Association between exposure to ambient air pollution and hospital admission, incidence, and mortality of stroke: an updated systematic review and meta-analysis of more than 23 million participants

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Abstract

Background: Previous studies have suggested that exposure to air pollution may increase stroke risk, but the results remain inconsistent. Evidence of more recent studies is highly warranted, especially gas air pollutants.

Methods: We searched PubMed, Embase, and Web of Science to identify studies till February 2020 and conducted a meta-analysis on the association between air pollution (PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; PM$_{10}$, particulate matter with aerodynamic diameter less than 10 μm; NO$_2$, nitrogen dioxide; SO$_2$, sulfur dioxide; CO, carbon monoxide; O$_3$, ozone) and stroke (hospital admission, incidence, and mortality). Fixed- or random-effects model was used to calculate pooled odds ratios (OR)/hazard ratio (HR) and their 95% confidence intervals (CI) for a 10 μg/m$^3$ increase in air pollutant concentration.

Results: A total of 68 studies conducted from more than 23 million participants were included in our meta-analysis. Meta-analyses showed significant associations of all six air pollutants and stroke hospital admission (e.g., PM$_{2.5}$: OR = 1.008 (95% CI 1.005, 1.011); NO$_2$: OR = 1.023 (95% CI 1.015, 1.030), per 10 μg/m$^3$ increase in air pollutant concentration). Exposure to PM$_{2.5}$, SO$_2$, and NO$_2$ was associated with increased risks of stroke incidence (PM$_{2.5}$: HR = 1.048 (95% CI 1.020, 1.076); SO$_2$: HR = 1.002 (95% CI 1.000, 1.003); NO$_2$: HR = 1.002 (95% CI 1.000, 1.003), respectively). However, no significant differences were found in associations of PM$_{10}$, CO, O$_3$, and stroke incidence. Except for CO and O$_3$, we found that higher level of air pollution (PM$_{2.5}$, PM$_{10}$, SO$_2$, and NO$_2$) exposure was associated with higher stroke mortality (e.g., PM$_{10}$: OR = 1.006 (95% CI 1.003, 1.010); SO$_2$: OR = 1.006 (95% CI 1.005, 1.008).

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Conclusions: Exposure to air pollution was positively associated with an increased risk of stroke hospital admission (PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO, and O$_3$), incidence (PM$_{2.5}$, SO$_2$, and NO$_2$), and mortality (PM$_{2.5}$, PM$_{10}$, SO$_2$, and NO$_2$). Our study would provide a more comprehensive evidence of air pollution and stroke, especially SO$_2$ and NO$_2$.

Keywords: Stroke, Air pollution, Hospital admission, Incidence, Mortality

Introduction
Stroke, characterized by acute cerebral blood circulation disorder, is caused by artery stenosis, occlusion, or rupture caused by various inducing factors in patients with cerebrovascular diseases [1]. Stroke has become a leading contributor to the global burden of disease and the second leading cause of death worldwide [2, 3]. According to the Global Burden of Disease Study (GBD) report, there were approximately 80.1 million stroke patients, and 5.5 million deaths were attributed to stroke in 2016 globally [4]. Considering stroke is characterized with high incidence, high mortality, and contribute to severe burden disease, identifying potential risk factor of stroke is of great significance for public health. In parallel, air pollution has also been regarded as one of the major environmental problems and a risk factor of many cardio-vascular diseases (CVD), including stroke [5]. GBD 2019 showed that air pollution was globally the sixth leading cause of stroke death during 1990 to 2017, and 28.1% disability-adjusted life years (DALYs) of stroke attribute to environmental factors exposure [6, 7].

Air pollution is the most significant environmental risk factor for all-cause mortality [8]. Increasing number of human epidemiologic studies has been conducted to assess the potential association between air pollution exposure and stroke admission, incidence, and mortality in recent years. However, the results were inconsistent, and the associations between exposure to air pollution and stroke have not been fully understood. Some studies reported positive association between air pollution exposure and stroke hospital admission/incidence/mortality, whereas others did not [4, 9–14]. For example, Huang et al. 2019 indicated that exposure to PM$_{2.5}$ was associated with increased stroke incidence and the adjusted risk ratio (RR) was 1.130 (95%CI: 1.090, 1.170) for each increase of 10 μg/m$^3$ in n PM$_{2.5}$ concentration [4]. The adjusted risk ratio (RR) was 1.130 (95% CI 1.090, 1.170) for each increase of 10 μg/m$^3$ in PM$_{2.5}$ concentration, while Wing et al. suggested no association was found between PM$_{2.5}$ exposure and stroke incidence (RR = 0.950, 95% CI 0.710, 1.280) [11]. Previous meta-analyses have explored the associations between air pollution exposure and stroke [15–19]. However, these studies were mainly focused on the studies of particulate matter (PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; PM$_{10}$, particulate matter with aerodynamic diameter less than 10 μm) and stroke outcomes [16–19]; results of gas air pollutants (NO$_2$, nitrogen dioxide; SO$_2$, sulfur dioxide; CO, carbon monoxide; O$_3$, ozone) were scarce. Moreover, to the best of our knowledge, more than 30 studies exploring the association between air pollution exposure and stroke, especially conducted from the multi-city level and with large sample sizes, were published after the most recent meta-analysis. The more recent and comprehensive studies should be included in the meta-analysis to conclude an updated pooled effect estimate.

We therefore conducted an updated systematic review and meta-analysis to assess the association between 6 main air pollutants (PM$_{2.5}$, PM$_{10}$, NO$_2$, SO$_2$, CO, and O$_3$) and 3 stroke outcomes (hospital admission, incidence, and mortality). This systematic review and meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) criteria (Table S1).

