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Systematic Review/Meta-analysis

Association Between Air Pollution Exposure and Risk of Hemorrhagic Stroke: A Systematic Review and Meta-analysis

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See editorial by Kurasz et al., pages 1943-1944 of this issue.

ABSTRACT

Background: Air pollution has been associated with multisystem health adversities. However, the association between short-term air pollution and hemorrhagic stroke has not been sufficiently evaluated in recent years. Considering that hemorrhagic stroke has a high incidence rate (28.8% of incident strokes) and accounts for almost 7.2 million deaths per year globally, it is important to identify risk factors and use it to guide preventative measures.

Methods: A systematic search was conducted on 4 databases (Embase, OVID Medline, Web of Science, PubMed). Studies selected for review included time series, case-crossover, and cohort studies, published in English, from all time periods, and investigated the risk of hemorrhagic stroke after exposure to air pollution (particulate matter $\leq$ 2.5 μm in diameter [$PM_{2.5}$], particulate matter $\leq$ 10 μm in diameter [PM_{10}], nitrogen dioxide [NO_2], sulfur dioxide [SO_2], ozone [O_3], or carbon monoxide [CO]). Data for different risk outcomes (risk ratio, odds ratio) were meta-analyzed using an inverse variance statistical analysis and random effects model.

Results: Among the 2435 studies identified, 31 were included and deemed eligible for review and meta-analysis. The results illustrated a

RÉSUMÉ

Contexte : La pollution atmosphérique est associée à des effets néfastes sur la santé en général. Le lien entre la pollution atmosphérique à court terme et l'accident vasculaire cérébrale (AVC) hémorragique n'a toutefois pas été suffisamment étudié ces dernières années. Étant donné la fréquence élevée de l'AVC hémorragique (il représente 28,8 % des nouveaux cas d'AVC) et sachant qu'il est la cause de près de 7,2 millions de décès par an dans le monde, il est important d'en connaître les facteurs de risque et de les utiliser pour orienter les mesures de prévention.

Méthodologie : Nous avons réalisé une recherche systématique dans quatre bases de données (Embase, OVID Medline, Web of Science, PubMed). Les études retenues comprenaient des séries temporelles, des études de cas croisées et des études de cohorte, en anglais et sans égard à la période de temps, portant sur le risque d'AVC hémorragique après exposition à des polluants atmosphériques ($PM_{2,5}$, PM_{10}, NO_2, SO_2, O_3 ou CO). Les données relatives au risque (rapport de risques [RR], rapport de cotes [RC]) ont été soumises à une méta-analyse reposant sur une analyse statistique par variance inverse et un modèle à effets aléatoires.

Keywords: hemorrhagic stroke; air pollution; intracerebral hemorrhage; subarachnoid hemorrhage; stroke risk; cardiovascular health; cerebrovascular health

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See page 2207 for disclosure information.

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Air pollution is a mixture of hazardous particles and gaseous contaminants released into the atmosphere from natural and anthropogenic sources.[1] Common sources include power generation facilities, forest fires, and traffic-related and industrial emissions.[2] These air pollution sources, along with many others, are associated with approximately 4.2 million premature deaths annually.[3]

Common air pollutants include but are not limited to: particulate matter $\leq$ 10 μm in diameter (PM_{10}), fine particulate matter $\leq$ 2.5 μm in diameter ($PM_{2.5}$), nitrogen

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statistically significant increase in the risk of hemorrhagic stroke per 10 μg/m^3 increase in NO_2 exposure (risk ratio, 1.0142; 95% confidence interval, 1.0000-1.0286; $P = 0.05$), and CO exposure (odds ratio, 1.0008; 95% confidence interval, 1.0000-1.0016; $P = 0.05$).
Conclusions: Among the 6 air pollutants studied, NO_2 and CO exposure was associated with a statistically significant increase in the risk of hemorrhagic stroke. This can help guide effective preventative protocols and public health measures in an effort to reduce the burden of cardiovascular and cerebrovascular disease.

