution. The concentrations of several air pollutants
26 (such as PM_{2.5}, PM₁₀, SO₂ and NO₂) were equal or higher than the national ambient
27 air quality in the recent years [21, 22]. Therefore, Changzhou was chosen as a suitable
28 place to study the effect of air pollution on the incidence and mortality of IS. In this
29 research, a comprehensive time-series study was conducted in Changzhou to examine
30 the association between main air pollutants and daily IS counts and deaths. To explore
31 the modification effect, the association of modifiers between air pollution and daily IS
32 counts and deaths was also evaluated. This work will help provide insights into the
33 relationship between stroke and air pollutants and have implications for the
34 prevention of IS onset and IS-related deaths.
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MATERIALS AND METHODS

Data collection

Air pollution data, including daily 24-hour average levels of PM_{2.5}, PM₁₀, NO₂, SO₂ and CO between January 9, 2015, and December 31, 2016, were obtained from ten air quality monitoring stations run by the Changzhou Environmental Monitoring Center. The daily mean levels for air pollutants were averaged from all the stations, and approximately all the patients whose cases were recorded in this study resided less than 40 km from the nearest monitoring station. Thus, the monitoring data could be used as an appropriate proxy for personal exposure [23-25]. Daily meteorological data on temperature (°C) and relative humidity (%) were collected from the Changzhou Meteorological Bureau.

Daily IS and IS mortality data from 9 January 2015 to 31 December 31 2016 were obtained from the database of the Changzhou Center for Disease Control and Prevention (CDC). This database belonged to the government-controlled network reporting system for chronic diseases, which was established in Changzhou in 2012. Cardiovascular physicians were responsible for the diagnosis of IS according to the cerebrovascular ICD-10 codes for IS (I63). Demographic data were collected from the Changzhou Municipal Bureau of Statistics. Daily IS counts and deaths were also stratified into groups by sex (male and female) and age group (<65 and ≥ 65 years) to explore the effect modification of individual characteristics.

Statistical analysis

Daily IS counts, daily IS death counts, air pollutant levels and weather data were

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3 linked by date for the subsequent time-series study, which was used to analyse the
4
5 effects of each air pollutant on IS counts and deaths. After evaluating the distribution
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7 patterns of daily IS counts and deaths, Poisson distributions were identified. Poisson
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9 regression was used in a generalized additive model (GAM) to analyse the data. A
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11 multivariable regression model was used to detect the air pollutant-related
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13 associations and control for the potential confounding factors, such as calendar time,
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15 day of week (DOW), daily average relative humidity and temperature. The five
16
17 degrees of freedom (df) was used to adjust for all the confounding factors mentioned
18
19 above except for DOW (df=7). Furthermore, to explore the potential modifications,
20
21 data were stratified by sex, age (<65 as young individuals and ≥65 as elderly
22
23 individuals) and season (warm season as 1 May to 31 October and cold season as 1
24
25 November to 30 April). Associations between air pollutants and IS and IS-related
26
27 death were separately examined according to the following equation:

$$\text{Log}[E(T/D_n)] = \text{intercept} + \beta_1 \text{AirPollution}_{n-i} + \beta_2 \text{DOW} + \text{ps}(\text{calendar time, df=7}) + \text{ps}(\text{Temp}_{n-i}, \text{df=5}) + \text{ps}(\text{Relative Humidity}_{n-i}, \text{df=5})$$

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38 $E(T/D_n)$ represents the estimated numbers of IS onset or death on day n;

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40 $\text{AirPollution}_{n-i}$ represents the average level of different air pollutants on day n and i is
41
42 the day lag; β is the vector of the coefficients; DOW is the day of week; ps ()
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44 represents a penalized spline function; Temp_{n-i} and $\text{Relative Humidity}_{n-i}$ represent
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46 average temperature and relative humidity on day n and i is the day lag.
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49
50 In addition, for both daily IS counts and deaths, single-pollutant models were
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52 fitted with different single lag days (lag0, lag1, lag3 and lag5) to detect the effects of
53
54 air pollution on IS. As underestimation may occur in single-day models, multiple-day
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3 lag models (lag0-1, lag0-3 and lag0-5) were also applied in this study. The smoothing
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5
6 function was used in the analysis of the exposure-response relationship between the
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8 log-relative risk of daily IS counts or deaths and air pollutant concentrations using a 5
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11 df in a single-pollutant model.