Methods
Search strategy
Literature was searched in three databases (PubMed, Embase, and Web of Science), with published date until 1 February 2020. The search strategy was pairwise of combinations of terms concerning air pollution (e.g., air pollution, particulate matter, particles, PM$_{2.5}$, PM$_{10}$, nitrogen oxides (NOx), NO$_2$, SO$_2$, CO, and O$_3$) and stroke (e.g., stroke, cerebrovascular disease, cerebrovascular disorder, cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage).

We first selected articles by screening titles and abstracts and then the full texts of potentially eligible studies were further evaluated. Reference lists of all the included studies were also manually searched. Literature selection was finished by two independent authors (ZP and FF L), and conflicts between the two authors were resolved by discussing with an arbitrator (H X).

Inclusion and exclusion criteria
Articles that met the following criteria were included: (1) provided quantitative measure of the associations between air pollution exposure with stroke admission, incidence, and/or mortality (relative risk (RR), odds ratio (OR), or hazard ratio (HR), and their 95% confidence interval (95%CI)); (2) cohort, cross-sectional, time series,
cross-sectional, case-control, case-crossover, or panel studies; (3) focused on outdoor (ambient) air pollution exposure but not indoor air pollution; (4) original peer-reviewed human subject research studies; (5) published in English. Studies were excluded if they were (1) toxicological studies, summaries, or reviews, and (2) articles without effect estimates after contacting the authors. In addition, for more than one article conducted from the same population, only the most recent studies were included.

Data extraction
Data were extracted from all eligible studies, including the following: (1) study characteristics (first author, published year, study location, and period); (2) study population (sample size, proportion of males, range of age, mean age); (3) outcome (type of stroke and outcome was admission, incidence, and/or mortality); (4) air pollution assessment method and increment of air pollution used in effect estimates (per interquartile range (IQR), standard deviation (SD), or per 10 μg/m³); (5) effect estimates of the association between air pollution and stroke risk (OR, RR, HR with 95% CI). The effect estimates of single-pollutant model, generally called “main model” or “fully adjusted model,” were extracted [20].

Quality assessment
Two authors (ZP N and FF L) worked independently, and inconsistencies in quality assessment were resolved through discussion. We employed the Newcastle-Ottawa Scale (NOS) to evaluate the quality of included studies. The NOS Tool has designed 8 items to assess the critical appraisal of the potential risk of bias. Total score of NOS ranged from 0–9. Study score higher than or equal to 7 was regarded as high-quality; otherwise, the study was regarded as “low quality” [21].

Statistical analyses
This meta-analysis focused on examining the association between air pollution and three stroke outcomes, including admission, incidence, and/or mortality. We extracted effect estimates (OR, HR, RR, and 95% CI) from individual studies and then converted them into a standardized form of per 10 μg/m³ increases in air pollution. The significance of the pooled OR, RR, or HR was determined by the Z test [22], and p value less than 0.05 was considered statistically significant. Standard error (SE) for each effect estimate was calculated by using the formula: (upper limit – lower limit)/3.92.

Heterogeneity among studies was evaluated using I² statistics and Q test [23]. If the values of I² > 50% or p < 0.01, the heterogeneity was “high” and random effect model was used to pool estimates. Otherwise, heterogeneity was considered as “low or moderate,” and fixed-effect model was used to pool estimates.

Begg’s test and Egger’s test were conducted to assess publication bias. The influence of individual studies on the pooled estimates was examined by removing each study from the analysis one by one. Moreover, we also performed sensitivity analysis and subgroup analysis to evaluate if the exposure period would change the significance of the pooled results. Because long-term studies were limited, sensitivity analysis was conducted by omitting long-term exposure (cohort) studies. Subgroup analysis was only performed if the number of short-term exposure studies or long-term exposure studies was more than 3. Publication bias and sensitivity analysis were only performed if the number of included studies was more than 5. All statistical analysis was performed in Stata version 15.0 (StataCorp, College Station, TX, USA).

Results

Literature search and characteristics of included studies
After removing duplicates, 737 records were identified in the initial literature search. By reviewing title and abstracts, 93 studies were downloaded for full-text reading. According to the inclusion and exclusion criteria, a total of 68 studies were included in our meta-analysis (Fig. 1).

Table 1 provides the characteristics of 68 studies included in meta-analysis. As for air pollution involved in the study, there were 26 studies that reported the association between air pollution exposure and stroke hospital admission, 19 reported air pollution exposure and stroke incidence, 19 reported air pollution exposure and stroke mortality, and 3 reported both stroke incidence and mortality. The sample size of included studies ranged between 407 and 8,834,533; more than 23 million participants were included in meta-analysis eventually. Furthermore, the studies included were conducted from 18 countries. Time-series and cross-sectional were the most commonly adopted study designs. In our meta-analysis, all 68 included studies were considered as “high quality,” and the average NOS score was 8.26 for all studies (Table S2).

Air pollution and stroke hospital admission
A total of 29 studies were performed to assess the association for air pollution and stroke hospital admission, and the results were inconsistent. Most studies showed a positive correlation between exposure to air pollution and the risk of hospital admission for stroke. In meta-analysis, we enrolled 13 studies on PM_{2.5}, 11 studies on PM_{10} and NO\textsubscript{2}, 10 studies on SO\textsubscript{2} and O\textsubscript{3}, and 6 studies on CO with stroke hospital admission and suggested an increased stroke hospital admission risk after air pollution exposure. The pooled odds ratio (OR) of stroke with
a 10 μg/m³ increase in PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO, and O$_3$ was 1.008 (95% CI 1.005, 1.011), 1.004 (95% CI 1.001, 1.006), 1.013 (95% CI 1.007, 1.020), 1.023 (95% CI 1.015, 1.030), 1.000 (95% CI 1.000, 1.001), and 1.002 (95% CI 1.000, 1.003), respectively (Table 2, Figure S1-S6). Heterogeneity among studies was significant ($I^2 \geq 50\%$, $p < 0.001$).