Résultats : Parmi les 2 435 études trouvées, 31 ont été incluses et jugées admissibles à l'examen et à la méta-analyse. Les résultats ont mis en évidence une augmentation statistiquement significative du risque d'AVC hémorragique par 10 μg/m^3 d'augmentation de l'exposition au NO_2 (RR = 1,0142; intervalle de confiance [IC] à 95 % : 1,0000 à 1,0286; $p = 0,05$) et au CO (RC = 1,0008; IC à 95 % : 1,0000 à 1,0016; $p = 0,05$).
Conclusions : Parmi les six polluants atmosphériques étudiés, l'exposition au NO_2 et au CO a été associée à une augmentation statistiquement significative du risque d'AVC hémorragique. Ces connaissances peuvent contribuer à orienter la mise en place de protocoles de prévention et de mesures de santé publique efficaces visant à réduire le fardeau des maladies cardiovasculaires et vasculaires cérébrales.

dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO).[4] Particulate matter consists of small solid and liquid particles suspended in the air, containing organic and nonorganic compounds.[5] Common sources include dust from roads, mining and construction sites, and byproducts of fossil fuel combustion.[6] Gaseous air pollutants include NO_2, SO_2, O_3, and CO, and are commonly emitted from vehicle exhausts, power plants, industrial processes, and wildfires.[7]

The primary mode of entry of air pollution is inhalation, which leads to inflammation in the respiratory tract.[8] Air pollutants might also translocate across the alveolar-capillary membrane into the vasculature, contributing to systemic inflammatory effects.[9] Previous literature has shown that air pollutants are associated with elevated levels of proinflammatory proteins, such as C-reactive protein and interleukin-6, as well as decreased levels of regulatory, anti-inflammatory proteins, such as adiponectin.[10] This suggests that ambient air pollutants can impair physiological defense mechanisms and contribute to multisystem health adversities, including respiratory and cardiovascular disease.[11]

Hemorrhagic stroke—internal bleeding in the brain due to the rupture of a blood vessel—is of particular concern because it has a high incidence rate (28.8% of incident strokes) and accounts for almost 7.2 million deaths annually.[12,13] There are 2 types of hemorrhagic stroke: intracerebral hemorrhage—a hematoma in the parenchyma which can extend into the ventricles—and subarachnoid hemorrhage—an accumulation of blood in the subarachnoid space.[14,15] Intracerebral hemorrhage is associated with high morbidity and mortality due to its rapidly progressive nature, inducing neurologic deterioration, and potential sudden loss of consciousness.[14] Considering hemorrhage stroke's high burden of disease, it is important to identify risk factors and use them to guide preventative measures.[13]

The main risk factors for hemorrhagic stroke include: alcohol, smoking, hypertension, substance abuse, and pregnancy.[12] Although air pollution as a risk factor for other cardiovascular diseases—such as myocardial infarction and ischemic stroke—has been extensively studied, the risk of hemorrhagic stroke associated with air pollution has not been sufficiently evaluated.[16-19] As such, the primary objective of this study was to conduct a comprehensive, up-to-date meta-analysis to assess the effect of air pollution exposure on the risk of hemorrhagic stroke.

Methods

Search strategy

A systematic literature search was conducted on March 10, 2025 of the Embase, OVID Medline, Web of Science, and PubMed databases using detailed search terms, "hemorrhagic stroke", "intracerebral hemorrhage", "subarachnoid hemorrhage", "air pollution", "particulate matter", "carbon monoxide", "sulfur dioxide", "nitrogen dioxide", and "ozone". The detailed search strategy is outlined in Supplemental Table S1. No limitations on publication year were implemented. Our study protocol was registered on PROSPERO (CRD420251031712) on April 13, 2025, after completion of the literature search; this delayed registration is reported herein for transparency.

Primary outcome measure

The primary outcome measure was hemorrhagic stroke risk, measured according to risk ratio (RR) or odds ratio (OR). Risk was standardized, when possible, to a pollutant concentration increment of 10 μg/m^3 for $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO. Risk was also evaluated on the basis of a 10 parts per billion (ppb) increment in pollutant concentrations for NO_2, SO_2, O_3, and CO. For the primary analysis, risk outcomes from the shortest reported lag were used to grasp the short-term effects of air pollution. Hemorrhagic stroke risk was stratified according to risk scale (RR, OR), air pollutant exposure, and concentration increment (10 μg/m^3, 10 ppb).[20]

Study selection

The inclusion criteria included: (1) time series, case-crossover, or cohort study designs; (2) studies published in English; (3) exposure to at least 1 of the following air pollutants: $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, or CO; and (4) risk of hemorrhagic stroke as an outcome.

The exclusion criteria included: (1) participants with a previous history of stroke; and (2) studies in which hemorrhagic stroke mortality, rather than incident events, was the outcome. Mortality was excluded because incidence/admission and mortality reflect related but distinct outcomes with different determinants, although this decision might reduce the capture of fatal events that occurred before hospital presentation.