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13 Statistical software R (version 3.2.3, R Foundation for Statistical Computing,
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15 Austria) was used for data analysis and result output. The baseline data was presented
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17 as the mean \pm standard deviation (SD) for continuous variables. All tests were
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19 two-sided, and $P < 0.05$ was considered as statistically significant.
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22 23 **Public and patient involvement**

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25 Public and patient involvement (PPI) was central and integral in the present study.
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27 The PPI group consisted of three male and four female representative patients who
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29 were recruited and chaired by HD. The members of the existing group were involved
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31 throughout all stages of this research to make contributions. At the outset, they helped
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33 researchers with choosing topics and designing the study by providing constructive
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35 suggestions. Furthermore, they took part in the conference presentations and group
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37 discussions to help filter and interpret data collected from the database mentioned
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39 above. They also contributed to discussions about the implications of the results by
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41 drawing on their experiences. Findings were disseminated to all PPI members at the
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43 end of the study.
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52 53 **RESULTS**

54 55 **Descriptive Analysis**

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3 During this study period, there were 32,840 IS cases and 4,028 IS deaths recorded.
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5 For IS, on average, 45.4 cases were identified each day (Table S1). Of these, 52.2%
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7 were males and 81.3% were the elderly (≥ 65). In addition, for IS-related death, there
8
9 were 5.6 deaths recorded on average each day (Table S1). Of these, 48.2% were males
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11 and 96.4% were the elderly.
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15 The daily average meteorological data were 17.0°C for temperature and 75% for
16
17 relative humidity. The daily average levels were 51.8 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 85.3 $\mu\text{g}/\text{m}^3$ for
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19 PM_{10} , 22.3 $\mu\text{g}/\text{m}^3$ for SO_2 , 38.7 $\mu\text{g}/\text{m}^3$ for NO_2 and 1 mg/m^3 for CO (Table 1).
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21 According to the WHO air quality guidelines (25 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 50 $\mu\text{g}/\text{m}^3$ for PM_{10}
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23 and 20 $\mu\text{g}/\text{m}^3$ for SO_2), the corresponding average levels of $\text{PM}_{2.5}$, PM_{10} and SO_2 in
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25 Changzhou were far beyond the WHO standard.
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29 30 **Estimated Effects of Air Pollutants**

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32 Figure 1 summarizes the percentage change (95% CI) in daily IS counts and deaths
33
34 with an interquartile range (IQR) increase in air pollutant levels for different single or
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36 multiple lag days in single-pollutant models. For daily IS counts, a statistically
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38 positive association was observed only for an IQR increment of NO_2 levels, and this
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40 association was more significant for multi-day exposure than for single day exposure.
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42 The highest association was observed for lag 0-5 (0.208%, 0.036%-0.381%) and was
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44 used in the subsequent study. For daily IS deaths, statistically positive associations
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46 were observed for the different IQRs increments of PM_{10} , SO_2 and NO_2 . All
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48 associations were the most significant at lag5 (0.268%, 0.007%-0.528% for PM_{10} ;
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50 0.34%, 0.088%-0.592% for SO_2 ; 0.263%, and 0.004%-0.522% for NO_2) than at other
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4 days and thus a 5 day lag model was used in the subsequent analysis.
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6 Concentration-response relationships of air pollutants with daily IS counts or
7
8 deaths are presented in Figure 2. For IS counts, the curve of NO₂ was linear positive
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10 and flat at higher concentrations. For daily IS deaths, the concentration-response
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12 curves of PM₁₀ and SO₂ were similar, that is, flat at low levels and dramatically linear
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14 positive at high levels, whereas the curve for NO₂ suggest a linear rise in daily IS
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16 deaths.
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20 The effect of NO₂ on the increase of daily IS counts was more pronounced
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22 among males than among females, and the effects of NO₂ and SO₂ on daily IS counts
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24 were stronger in the cold season than in the warm season. No significant association
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26 was observed when modifying by age (Table 2). For daily IS deaths, the estimated
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28 effect of PM₁₀ was more pronounced among males, whereas the effects of NO₂ and
29
30 SO₂ were more robust among females. Moreover, PM_{2.5}, PM₁₀, NO₂ and CO were
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32 found to have greater deleterious effects among young individuals, and SO₂ showed
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34 greater risk in the elderly. In addition, when modifying by seasons, statistical
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significance was noted only for SO₂ in the cold season (Table 2).