**Air pollution and stroke incidence**

Twenty-three studies have investigated the association of air pollution on stroke incidence (Table 1). For meta-analysis, we extracted 18 studies on PM$_{2.5}$, 13 studies on PM$_{10}$, 10 studies on O$_3$, 7 studies on NO$_2$, and 4 studies on SO$_2$ and CO. Ten of these studies suggested increased risks for stroke incidence for at least one of the investigated pollutants. Meta-analysis showed that exposure to PM$_{2.5}$, SO$_2$, and NO$_2$ was associated with increased risks of stroke incidence, and the pooled HR with a 10 μg/m³ increase was 1.048 (95% CI 1.020, 1.076), 1.002 (95% CI 1.000, 1.003), 1.002 (95% CI 1.000, 1.003), respectively. However, no significant differences were found in associations of PM$_{10}$, CO, O$_3$, and stroke incidence (Table 3, Figure S7-S12).

**Air pollution and stroke mortality**

Twenty-two population-based studies have explored the association for exposure to air pollution and stroke mortality. As for meta-analysis, 11 articles on PM$_{2.5}$, 10 articles on NO$_2$, 9 articles on PM$_{10}$, 6 articles on O$_3$, and 4 articles on CO exposure were included. Meta-analysis showed that exposure to ambient PM$_{2.5}$ (OR = 1.008 95% CI 1.005, 1.012, per 10 μg/m³ increment), PM$_{10}$ (OR = 1.006, 95% CI 1.003, 1.010, per 10 μg/m³ increment), SO$_2$ (OR = 1.006, 95% CI 1.005, 1.008, per 10 μg/m³ increment), and NO$_2$ (OR = 1.009, 95% CI 1.003, 1.016, per 10 μg/m³ increment) was associated with increased risks of mortality due to stroke. No significant difference was shown in association between CO, O$_3$ exposure, and stroke mortality (Table 4, Figure S13-S18).

