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# An evidence-based appraisal of global association between air pollution and risk of stroke

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ABSTRACT

*Background:* The aim of this study was to evaluate the transient effects of air pollutants on stroke morbidity and mortality using the meta-analytic approach.
*Methods:* Three databases were searched for case-crossover and time series studies assessing associations between daily increases in particles with diameter <2.5 μm ($PM_{2.5}$) and diameter <10 μm ($PM_{10}$), sulfur dioxide ($SO_2$), carbon monoxide (CO), nitrogen dioxide ($NO_2$), ozone, and risks of stroke hospitalizations and mortality. Risk estimates were combined using random-effects model.
*Results:* A total of 34 studies were included in the meta-analysis. Stroke hospitalizations or mortality increased 1.20% (95%CI: 0.22–2.18) per 10 μg/m$^3$ increase in $PM_{2.5}$, 0.58% (95%CI: 0.31–0.86) per 10 μg/m$^3$ increase in $PM_{10}$, 1.53% (95%CI: 0.66–2.41) per 10 parts per billion (ppb) increase in $SO_2$, 2.96% (95%CI: 0.70–5.27) per 1 ppm increase in CO, and 2.24% (95%CI: 1.16–3.33) per 10 ppb increase in $NO_2$. These positive associations were the strongest on the same day of exposure, and appeared to be more apparent for ischemic stroke (for all 4 gaseous pollutants) and among Asian countries (for all 6 pollutants). In addition, an elevated risk (2.45% per 10 ppb; 95%CI: 0.35–4.60) of ischemic stroke associated with ozone was found, but not for hemorrhagic stroke.
*Conclusion:* Our study indicates that air pollution may transiently increase the risk of stroke hospitalizations and stroke mortality. Although with a weak association, these findings if validated may be of both clinical and public health importance given the great global burden of stroke and air pollution.
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## 1. Introduction

According to a 2004 report released by World Health Organization, stroke is a leading cause of death and disability globally, which accounts for approximately 5.5 million deaths every year representing nearly 10% of all deaths; while 44 million disability-adjusted life-years are lost annually due to stroke. Therefore, the primary prevention efforts toward stroke should be explored given the great stroke burden in terms of mortality and disability worldwide [1].

Currently, there is increasing evidence of an association between acute exposure to air pollution and elevated risk of cardiovascular disease morbidity as well as mortality [2,3]. In particular, American Heart Association (AHA) concluded that the evidence of fine particles (diameter < 2.5 μm, $PM_{2.5}$) exposure as a causal risk factor for cardiovascular morbidity and mortality is sufficient in their 2010 scientific statement [4], in which the conclusion was drawn on the basis of a comprehensive review of current evidence.

However, the AHA statement is specifically designed as hazard identification, and it does not quantify the magnitude of the stroke risk associated with particulate pollutants. In addition, results from observational studies assessing transient effects of other pollutants have been inconclusive [2], varying from a positive to a null association, which mainly hampered by the lack of power of any individual study [5–38]. Moreover, most previous air pollution studies only focused on stroke in general, few studies have distinguished between ischemic and hemorrhagic strokes and have yielded inconsistent results [7,12,17,23,26,28,31,34], which also could be, at least in part, explained by the limited power for single study; however, this issue is important because there may be major differences in the underlying mechanisms that may trigger ischemic stroke compared to hemorrhagic stroke [12,15,39].

On the other hand, given the limited number of studies that evaluated the shape of concentration–response function between air pollution and stroke among different pollution settings [8,10,31,32], the open questions about the differences in ambient air pollution–stroke association between low and high pollution settings still remained. On a global scale, quantifying the evidence by different regions characterized by various pollution levels, for example, most Asian countries such as China and Korea (characterized as high pollution settings) vs. European

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countries and USA (characterized as low pollution settings), using the meta-analytic technique, would help us to better understand this issue.

We therefore conduct a systematic review and meta-analysis of case-crossover and time series studies to quantitatively assess the transient acute effects of air pollutants including $PM_{2.5}$, inhalable particles (diameter < 10 μm, $PM_{10}$), sulfur dioxide ($SO_2$), carbon monoxide (CO), nitrogen dioxide ($NO_2$), and ozone ($O_3$) on stroke hospitalization and stroke mortality. Here, the "transient acute effect" means the immediate change in the risk of acute-onset stroke hospitalization or mortality due to short-term exposure to air pollution [40]. We also conducted a secondary analysis by stroke subtypes (ischemic vs. hemorrhagic strokes), geographic locations (Asian countries vs. European countries and USA), and other characteristics of interests.