Table 3 shows the percentage increases in daily IS counts and daily IS deaths
with each IQR increment in air pollutant levels in the two-pollutant models. For daily
IS counts, the estimated effects of NO₂ and SO₂ were more serious when adjusted for
PM_{2.5} and PM₁₀. For daily IS deaths, statistical significance was identified for SO₂
when adjusted for CO.

DISCUSSION

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4 In this population-based time-series study, a total of 32,840 IS cases and 4,028 IS
5
6 death were identified in Changzhou from 2015 to 2016. A significant association of
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8 NO₂ with daily IS counts was observed even when adjusted by PM_{2.5} and PM₁₀. The
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10 estimated IS risk of NO₂ was more robust in the elderly and in the cold season. In
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12 addition, PM₁₀, SO₂ and NO₂ were positively associated with daily IS deaths. Young
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14 individuals had a higher IS mortality risk for PM_{2.5}, PM₁₀, NO₂ and CO. In addition,
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16 the IS mortality risk of SO₂ was more robust in the elderly, females and cold season;
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18 statistical significance was also identified for SO₂ when adjusted for CO. To the best
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20 of our knowledge, in China, this is the first comprehensive study to explore the acute
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22 effect of air pollutants on the morbidity and mortality of stroke concurrently.
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28 PM₁₀ can cause endothelial dysfunction, inflammatory response and
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30 neuro-functional impairment and, subsequently, induce ischaemia-like injuries in the
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32 brain [26]. In the current study, an IQR increment in PM₁₀ concentrations was
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34 associated with a 0.268% increment in daily IS deaths, which was consistent with
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36 previous investigations [27, 28]. Moreover, the function curve for PM₁₀/ daily IS
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38 deaths was flat at <150 µg/m³ and became dramatically sharp at high levels. A
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40 previous multicity time-series study indicated an acute, deleterious and significant
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42 effect of PM₁₀ on IS mortality, and the estimated rate ratios were 1.016 [29].
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47 Long-term exposure to PM₁₀ was positively associated with IS-related death and the
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49 estimated relative risk was 1.37 [30]. Moreover, in this study, a greater estimated IS
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51 mortality risk was observed among males and young individuals. It is plausible that
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53 males and young people spent more time outdoors and were exposed to higher levels
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3 of PM₁₀ than females and the elderly [31].
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6 NO₂, a representative pollutant of vehicle exhaust, has been found to induce
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8 excitotoxicity and endothelial and inflammatory responses and to damage synaptic
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10 plasticity in the brain [32-34]. In China, a multicity case-crossover study
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12 demonstrated that an IQR increase (25.4 µg/m³) in NO₂ corresponded to a 2.6%
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14 increment in IS emissions. Stroke mortality was also positively associated with
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16 ambient NO₂ levels [35]. In the present study, we indicated that IQR increments in
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18 NO₂ (12 µg/m³) were associated with 0.208% and 0.263% increases in daily IS counts
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20 and IS deaths, respectively. An approximately linear concentration-response
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22 relationship was identified for NO₂ and daily IS counts or daily IS deaths, which was
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24 consistent with the previous studies [36, 37]. The positive association for NO₂ and
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26 daily IS counts could be observed even below the National Ambient Air Quality
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28 Standards of China (80 µg/m³). For daily IS counts, the effects of NO₂ were
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30 statistically positive and stronger when adjusted for other pollutants, except for SO₂
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32 (no statistical association was detected, but a stronger association was observed),
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34 suggesting that the adverse effect of NO₂ on IS onset was stable and that NO₂
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36 contributed most to the increased risk of IS. Moreover, the effects of NO₂ were more
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38 serious in the cold season and in males. For IS deaths, young females were found to
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40 experience higher risk. An underlying reason may be that the exposure levels of NO₂
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42 were much higher at these conditions, which was similar to that of PM₁₀. The risk
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44 factors for stroke, such as hypertension, atrial fibrillation and diabetes mellitus are