**Publication bias and sensitivity analysis**

Publication bias of studies on PM$_{10}$ exposure and stroke hospital admission may exist, since $p$ values of Begg's
| Reference | Study Location and period | Study population | Study design | Exposure | Exposure assessment method | Type of stroke | Outcome |
|----------------|--------------------------|------------------|-------------|----------|---------------------------|---------------|---------|
| Huang et al. [4] | 15 provinces in China, 2000–2015 | 117,575 Chinese men and women without stroke from the Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) project | Cohort | PM$_{2.5}$ | A satellite-based spatiotemporal model, 1 × 1-km spatial resolution | All types of stroke | Incidence |
| Tian et al. [24] | 172 cities in China, 2014–2016 | 2,032,667 hospital admissions for ischemic stroke in 172 cities in China | Time-series | PM$_{2.5}$ | 1–17 monitors in each city operated by the National Air Pollution Monitoring System | Ischemic stroke | Hospital admission |
| Chen et al. [25] | Jinan, China, 2013–2015 | 56,922 stroke admissions | Case-crossover | PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, O$_3$ | 14 fix-sited monitoring stations in urban areas of Jinan operated by Jinan Environment Monitoring Center | All types of stroke | Hospital admission |
| Chen et al. [26] | China, 2007–2008 | 12,291 ischemic stroke patients from first national hospital-based prospective registry cohort of stroke in China | Cohort | PM$_{2.5}$, PM$_{10}$, NO$_2$ | Monitoring data, satellite remote sensing, meteorological and land use information | Ischemic stroke | Mortality |
| Xue et al. [27] | China, 2013–2015 | 1356 first-ever stroke events | Case-crossover | O$_3$ | 1463 continuous air pollution monitoring sites operated by the China Environmental Protection Ministry | All types of stroke | Incidence |
| Qian et al. [28] | Shanghai, China, 2012–2014 | 5286 fatal intracerebral hemorrhage (ICH) case | Case-crossover | PM$_{2.5}$ | The Shanghai Environmental Monitoring Center | Hemorrhagic stroke | Incidence |
| Tian et al. [12] | 184 major cities in China, 2014–2017 | 8,834,533 hospital admissions for cardiovascular causes in 184 Chinese cities | Time-series | PM$_{2.5}$ | The National Air Pollution Monitoring System | Ischemic, hemorrhagic stroke | Hospital admission |
| Tian et al. [10] | 172 cities in China, 2014–2016 | 2,032,667 hospital admissions for ischemic stroke in 172 cities in China | Time-series | PM$_{2.5}$, SO$_2$, NO$_2$, O$_3$, CO | 1–17 monitors in each city operated by the National Air Pollution Monitoring System | Ischemic stroke | Hospital admission |
| Dong et al. [1] | Changzhou, China, 2015–2016 | 32,840 ischemic stroke (IS) cases, 4028 IS deaths | Time-series | PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO | 10 air quality monitoring stations operated by the Changzhou Environmental Monitoring Center | Ischemic stroke | Mortality, incidence |
| Zhong et al. [29] | Changsha city, China, 2008–2009 | 1536 stroke patients | Case-crossover | PM$_{10}$, NO$_2$, SO$_2$ | the Changsha Municipal Public Weather Information Service Website | All types of stroke | Hospital admission |
| Vivanco-Hidalgo et al. [30] | Barcelona, Spain, 2005–2014 | 27,421,536 stroke patients | Time-series | PM$_{2.5}$ | An urban background research site located in southwest Barcelona | Ischemic stroke | Incidence |
| Yitshak-Sadeh et al. [31] | New England, 2001–2011 | 2,015,660 stroke admissions | Time-series | PM$_{2.5}$ | Monitor PM data and aerosol optic depth (AOD) values (1 × 1 km) | Ischemic stroke | Hospital admission |
| Liu et al. [32] | 272 cities in China, 2013–2015 | 294,199 deaths due to stroke in 272 Chinese cities | Time-series | CO | The National Urban Air Quality Real-time Publishing Platform | All types of stroke | Mortality |
| Wang et al. [33] | 6 subtropical cities in China, 2013–2016 | 54,236 stroke deaths from six Chinese subtropical cities | Case-crossover | PM$_{2.5}$, PM$_{10}$ | Municipal air monitoring system | All types of stroke | Mortality |
| Collart et al. [34] | Wallonia, Belgium, 2008–2011 | 113,147 hospital admissions due to stroke | Time-series | NO$_2$ | ISSeP (the Scientific Institute of Public Services) | All types of stroke | Hospital admission |
| Chen et al. [35] | 30 counties in China, 2013–2015 | 49,669 stroke deaths | Time-series | PM$_{2.5}$ | Fixed-site monitoring station operated by the closest spatial distance to the county center. Daily air pollution data for PM2.5 and O3 concentrations were collected from the National Air | All types of stroke | Mortality |
| Reference                  | Study Location and period          | Study population                                                                 | Study design | Exposure | Exposure assessment method                     | Type of stroke | Outcome          |
|---------------------------|-----------------------------------|----------------------------------------------------------------------------------|--------------|----------|------------------------------------------------|----------------|------------------|
| Wang et al. [36]          | 272 cities in China, 2013–2015    | 294,199 deaths due to stroke in 272 Chinese cities                               | Time-series  | SO₂      | The National Urban Air Quality Real-time Publishing Platform | All types of stroke | Mortality        |
| Chen et al. [9]           | 272 cities in China, 2013–2015    | 294,199 deaths due to stroke in 272 Chinese cities                               | Time-series  | PM₂.₅   | The National Urban Air Quality Real-time Publishing Platform | All types of stroke | Mortality        |
| Yin et al. [37]           | 272 cities in China, 2013–2015    | 294,199 deaths due to stroke in 272 Chinese cities                               | Time-series  | O₃       | The National Urban Air Quality Real-time Publishing Platform | All types of stroke | Mortality        |
| Ha et al. [38]            | USA, 2002–2008                    | 228,438 deliveries                                                              | Case-crossover | PM₂.₅, PM₁₀, SO₂, O₃, CO | Community Multiscale Air Quality (CMAQ) models | All types of stroke | Incidence        |
| Huang et al. [39]         | Beijing, China, 2013–2014         | 147,624 stroke admissions                                                        | Case-crossover | SO₂, NO₂, O₃, CO | The Centre of City Environmental Protection Monitoring Website Platform of Beijing | All types of stroke | Hospital admission |
| Guo et al. [5]            | South China, 2013–2015            | 95,562 ischemic stroke cases                                                    | Time-series  | PM₂.₅, PM₁₀, NO₂, SO₂, O₃, CO | The Qingyue Open Environmental Data (QOED) Center | Ischemic hospital admission | Ischemic stroke  |
| Liu et al. [40]           | 14 large cities in China, 2014–2015 | 200,958 ischemic stroke and 41,746 hemorrhagic stroke hospitalizations         | Case-crossover | PM₁₀, SO₂, O₃, CO | The National Air Pollution Monitoring System | Ischemic, hemorrhagic stroke | Hospital admission |
| Wing et al. [11]          | Texas, USA, 2000–2012             | 3216 first-ever ischemic strokes                                                 | Case-crossover | PM₂.₅, O₃ | The Texas Commission on Environmental Quality’s Texas Air Monitoring Information System from a centrally located monitor | Ischemic stroke | Incidence        |
| Liu et al. [41]           | 26 cities in China, 2014–2015     | 348,379 stroke admissions                                                        | Case-crossover | PM₂.₅, PM₁₀ | The National Air Pollution Monitoring System | Ischemic, hemorrhagic stroke | Hospital admission |
| McClure et al. [42]       | USA, 2003–2011                    | 30,239 participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, 746 incidences | Case-crossover | PM₂.₅ | Moderate Resolution Imaging Spectroradiometer instrument on the NASA Aqua satellite (10 km × 10 km) | All types of stroke | Incidence        |
| Tian et al. [43]          | Beijing, China, 2010–2012         | 63,956 first hospital admissions due to stroke                                  | Case-crossover | PM₂.₅ | An ambient air quality monitoring station on the rooftop of embassy building located in Chaoyang district, Beijing | Ischemic stroke | Hospital admission |
| Lin et al. [44]           | 6 low- and middle-income countries, 2007–2010 | 45,625 participants from the Study on Global Aging and Adult Health            | Cohort       | PM₂.₅ | Global estimates of ambient fine particulate matter concentrations from satellite-based aerosol optical depth | All types of stroke | Incidence        |
| Hong et al. [45]          | Changzhou, China, 2015–2016       | 32,840 ischemic stroke (IS) cases, 4028 IS deaths                               | Time-series  | O₃       | 10 air quality monitoring stations operated by the Changzhou Environmental Monitoring Center | Ischemic stroke | Incidence, mortality |
| Stockfelt et al. [46]     | Gothenburg, Sweden, 1990–2011     | 1391 cases of stroke from the Primary Prevention Study (PPS) cohort and GOT-MONICA cohort | Cohort       | PM₂.₅, PM₁₀ | High-resolution dispersion modeling was performed for the period 1990–2011 over a Gothenburg region domain (93 × 112 km) | All types of stroke | Incidence        |
| Qiu et al. [47]           | Hong Kong, China, 1998–2010       | 6,733 cases of incident stroke                                                  | Cohort       | PM₂.₅ | Satellite-based aerosol optical depth (AOD) recordings and monitoring data from ground-based stations | All types of stroke | Incidence        |
| Crichton et al. [48]      | South London, England, 2005–2015  | 1800 incidence due to stroke                                                    | Time-series  | PM₂.₅, PM₁₀ | The KCLurban model developed at King’s College London | Ischemic, hemorrhagic stroke | Incidence        |
### Table 1
Descriptive summaries for all included studies (Continued)