## 2. Methods

### 2.1. Search strategy

We searched Medline (PubMed), Embase, and Web of Science from their inception to October 2013 and systematically identified case-crossover and time series studies that evaluated the transient effect of air pollution on the risk of stroke hospitalization and mortality. No language restriction was applied. The search strategy included terms for outcome (stroke, cerebrovascular diseases, ischemic stroke, and hemorrhagic stroke), exposure (air pollution, particulate matter, sulfur dioxide, carbon monoxide, nitrogen dioxide, and ozone), and study design (case-crossover studies and time series studies). The reference lists of the retrieved original peer-review articles as well as pertinent review articles were also scanned to identify any additional relevant studies.

### 2.2. Study selection and data extraction

A published article was included if it 1) had a case-crossover or time series design, 2) evaluated the transient acute association between gaseous (carbon monoxide, sulfur dioxide, nitrogen dioxide, ozone) or particulate ($PM_{2.5}$ or $PM_{10}$) air pollutants and stroke hospitalization or mortality, and 3) presented odds ratio (OR), relative risk (RR) with its 95% confidence interval (CI) or standard error. If an article was duplicated, or derived from the same population as previously published and presented risk estimates for the same pollutants, the most recent publication was included.

Using a unified data form, two investigators (W.S.Y. and W.Y. W.) independently evaluated study eligibility and conducted data extraction; discrepancies were settled by consensus or by involving a third reviewer (W.Y.F.) for adjudication. Relevant variables included in the data form were as follows: study name (together with the first author's name and year of publication), study region, study periods, study design, number of cases, outcome measurement, and adjustments. If any of the above-mentioned data was not available in the articles, the first or corresponding authors were contacted by email for additional information.

### 2.3. Quality assessment

There is, to our knowledge, no validated scale to evaluate methodological quality for studies with case-crossover or time series design, we thus adapted a quality scale from validated scales for other types of observational studies (e.g. cohort and case-control designs) and particularly selected several items from the Newcastle–Ottawa Scale (NOS) [41] and the Cochrane risk of bias tool [42], and this method was also suggested by Mustafic et al. [43]. We created a 6-point scoring system, in which a study was judged on 4 broad perspectives as follows: 1) the quality of air pollutant assessments, 2) the validation of stroke data, 3) the extent of adjustment for potential confounders, and 4) the generalizability of the findings.

For the quality of air pollutant assessments [43], studies received 1 point if measurements were performed at least daily with <25% missing data; whereas those with ≥25% missing data and/or with measurement frequency <1 time per day received no point.

For the validation of stroke data, studies were assigned one point if the outcome of interest was coded based on the International Classification of Diseases or according to medical records, while no point was given for the absence of the above 2 criteria.

For the extent of adjustment for potential confounders [43], studies received no point if no adjustment has been made for long term trends, seasonality, or temperature; studies can be given one point if the above 3 adjustments had been done; those that also adjusted for humidity and/or day of week received an additional 1 point; those that adjusted for holidays and/or influenza epidemics together with the adjustments corresponding with a score of 2, can be assigned a full score of 3.

For the generalizability of the findings [41,42], we considered the results to be applicable and assigned one point if the stroke cases in the study should be all eligible stroke cases over a defined period of time, and in a defined catchment area or in a defined hospital or clinic, group of hospitals, health maintenance organization, or an appropriate sample of those cases (e.g. randomly selected). No point was given if not satisfying the above requirements in part, or not stated.

Studies were judged to be of good quality if they obtained the full score for all the 4 components; studies were considered to be of low quality if any component from the above 4 components received zero point; all other studies were deemed to be of intermediate quality [43].