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46 more frequent, and the estimated effects are stronger among females [38]. Females are
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3 considered to be more sensitive to stroke onset and deaths. Thus, our findings
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5 regarding the higher risk of IS deaths observed among females were reasonable.
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8 SO₂ was considered a strong ambient, gaseous pollutant and irritant that could
9
10 elevate the expression of vasoregulatory pathways and proinflammatory enzymes
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12 such as ET-1, iNOS, COX-2, ICAM-1 and TNF- α [39]. In addition, exposure to it was
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14 demonstrated to contribute to the development and progression of IS [18]. In the
15
16 present study, SO₂ was significantly associated with daily IS counts when adjusted by
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18 PM_{2.5} or PM₁₀. In addition, exposure to SO₂ also had statistical associations with daily
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20 IS deaths (the percentage increase was 0.34%), which agreed with previous studies
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22 [19, 40]. The function curve for SO₂ and daily IS deaths was flat at <35 $\mu\text{g}/\text{m}^3$ and
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24 became dramatically sharp at high levels, suggesting that acute and robust increments
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26 of SO₂ might exacerbate IS deaths. Furthermore, the associations were more
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28 pronounced among females, suggesting that females are more susceptible to
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30 IS-related deaths when exposed to gaseous pollutants (NO₂ and SO₂). In addition, SO₂
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32 exhibited a higher risk of IS deaths in the elderly [41]. Thus, it can be deduced that
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34 the elderly are more likely to have pre-existing respiratory or cardiovascular burdens,
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36 and these vulnerable conditions could influence the effect of SO₂ on stroke [42]. We
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38 also found that exposure to SO₂ had more serious effects on both IS onset and deaths
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40 in the cold season than in the warm season.
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50 Examining the deleterious effect of air pollutants on the incidence and outcomes
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52 of stroke is of significance, and previous studies mainly have focused on one aspect of
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54 IS in China. This study is one of the first to comprehensively explore the relationship
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4 between air pollutant levels and morbidity or mortality of IS. As numerous individuals
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6 were included to explore the associations, the results of this work strongly support the
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8 conclusion and may help provide insights into the relationship between air pollutants
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10 and IS. Furthermore, due to the severe air pollution and enormous stroke burden that
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12 Changzhou is now experiencing, the findings of this study may provide clues for the
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14 primary prevention of the onset or death related to IS, especially for sensitive
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16 populations. However, limitations should be noted in this study. Because individuals
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18 were identified retrospectively and not all hospitals were included, diagnostic errors
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20 and selection bias may exist. We relied on routine measurements from ten fixed-site
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22 monitoring stations instead of more accurate measurement based on the individuals'
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24 residence and indoor exposure. Thus, we were not able to quantify the exposure of
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26 individuals precisely. Moreover, the data regarding IS cases and air pollutant levels
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28 were collected from only one city, and it is difficult to extrapolate the results to other
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30 areas in China. Further national or multi-cities studies are required.
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38 In conclusion, our results suggested that short-term exposure to ambient NO₂ was
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40 associated with increased IS risk. In addition, SO₂ was associated with increased IS
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42 counts and deaths. These findings may have significant public health implications for
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44 the prevention of IS and IS-related death. Further studies are recommended to validate
45
46 our research.
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52 **Acknowledgements** The authors are grateful to the PPI group chaired by HD, who
53
54 supported the wider programme of work of which the qualitative interviews are a part.
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3 The authors are also grateful to the patient representative and to other members of the
4 study advisory group.
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6