| Reference | Study Location and period | Study population | Study design | Exposure | Exposure assessment method | Type of stroke | Outcome |
|-----------|---------------------------|------------------|-------------|----------|----------------------------|----------------|---------|
| Huang et al. [49] | Beijing, China, 2013–2014 | 147,624 stroke admissions | Case-crossover | NO2, O3 | The Centre of City Environmental Protection Monitoring Website Platform of Beijing | Ischemic, hemorrhagic stroke | Hospital admission |
| Lin et al. [50] | Guangzhou, China, 2007–2011 | 9066 stroke deaths | Time-series | PM2.5, PM10 | An automatic air monitoring system was installed on the rooftop of Panyu Meteorological Centre | All types of stroke | Mortality |
| Han et al. [51] | South Korea, 2004–2014 | 1,477 consecutive hemorrhagic stroke events | Case-crossover | PM10, NO2, O3 | The Climate and Air Quality Management Division of South Korea | Hemorrhagic stroke | Incidence |
| Montresor-López et al. [13] | South Carolina, USA, 2002–2006 | 21,301 stroke patients | Case-crossover | O3 | The US Environmental Protection Agency (USEPA), Hierarchical Bayesian Model (HBM) | All types of stroke | Hospital admission |
| Korek et al. [52] | Stockholm, Sweden, 1991–2010 | 22,587 individuals in four cohorts | Cohort | PM10 | The Airviro Air Quality Management System | All types of stroke | Incidence |
| Chang et al. [53] | Tropical City, Taiwan, 2006–2010 | 27,392 admissions due to stroke | Case-crossover | PM2.5 | 6 air quality monitoring stations in Kaohsiung city operated by the Taiwanese Environmental Protection Administration (EPA) | All types of stroke | Hospital admission |
| Tian et al. [54] | Hong Kong, 2004–2011 | 140,774 emergency hospital admissions | Time-series | CO | 4 general monitoring stations operated by the Environmental Protection Department (EPD) of Hong Kong | All types of stroke | Hospital admission |
| To et al. [55] | Canada, 1998–2006 | 89,835 women of the Canadian National Breast Screening Study (CNBSS) | Cohort | PM2.5 | Satellite-based estimates of surface concentrations of PM2.5 | All types of stroke | Incidence |
| Hoffmann et al. [56] | Germany, 2008–2009 | 4433 subjects from the German Heinz Nixdorf Recall cohort | Cohort | PM2.5, PM10 | Land-use regression (LUR) models | All types of stroke | Incidence |
| Chen et al. [57] | Taiwan, 2006–2010 | 27,392 hospital admissions due to stroke | Case-crossover | PM2.5, PM10 | 6 air quality monitoring stations established in Kaohsiung city operated by the Taiwanese Environmental Protection Administration (EPA) | All types of stroke | Hospital admission |
| Amancio and Nascimento [58] | Brazil, 2005–2009 | 1,032 deaths due to stroke | Time-series | PM10, SO2 | A measuring station in downtown São José dos Campos | All types of stroke | Mortality |
| Chen et al. [59] | Taiwan, 2004–2008, | 12,982 ischemic, 3362 hemorrhagic stroke cases | Time-series | PM2.5 | The Sinjhuang Supersite located in the center of the Taipei metropolitan area | Hemorrhage, ischemic stroke | Hospital admission |
| Stafoggia et al. 2014 [60] | European, 2006–2010 | 99,446 study participants from 11 European Cohorts within the European Study of Cohorts for Air Pollution Effects (ESCAPE) Project | Cohort | PM2.5, PM10, NO2 | Land-use regression (LUR) models | All types of stroke | Incidence |
| Chiu et al. [61] | Taipei, Taiwan, 2006–2010 | 12,520 hemorrhagic stroke (HS) hospital admissions for the 47 hospitals | Case-crossover | PM2.5 | Air quality monitoring stations operated by the Taiwanese Environmental Protection Administration (EPA) | Hemorrhagic stroke | Hospital admission |
| Chen et al. [62] | 8 cities in China, 1996–2008 | 4820,000 subjects of 8 Chinese cities, approximately | Time-series | PM10, SO2, NO2 | 2–12 monitoring stations in each city operated by the Ministry of Environmental Protection of China | All types of stroke | Mortality |
| Carlsen et al. [63] | Reykjavík, Iceland, 2003–2010 | 24,439 emergency hospital admissions due to stroke | Time-series | PM10, NO2, O3 | The Environmental Branch of the Municipality of Reykjavik (2003–2010) | All types of stroke | Hospital admission |
| Reference | Study Location and period | Study population | Study design | Exposure | Exposure assessment method | Type of stroke | Outcome |
|-----------|--------------------------|-----------------|-------------|----------|---------------------------|----------------|---------|
| Johnson et al. [64] | Canada, 2007–2009 | 4,696 stroke (cases) and 37,723 injury patients (controls) | Case-crossover | NO₂ | Land-use regression (LUR) model for the city of Edmonton | All types of stroke | Hospital admission |
| Atkinson et al. [65] | England, 2003–2007 | 836,557 patients | Cohort | PM₁₀, NO₂, NOₓ, O₃ | Air dispersion models (1 × 1-km grids) | All types of stroke | Incidence |
| Xu et al. [66] | Pennsylvania, USA, 1994–2000 | 26,210 hospital admissions due to stroke | Case-crossover | O₃ | The repository of ambient air quality database of the US Environmental Protection Agency | All types of stroke | Hospital admission |
| Xiang et al. [67] | Wuhan, China, 2006–2008 | 10,663 stroke hospital admissions from 4 major hospitals | Case-crossover | PM₁₀, SO₂, NO₂ | 9 fixed-site stations operated by the Wuhan Environmental Monitoring Center | All types of stroke | Hospital admission |
| Yorifuji et al. [68] | Shizuoka, Japan, 1999–2009 | 14,001 elderly residents | Cohort | NO₂ | Land use regression (LUR) model | Hemorrhage, ischemic stroke | Mortality |
| Qian et al. [69] | Shanghai, China, 2003–2008 | 66,366 stroke deaths for adults aged over 65 | Case-crossover | PM₁₀, SO₂, NO₂ | 6 fixed-site stations operated by Shanghai Environmental Monitoring Center | All types of stroke | Mortality |
| Andersen et al. [70] | Denmark, 1971–2006 | 52,215 participants of the Danish Diet, Cancer and Health cohort | Cohort | NO₂ | The Danish geographic information system-based air pollution and human exposure modeling system | All types of stroke | Incidence, Mortality |
| Nascimento et al. [71] | São Paulo State, Brazil, 2007–2008 | 407 hospitalizations due to stroke | Time-series | PM₁₀, SO₂, O₃ | Measuring station of the São Paulo State Environmental Agency | All types of stroke | Hospital admission |
| O’Donnell et al. [72] | Canada, 2003–2008 | 9,202 patients hospitalized due to ischemic stroke | Case-crossover | PM₂.₅ | 19 monitoring stations in the vicinity of the 11 regional stroke centers participating in the Registry | Ischemic Stroke | Incidence |
| Lipsett et al. [73] | California, USA, 1996–2005, | 124,614 women living in California | Cohort | PM₂.₅, PM₁₀, SO₂, NO₂, CO, O₃ | Fixed-site monitors, inverse distance weighting (IDW) interpolation | All types of stroke | Incidence |
| Yorifuji et al. [68] | Tokyo, Japan, 2003–2008 | 41,440 deaths due to stroke | Time-series | PM₂.₅, NO₂ | 2 monitoring stations in Tokyo’s 23 wards | Hemorrhagic stroke | Mortality |
| Ren et al. [74] | Massachusetts, USA, 1995–2002 | 157,197 non-accident deaths aging 35 years or older | Case-crossover | O₃ | The Environmental Protection Agency, USA | All types of stroke | Mortality |
| Zanobetti and Schwartz [75] | USA, 1999–2005 | 330,613 deaths for stroke in 112 US cities | Time-series | PM₂.₅ | Air Quality System Technology Transfer Network | All types of stroke | Mortality |
| Kettunen et al. [76] | Helsinki, Finland, 1998–2004 | 3265 deaths due to stroke | Time-series | PM₂.₅, PM₁₀, NO₂, NOₓ, CO, O₃ | The Environmental Protection Agency, USA | All types of stroke | Mortality |
| Franklin et al. [77] | USA, 1997–2002 | 1310,781 deaths in 27 US communities | Case-crossover | PM₁₀ | National, State, and Local Ambient Monitoring Stations | All types of stroke | Mortality |
| Qian et al. [78] | Wuhan, China, 2001–2004 | 89,131 non-accidental death cases | Time-series | PM₁₀ | Wuhan Environmental Monitoring Center | All types of stroke | Mortality |
| Villeneuve et al. [79] | Edmonton, Canada, 1992–2002 | 12,422 stroke visits | Time-series | PM₂.₅, PM₁₀, SO₂, NO₂, CO, O₃ | Fixed-site monitoring stations maintained by Environment Canada | All types of stroke | Hospital admission |
test were less than 0.05. Publication bias of studies was remarkable in association of exposure to PM$_{2.5}$ and O$_3$ and stroke incidence according to funnel plots and Egger’s test. For PM$_{2.5}$ and stroke mortality, the $p$ value of Egger’s test was 0.009, suggesting publication bias may exist. Other publication bias test indicated that no substantial publication bias of studies was observed according to funnel plots, Begg’s test, and Egger’s test (Table S3, Figure S19-34). Sensitivity analysis showed that the relation of exposure to CO and stroke hospital admission might be influenced by Tian et al.’s study [10]. And the association between exposure to NO$_2$ and stroke incidence may be influenced by Dong et al.’s study [1]. The pooled OR of exposure to air pollution and stroke mortality might be influenced by some studies (PM$_{2.5}$: Wang et al.’s study [33]; O$_3$: Yin et al.’s study [37]). We recalculated the pooled OR/HR and 95% CI after removing those studies (Table S3). Due to limited studies after excluding those studies, the pooled estimated effects of SO$_2$ and stroke incidence and O$_3$ and stroke mortality were not recalculated. Other sensitivity analyses indicated that excluding each individual study did not change the results, suggesting the results of the meta-analysis were stable (Table S4, Figure S35-50). Sensitivity analyses by exposure period found that the pooled effect estimates were not changed significantly after excluding the long-term (cohort) studies (Table S5). Subgroup analysis suggested that both short-term and long-term exposure to air pollution would increase the risk of stroke incidence (PM$_{2.5}$, PM$_{10}$, and NO$_2$) and mortality (NO$_2$) (Table S6).