### 2.4. Data synthesis

The RRs were used as the common measure of association across studies, and the ORs from case-crossover studies were considered equivalent to RRs in time series studies [44,45]. Time series analysis is the most commonly used technique to assess what fraction of the daily variations in counts of hospital admissions/deaths due to the daily variations in air pollution of the preceding days through relative risk regression analysis accounting for variables that varied in time such as meteorological parameters, but are less effective control for secular trends such as seasonal effects [46]. Because the unit of observation in time series studies is the day but not the individual, usual risk factors for stroke (e.g. smoking, diabetes, or hypertension) do not vary in the short-term time window analyzed with air pollution daily variations, can thus be excluded as confounders.

The case-crossover design is considered to be an alternative to time series analysis, in which cases serve as their own controls, and risk estimates are based on comparisons of exposure in a case period when the event occurred with exposure in specified control periods through matched case–control methods [40]. The case-crossover design can thus control for individual characteristics such as age, sex, socioeconomic status, smoking, and comorbidity fixed. Also, through choosing the control period within a few weeks of outcome, this approach decreased any potential confounding role of the long-term time trends, seasonality, and day of week. Overall, both time series and case-crossover designs can provide reasonable estimates of transient effect (i.e. an immediate change in risk) of short-term exposure to elevated concentrations of ambient air pollutants on an acute-onset disease outcome [45], although risk estimates that obtained from case-crossover approach is less precise (with wider confidence intervals) than those in time series design [45].

Because most of the included studies used generalized linear models and assumed a linear relationship between air pollution and outcome, and the current available studies with exposure-response analysis also supported a linear shape for stroke [8,10,31,32], we therefore firstly created a standardized increment in pollutant concentration as follows: 10 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10}$, 10 parts per billion (ppb) for $NO_2$, $SO_2$, and $O_3$, and 1 part per million (ppm) for CO. The reason for choosing the above values as the standardized increments to present risk estimates is that these levels were most frequently used in previous air pollution studies. Secondly, we recalculated the risk estimates for the standardized increment for each pollutant for every included study using the following formula:

$$RR_{standardized} = e^{\left(\frac{Ln\left(RR_{origin}\right)}{Increment_{origin}} \times Increment_{standardized}\right)}$$

where RR is the relative risk, and Ln is the log to base e. In the third stage, we combined the recalculated study-specific RR using random-effects model [47]. Heterogeneity within the studies was evaluated using Cochran's Q and $I^2$ statistics, and the null hypothesis that the studies are homogeneous was rejected if the $p$ value for heterogeneity was less than 0.10 [48] or the $I^2$ value was >50%. Publication bias was evaluated using Begg's rank correlation method [49]. We also performed a meta-regression analysis to investigate the sources of heterogeneity according to study level characteristics, including sex, study population, study design, stroke subtype, and adjustment for confounding factors.

Subgroup analysis was conducted by study design (time series vs. case-crossover studies), geographical location (Asia vs. Europe and North America), and stroke subtype (ischemic vs. hemorrhagic stroke). Population-attributable risks (PARs) per pollutant were also estimated using our overall risk estimates and the following equation: $PAR\% = 100 \times P_e(RR - 1) / (P_e[RR - 1] + 1)$, for which $P_e$ is the prevalence of the exposure (air pollution) in the population and is assumed to be 100%.

We combined adjusted risk estimates that controlled for meteorological, temporal, and seasonal parameters for every included study. Most of the included studies provided multiple estimates for single lags (e.g. lag 0, lag 1, and lag 2). In this case, the shortest lag was used in our overall analysis. We also combined the risk estimates according to different lags including lag 0, lag 1, and lag 2 for each pollutant. Some studies separated risk estimates according to season (cold vs. warm season) [20,21] or temperature [28], study region [14], and stroke subtype [17,20,22,23,26], and did not report overall risk estimates. In this case, the stratified estimates were included in our analysis. Several studies [8,9,16,27–30,35] only provided cumulative lags such as lag 0-1, lag 0-2, and lag 0-3. In this case, we only included these in the overall analysis, but not for the single lag analysis.

All data analyses were carried out using R 2.15.3 (meta 3.1-2) (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### 3.1. Literature search and study characteristics

A flow diagram of the literature search strategy employed in the present study is shown in Fig. 1. A total of 34 studies that consisted of 20 time series [8,9,11,15,18,19,21,24,25,27,29–38] and 14 case-crossover [5–7,10,12–14,16,17,20,22,23,26,28] studies were included in the final analysis.

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