7
8 **Contributors** The study was conceived and designed by HD, YL and ZZ, and overall
9 study management was by XY, S-LW and ZZ, ZC, GL and YYao contributed to data
10 collection and processing. SY performed the statistical analysis, HD, YYu and YL
11 helped in manuscript preparation and interpretation of the results. All authors
12 contributed to the revision of the manuscript and reviewed and approved the final
13 version.
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17
18 **Funding** This work was supported by the Natural Science Foundation of China
19 (81502801), a project funded by the Priority Academic Program Development of
20 Jiangsu Higher Education Institutions (2014), a collegiate Natural Science
21 Foundations of Jiangsu province (16KJB330005), the science and technology support
22 programme funded by Changzhou Municipal Science and Technology Bureau
23 (CE20145046) and the Science and Technique Foundation for Youths by Health and
24 Family Planning Commission of Changzhou (QN201603).
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40 **Disclaimer** The funding sponsors had no role in the design of the study, in the
41 collection, analysis or interpretation of data, in the writing of the manuscript or in the
42 decision to publish the research results.
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47 **Ethical approval** The present study was approved by the Institutional Review Board
48 of the Changzhou Center for Disease Control and Prevention, and all procedures were
49 in accordance with prevailing ethical principles.
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54 **Competing interests** None declared.
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3 **Patient consent** Not needed.
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6 **Provenance and peer review** Not commissioned; externally peer reviewed.
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8 **Data sharing statement** No additional data are available.
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Figure legends

Figure 1 The percentage change in daily ischaemic stroke (IS) counts and daily IS deaths with an interquartile range increase in air pollutant levels on different lag days in single-pollutant models in Changzhou, 2015-2016. The data are expressed as the mean with a 95% confidence interval.

Figure 2 The concentration-response relationships of daily ischaemic stroke (IS) counts, daily IS deaths with air pollutants on different lag days (lag 0-5 for daily IS counts and lag 5 for daily IS deaths) in single-pollutant models in Changzhou, 2015-2016.

Table 1 The means, medians and interquartile ranges (IQRs) for daily air pollutants and weather conditions variables in Changzhou, 2015-2016

Variables	Mean±SD	Min	25th	Median	75th	Max	IQR
Weather Condition							
Temperature (°C)	17.1±8.9	-6.6	9.4	18.3	24.1	34.6	5.8
Humidity (%)	75.3±14.2	35.0	66.0	76.0	86.0	100.0	10.0
Air Pollutions							
PM _{2.5} (µg/m ³)	51.8±30.6	6.8	29.4	44.4	64.4	181.1	20.0
PM ₁₀ (µg/m ³)	85.3±43.3	10.5	51.5	76.6	108.6	289.1	32.0
NO ₂ (µg/m ³)	38.7±16	10.9	26.5	35.8	47.8	117.3	12.0
SO ₂ (µg/m ³)	22.3±10	6.9	14.7	20.2	27.0	67.8	6.9
CO (mg/m ³)	1±0.3	0.4	0.8	1.0	1.2	2.6	0.2

PM_{2.5}, particulate matter <2.5 mm in diameter; PM₁₀, particulate matter <10 mm in diameter; NO₂, nitrogen dioxide; SO₂, sulfur dioxide; CO, carbon monoxide.

Table 2 The percentage change in daily IS counts and deaths with an interquartile range increase in air pollutants levels modifying by age, sex and seasons in Changzhou, 2015-2016