### Discussion

We conducted a systematic review and meta-analysis of 68 epidemiological studies and performed a comprehensive evaluation on exposure ambient air pollution and stroke, which were conducted from more than 23 million participants. Most studies suggested that exposure to a higher level of air pollution was associated with increased stroke risk. Meta-analysis showed that exposures to air pollutants were associated with increased risk of stroke hospital admission (PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO,

### Table 1 Descriptive summaries for all included studies (Continued)

| Reference | Study Location and period | Study population | Study design | Exposure | Exposure assessment method | Type of stroke | Outcome |
|-----------|--------------------------|------------------|-------------|----------|----------------------------|---------------|---------|
| Henrotin et al. [80] | Dijon, France, 1994–2004 | 1487 patients with ischemic stroke and 220 patients with hemorrhagic stroke | Case-crossover | PM$_{10}$, SO$_2$, CO, O$_3$ | The monitoring station located in the town center, Dijon | Hemorrhage, ischemic stroke | Incidence |
| Tsi et al. [81] | Kaohsiung, Taiwan, 1997–2000 | 23,179 hospital admissions due to stroke | Case-crossover | PM$_{10}$, SO$_2$, NO$_2$, CO, O$_3$ | 6 air-quality monitoring stations operated by the Environmental Protection Administration (EPA) | All types of stroke | Hospital admission |
| Yu et al. [14] | Seoul, Korea, 1991–1997 | 7137 ischemic deaths due to stroke | Time-series | SO$_2$, NO$_2$, CO, O$_3$ | 20 monitoring site and data operated by the Department of the Environment (Seoul) | Ischemic stroke | Mortality |