Variable	Total	Age		Sex		Seasons	
		≤65	>65	Female	Male	Warm	Cold
Daily IS counts*							
PM _{2.5}	-0.063 (-0.215-0.088)	-0.246 (-0.568-0.076)	-0.042 (-0.21-0.127)	-0.097 (-0.311-0.119)	-0.08 (-0.289-0.128)	-0.149 (-0.525-0.228)	-0.098 (-0.267-0.071)
PM ₁₀	-0.053 (-0.22-0.114)	-0.219 (-0.572-0.136)	-0.004 (-0.191-0.184)	-0.086 (-0.324-0.153)	-0.047 (-0.279-0.185)	-0.057 (-0.41-0.297)	-0.088 (-0.282-0.107)
NO ₂	0.208 (0.036-0.381)‡	0.258 (-0.075-0.592)	0.166 (-0.025-0.357)	0.168 (-0.055-0.391)	0.238 (0.002-0.475)‡	-0.136 (-0.481-0.21)	0.382 (0.169-0.596)‡
SO ₂	0.125 (-0.034-0.284)	-0.044 (-0.364-0.277)	0.113 (-0.062-0.289)	0.15 (-0.068-0.369)	0.056 (-0.162-0.275)	-0.309 (-0.651-0.033)	0.298 (0.099-0.498)‡
CO	-0.078 (-0.22-0.064)	-0.213 (-0.511-0.086)	-0.061 (-0.222-0.1)	-0.151 (-0.355-0.053)	-0.007 (-0.206-0.192)	-0.175 (-0.432-0.083)	-0.053 (-0.237-0.131)
Daily IS deaths†							
PM _{2.5}	0.228 (-0.005-0.462)	1.144 (0.329-1.965)‡	0.152 (-0.091-0.395)	0.124 (-0.19-0.439)	0.29 (-0.043-0.625)	-0.199 (-0.77-0.375)	0.184 (-0.088-0.456)
PM ₁₀	0.268 (0.007-0.528)‡	1.52 (0.656-2.391)‡	0.152 (-0.12-0.424)	0.093 (-0.261-0.448)	0.404 (0.03-0.78)‡	-0.012 (-0.53-0.509)	0.247 (-0.075-0.57)
NO ₂	0.263 (0.004-0.522)‡	0.894 (0.058-1.736)‡	0.195 (-0.073-0.463)	0.37 (0.027-0.715)‡	0.132 (-0.247-0.512)	0.275 (-0.222-0.775)	0.198 (-0.13-0.528)
SO ₂	0.34 (0.088-0.592)‡	0.67 (-0.175-1.523)	0.307 (0.045-0.57)‡	0.434 (0.096-0.772)‡	0.215 (-0.15-0.58)	0.017 (-0.493-0.531)	0.388 (0.081-0.696)‡
CO	0.175 (-0.042-0.392)	0.9 (0.166-1.639)‡	0.108 (-0.118-0.335)	0.189 (-0.11-0.49)	0.154 (-0.162-0.471)	0.02 (-0.401-0.443)	0.169 (-0.104-0.443)

*The multivariable regression model fits the pollutants for daily IS count data at lag 0-5 and adjusts for calendar time (df=5), DOW (df=7), daily average humidity (df=5) and average temperature (df=5).

†The multivariable regression model fits the pollutants for daily IS death data at lag 5 and adjusts for calendar time (df=5), DOW (df=7), daily average humidity (df=5) and average temperature (df=5).

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‡ Statistically positive association between air pollutants and daily IS counts or deaths

The data are expressed as the mean with a 95% confidence interval.

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Table 3 The percent increases in daily IS counts and deaths with each interquartile range increment in air pollutant levels in two-pollutant models in Changzhou, 2015-2016

Variables	PM _{2.5}	PM ₁₀	NO ₂	SO ₂	CO
Daily IS counts					
PM _{2.5}	-0.063 (-0.215-0.088)	0.25 (-0.314-0.817)	0.497 (0.259-0.735)‡	0.305 (0.083-0.527) ‡	-0.059 (-0.274-0.157)
PM ₁₀	-0.423 (-0.881-0.038)	-0.053 (-0.22-0.114)	0.539 (0.29-0.788)‡	0.262 (0.034-0.491) ‡	-0.065 (-0.293-0.163)
NO ₂	-0.346 (-0.558--0.134)	-0.438 (-0.691--0.185)	0.208 (0.036-0.381)‡	-0.007 (-0.267-0.253)	-0.341 (-0.556--0.124)
SO ₂	-0.24 (-0.46--0.019)	-0.244 (-0.49-0.003)	0.22 (-0.067-0.507)	0.125 (-0.034-0.284)	-0.166 (-0.356-0.023)
CO	-0.089 (-0.314-0.137)	0.029 (-0.223-0.281)	0.45 (0.215-0.685)‡	0.172 (-0.016-0.361)	-0.078 (-0.22-0.064)
Daily IS deaths					
PM _{2.5}	0.228 (-0.005-0.462)	0.436 (-0.36-1.238)	0.22 (-0.127-0.567)	0.28 (-0.071-0.632)	0.065 (-0.314-0.446)
PM ₁₀	0.211 (-0.463-0.89)	0.268 (0.007-0.528)‡	0.218 (-0.135-0.573)	0.295 (-0.055-0.646)	0.137 (-0.23-0.504)
NO ₂	0.106 (-0.201-0.414)	0.149 (-0.21-0.509)	0.263 (0.004-0.522)‡	0.351 (-0.096-0.8)	0.057 (-0.269-0.384)
SO ₂	0.066 (-0.25-0.383)	0.126 (-0.242-0.496)	0.066 (-0.387-0.521)	0.34 (0.088-0.592)‡	0.035 (-0.281-0.351)
CO	0.186 (-0.199-0.571)	0.233 (-0.187-0.656)	0.23 (-0.14-0.601)	0.346 (0.002-0.691)‡	0.175 (-0.042-0.392)

*The multivariable regression model fits the pollutants for daily IS counts data at lag 0-5 and

adjusts for the other pollutants, calendar time (df=5), DOW (df=7), daily average humidity (df=5)

and average temperature (df=5).

†The multivariable regression model fits the pollutants for daily IS deaths data at lag 5 and adjusts

for the other pollutants, calendar time (df=5), DOW (df=7), daily average humidity (df=5) and

average temperature (df=5).

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‡ Statistically positive association between air pollutants and daily IS counts or deaths

The data was expressed as the mean with 95% confidence interval.

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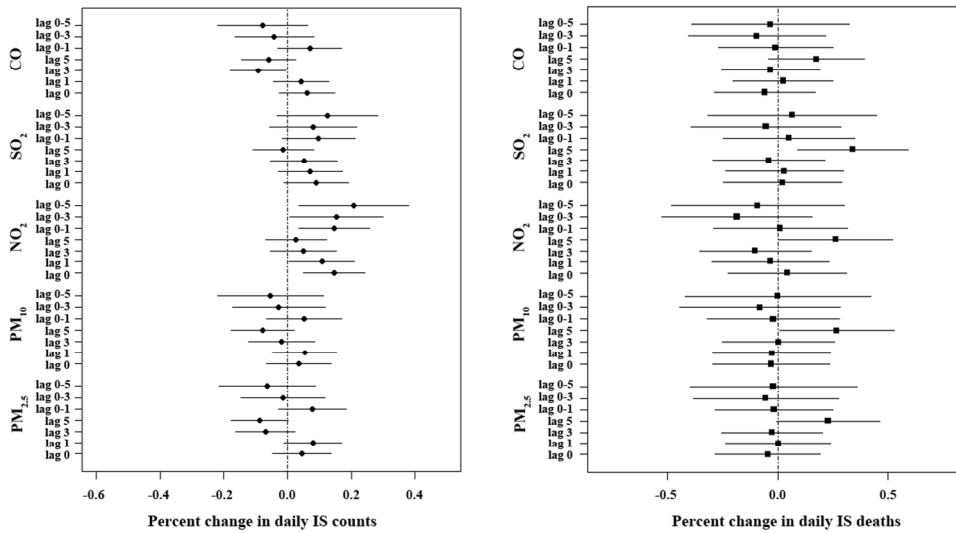


Figure 1 The percentage change in daily ischemic stroke (IS) counts and daily IS deaths with an interquartile range increase in air pollutants levels on different lag days in single-pollutant models in Changzhou, 2015-2016. The data was expressed as mean with 95% confidence interval.