PM$_{2.5}$ particulate matter with aerodynamic diameter less than 2.5 μm, PM$_{10}$ particulate matter with aerodynamic diameter less than 10 μm, SO$_2$ sulfur dioxide, NO$_2$ nitrogen dioxide, CO carbon monoxide, O$_3$ ozone

| Table 2 Association between exposure to air pollution and stroke hospital admission (per 10 μg/m$^3$ increment) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Air pollution | Hospital admission | HR (95% CI) | Heterogeneity $I^2$ (%) | P |
| PM$_{2.5}$ | 19 | 1.008 (1.005, 1.011) | 96.6 | 0.000 |
| PM$_{10}$ | 15 | 1.004 (1.001, 1.006) | 92.7 | 0.000 |
| SO$_2$ | 13 | 1.013 (1.007, 1.020) | 94.5 | 0.000 |
| NO$_2$ | 15 | 1.023 (1.015, 1.030) | 92.6 | 0.000 |
| CO | 8 | 1.000 (1.000, 1.001) | 92.7 | 0.000 |
| O$_3$ | 15 | 1.002 (1.000, 1.003) | 80.2 | 0.000 |

HR hazard ratio, NO. number, PM$_{2.5}$ particulate matter with aerodynamic diameter less than 2.5 μm, PM$_{10}$ particulate matter with aerodynamic diameter less than 10 μm, SO$_2$ sulfur dioxide, NO$_2$ nitrogen dioxide, CO carbon monoxide, O$_3$ ozone

| Table 3 Association between exposure to air pollution and stroke incidence (per 10 μg/m$^3$ increment) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Air pollution | Incidence | NO. | OR (95% CI) | Heterogeneity $I^2$ (%) | P |
| PM$_{2.5}$ | 18 | 1.048 (1.020, 1.076) | 82.3 | 0.000 |
| PM$_{10}$ | 13 | 1.017 (0.981, 1.055) | 51.9 | 0.010 |
| SO$_2$ | 4 | 1.002 (1.000, 1.003) | 20.3 | 0.288 |
| NO$_2$ | 7 | 1.002 (1.000, 1.003) | 0.0 | 0.512 |
| CO | 5 | 0.999 (0.997, 1.001) | 0.0 | 0.763 |
| O$_3$ | 10 | 0.999 (0.999, 1.000) | 34.1 | 0.135 |

OR odds ratios, NO. number, PM$_{2.5}$ particulate matter with aerodynamic diameter less than 2.5 μm, PM$_{10}$ particulate matter with aerodynamic diameter less than 10 μm, SO$_2$ sulfur dioxide, NO$_2$ nitrogen dioxide, CO carbon monoxide, O$_3$ ozone
and $O_3$, incidence ($PM_{2.5}$, $SO_2$, and $NO_2$), and mortality ($PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, and $CO$). Although the high heterogeneity may reduce the credibility of the pooled evidence to some extent, the large number of studies included and the consistency of the results indicated that our conclusions were credible to some extent.

The positive associations between exposure to $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, $CO$, and $O_3$ and stroke hospital admission were observed in other meta-analysis. Yang et al. meta-analyzed 34 case-crossover and time series studies and reported significant associations for $PM_{10}$ (per 10 $\mu g/m^3$ increment: $RR = 1.007$, 95% CI 1.001, 1.013) and $O_3$ (per 10 ppb increment: $RR = 1.036$, 95% CI 1.016, 1.056), but non-significant association for $PM_{2.5}$, $SO_2$, $NO_2$, and $CO$ [15]. The meta-analysis performed by Yang et al. was not consistent with our current study completely, which might be caused by the different number of the included studies. To our knowledge, more than 16 studies have been published after 2014, and studies included in Yang et al.’s study were mainly conducted in Europe and North America. Data from more recent studies, especially low- and middle-income countries were not considered. Moreover, many studies conducted from the multi-city level and with large sample sizes have been published in recent years, which were more likely to find a significant association between air pollution and stroke hospital admission. For example, Tian et al. performed a time-series of more than 2 million hospital admissions for ischemic stroke in 172 cities in China and suggested that elevated incidence of ischemic stroke hospital admissions was associated with exposure to higher level of $PM_{2.5}$ ($RR = 1.003$, 95% CI 1.002, 1.005, per 10 $\mu g/m^3$ increment), $SO_2$ ($RR = 1.013$, 95% CI 1.011, 1.017, per 10 $\mu g/m^3$ increment), and $NO_2$ ($RR = 1.018$, 95% CI 1.015, 1.022, per 10 $\mu g/m^3$ increment) [24].