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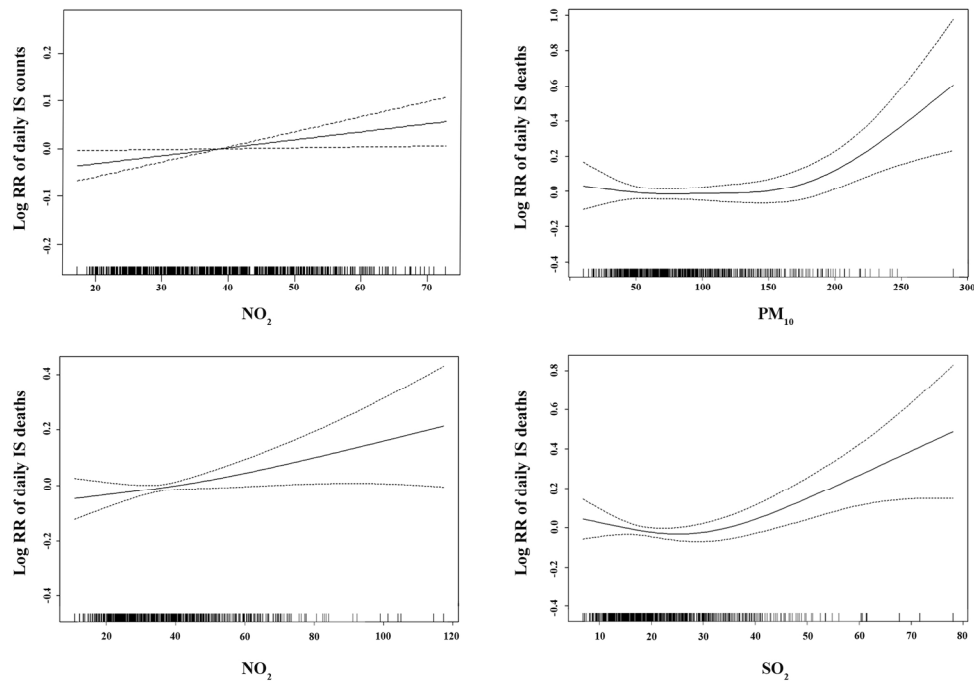


Figure 2 The concentration-response relationships of daily ischemic stroke (IS) counts, daily IS deaths with air pollutants on different lag days (lag 0-5 for daily IS counts and lag 5 for daily IS deaths) in single-pollutant models in Changzhou, 2015-2016.

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4 **Acute effects of air pollution on ischemic stroke onsets and deaths: A time-series**
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6 **study in Changzhou, China**
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11 Huibin Dong^{1, a}, Yongquan Yu^{2, a}, Shen Yao², Yan Lu³, Zhiyong Chen¹, Guiying Li¹,

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14 Yao Yao¹, Xingjuan Yao¹, Shou-Lin Wang², Zhan Zhang^{4*}
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19 **Supplementary data**
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Table S1 The descriptive statistics for daily ischemic stroke (IS) counts and deaths in Changzhou, 2015-2016*

Variables	Mean± SD	Min	25th	Median	75th	Max
Daily IS counts	45.4±11.2	14.0	38.0	45.0	53.0	99.0
Male	23.7±7	6.0	19.0	23.0	28.0	60.0
Female	21.8±6.1	6.0	18.0	22.0	26.0	48.0
<65	8.5±3.6	0.0	6.0	8.0	11.0	23.0
≥65	36.9±9.2	11.0	31.0	36.0	43.0	80.0
Daily IS deaths	5.6±2.9	0.0	3.0	5.0	7.0	19.0
Male	2.7±1.8	0.0	1.0	3.0	4.0	10.0
Female	2.8±2	0.0	1.0	3.0	4.0	10.0
<65	0.4±0.7	0.0	0.0	0.0	1.0	3.0
≥65	5.1±2.8	0.0	3.0	5.0	7.0	18.0

*A total of 32,840 IS cases and 4,028 IS deaths recorded were recorded during the study period.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1-4	Acute effects of air pollution on ischaemic stroke onsets and deaths: A time-series study in Changzhou, China (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	5-6	Explain the scientific background and rationale for the investigation being reported
Objectives	6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	7-9	Present key elements of study design early in the paper
Setting	7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	7	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7-8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	7*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	7-8	Describe any efforts to address potential sources of bias
Study size	7	Explain how the study size was arrived at
Quantitative variables	8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	7-9	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses
Results		
Participants	9-10*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	9-10*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest
Outcome data	10 - 11*	Report numbers of outcome events or summary measures
Main results	10-11	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	10-11	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	11-12	Summarise key results with reference to study objectives
Limitations	12- 13-15	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	12- 13-14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	14-15	Discuss the generalisability (external validity) of the study results
Other information		
Funding	164	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.