Three meta-analyses were conducted to examine the association between exposure to particulate matter ($PM_{2.5}$ and $PM_{10}$) and stroke incidence, whereas no meta-analysis of gas air pollutants was published before the current study. Li et al. performed a meta-analysis to explore the association between $PM_{10}$ and stroke incidence in time-series studies and case-crossover studies. These studies indicated that $PM_{10}$ was not associated with stroke incidence in the time-series design ($HR = 1.002$, 95% CI 0.999, 1.005, per 10 $\mu g/m^3$ increment), but significantly associated in case-crossover studies ($HR = 1.028$, 95% CI 1.001, 1.057, per 10 $\mu g/m^3$ increment). Meanwhile, $PM_{2.5}$ exposure was related to an increased risk of stroke incidence in time-series design ($HR = 1.006$, 95% CI 1.002, 1.010, per 10 $\mu g/m^3$ increment), but no significant association in case-crossover studies ($HR = 1.016$, 95% CI 0.937, 1.097, per 10 $\mu g/m^3$ increment) [16]. Only 12 studies published before 2010 were included in Li et al.’s study. We updated the literature search up to 2020, which generated more than 10 studies. Moreover, Li et al. separately analyzed the data from time-series and case-crossover studies, which would reduce the number of studies calculated the pooled estimates. These might explain the inconsistency in between our study and Li et al.’s study. Yu et al. updated the literature search before 2012 and identified 19 studies [19]. Yu et al. found that exposure to $PM_{10}$ was associated with an increased risk of stroke incidence ($HR = 1.004$, 95% CI 1.001, 1.008, per 10 $\mu g/m^3$ increment), but exposure to $PM_{2.5}$ was not significantly associated with stroke incidence ($HR = 0.999$, 95% CI 0.994, 1.003, per 10 $\mu g/m^3$ increment) [19]. The results of these published meta-analyses were not exactly the same as our study, which might be due to more than 15 studies published after Yu et al.’s study. Moreover, we conducted a meta-analysis of gas air pollutants and stroke incidence and found that exposure to a higher level of $SO_2$ and $NO_2$ was associated with higher risk of stroke incidence, which may fill the gap of meta-analysis of gas air pollutants and stroke incidence. We also found that compared to short-term exposure, long-term exposure to air pollution may be associated with a higher risk of stroke incidence ($PM_{2.5}$, $PM_{10}$, and $NO_2$), which may be explained by different pathophysiological pathways.

Studies investigating the association between exposure to air pollution and stroke mortality have been partly analyzed in two meta-analysis [15, 17]. Yang et al. evaluated the association between all 6 pollutants and suggested that stroke mortality increased 1.34% (95% CI 0.27, 2.42) per 10 $\mu g/m^3$ increase in $PM_{2.5}$, 0.65% (95% CI 0.54, 0.77) per 10 $\mu g/m^3$ increase in $PM_{10}$, 2.45% (95% CI 1.83, 3.07) per 10 parts per billion (ppb) increase in $SO_2$, 7.78% (95% CI 4.49, 11.60) per 1 ppm increase in $CO$, and 1.50% (95% CI 0.37, 2.63) per 10 ppb increase in $NO_2$, respectively [15]. Consistent with Yang et al.’s study, our meta-analysis also indicated that exposure to a higher level of $PM_{2.5}$, $PM_{10}$, $SO_2$, and $NO_2$
was related to higher risk of stroke mortality. No association was observed in both our study and Yang et al.’s study. However, Yang et al. reported a positive association in CO, whereas our study did not, which may be explained by the limited number of included studies. Scheers et al. performed a meta-analysis of exposure to PM$_{10}$ and stroke events (mortality and incidence) and suggested that exposure to PM$_{10}$ was positively associated with overall stroke events (mortality and incidence) (HR = 1.061, 95% CI 1.018, 1.105), but no significant association were observed in stroke mortality (HR = 1.080, 95% CI 0.992, 1.177) [17]. Inconsistency of Scheers et al.’s study and current study could be explained that Scheers et al.’s study included the studied estimated exposure to PM$_{10}$ from studies using PM$_{2.5}$, which may cause estimation bias to some extent.

Although accurate mechanisms of air pollution exposure and stroke remain unclear, several pathways including systemic inflammation, oxidative stress, thrombosis, and vascular endothelial dysfunction have been proposed [1, 9, 15, 82]. Vascular function injury may be central to mechanisms for air pollution-related stroke, which could lead to raised level of blood pressure and plasma viscosity [26]. It has been showed that exposure to air pollution was associated with increased thrombosis and vascular endothelial dysfunction by provoking oxidative stress and releasing systemic inflammatory cytokines [83]. Moreover, evidence also suggested that exposure to air pollution can lead to dysfunction of the autonomic system, which has been found as the major pathway that could result in air pollution-related adverse cardiovascular outcomes, such as stroke [84]. In addition, stroke status may aggravate the susceptibility of population to air pollution and increase the adverse cardiovascular effects of air pollution circularly [62].

A major strength of our meta-analysis is that our systematic review and meta-analysis covered six main air pollutants (PM$_{2.5}$, PM$_{10}$, NO$_2$, SO$_2$, CO, O$_3$) and a rich set of stroke outcomes (hospital admission, incidence, and mortality), which may be difficult to obtain from individual studies or isolated reviews or meta-analyses. However, some limitations should be acknowledged. Firstly, high heterogeneity existed in some meta-analysis, which may be due to different study designs, difference in exposure assessment method and population demographics, and the varied covariable adjustment strategies in different studies. Secondly, our study failed to perform the association between different subtypes of stroke (ischemic stroke, hemorrhagic stroke) and air pollution exposure separately because most included studies (48 out of 68 articles) did not report subtypes of stroke or results of ischemic stroke and hemorrhagic stroke specifically. Finally, the correlation between different air pollutants was not examined in our study because different air pollutants were controlled in different studies, and the results of those studies could not be pooled directly.

**Conclusion**

Our study demonstrated that exposure to air pollution was positively associated with an increased risk of stroke hospital admission (PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO, and O$_3$), incidence (PM$_{2.5}$, SO$_2$, and NO$_2$), and mortality (PM$_{2.5}$, PM$_{10}$, SO$_2$, and NO$_2$). Given the great global burden of stroke and air pollution, our findings could provide some scientific evidence to accurate prevention and treatment of stroke and air pollution exposure.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12199-021-00937-1.

**Additional file 1.**
Montresor-López JA, Yanosky JD, Mittleman MA, Sapkota A, He X, Hibbert JD, et al. Short-term exposure to ambient air pollution and risk of recurrent ischemic stroke. Environ Res. 2017;152:304–6. https://doi.org/10.1016/j.envpol.2016.06.033.

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