Screening was conducted using the online program, Covidence.[21] **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) guidelines were followed during this process.[22] Two authors (K.W. and M.Z.) independently screened candidate studies for inclusion and exclusion criteria. Discrepancies were evaluated by 2 different authors (K.S. and S.A.I.). Full-text screening was performed independently by 4 authors (K.S., K.W., M.Z., and S.A.I.), and any conflicts were resolved by discussion with the same 2 authors (K.S. and S.A.I.).

Data extraction

Two authors (K.S. and S.A.I.) independently extracted the following data from eligible studies: study name, design, country, air pollutant(s) analyzed, risk value and 95% confidence intervals, exposure increment of the risk value, lag (time delay between exposure and outcome), sample size, male:female ratio, and risk scale. The most short-term, available lag risk data (eg, lag0 values) were extracted from each study in an effort to minimize the time other confounding variables could have a potential influence on the outcome. The same 2 authors (K.S. and S.A.I.) checked for discrepancies, but none existed.

Risk of bias assessment

Two authors (K.S. and S.A.I.) independently assessed the included studies using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[23] Studies were classified as good if all applicable criteria were met, fair if 1 criterion was rated insufficient, and poor if 2 or more criteria were rated insufficient. However, these overall ratings were interpreted cautiously because the tool might be less sensitive to heterogeneity in exposure assessment methods and covariate adjustment strategies across short-term air pollution studies. Any conflicts were resolved with consensus by the same 2 authors (K.S. and S.A.I.).

Data synthesis

Meta-analysis was conducted using Review Manager version 5.4.1 (The Cochrane Collaboration, London, England). The pooled risk outcome was evaluated only when 2 or more studies used the same risk scale, air pollutant exposure, and pollutant concentration increment. If risk values were reported with interquartile range (IQR) exposure increments, they were converted to 10 $\mu g/m^3$ using the following formula: $\text{Risk value}_{10\ \mu g/m3} = \exp((\ln(\text{Risk value}_{\text{IQR }\mu g/m3\ \text{increment}})) \times 10\ \mu g/m^3$ increment / IQR $\mu g/m^3$ increment). Substantial heterogeneity was considered to be $I^2 > 75\%$. An inverse variance statistical analysis with a random-effects model was used for forest plots. Effect sizes were reported to 4 decimal places to preserve computational precision and ensure reproducibility of results derived from the statistical model. Publication bias was assessed using funnel plot symmetry for all outcomes, except those with fewer than 5 studies, because of poor statistical power.

Quality of evidence assessment

Two authors (K.S. and S.A.I.) independently conducted a quality of evidence assessment using Cochrane's Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Because we synthesized observational studies in this review, certainty was considered to begin at low because of the inherent risk of bias and confounding. Upgrading was considered only when prespecified GRADE criteria were met for large magnitude of effect, dose-response gradient, and residual confounding, whereas downgrading was considered for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Any conflicts were resolved through discussion among the same 2 authors (K.S. and S.A.I.).

Results

Study selection

A summary of study identification and screening is available in the PRISMA chart (Fig. 1). A literature search was conducted in the databases Web of Science, Embase, PubMed, and MEDLINE, which yielded 2435 studies. Among these, 1709 duplicates were removed. In total, 726 studies were screened in the abstract screening phase, and 105 were assessed in the full-text screening. Seventy-four studies were removed for the following reasons: wrong outcomes (n = 40), wrong study design (n = 23), full-text not available in English (n = 6), and lack of clarity regarding previous strokes (n = 5). Thirty-one studies were deemed eligible for meta-analysis.

Study characteristics

Table 1 shows the characteristics of the studies included in the meta-analysis.

Study design characteristics. Among the 31 studies included in the systematic review and meta-analysis, 22 (71%) used a case-crossover design, 7 (22.6%) a time-series design, and 2 (6.4%) an observational cohort design. Among these, 15 studies (48.4%) used RR as their effect size for hemorrhagic stroke risk outcome measure, and the other 16 studies (51.6%) used OR.

Participant characteristics. To synthesize qualitative findings, data were used from 585,692 participants. Six studies did not report the male:female participant ratio.[24-29] Among the 554,542 participants in the other studies, 332,144 (59.9%) were male, and 222,398 (40.1%) were female. With regard to the geographic distribution of data, 22 studies (71%) gathered data from participants in China, 3 studies (9.7%) from South Korea, 3 studies (9.7%) from the United States, 2 studies (6.4%) from Taiwan, 1 study (3.2%) from Poland, 1 study (3.2%) from Japan, and 1 study (3.2%) from Canada.

Methodological risk of bias analysis and quality of evidence assessment

Using the prespecified NHLBI approach, all included studies were classified as "good" quality because they met the applicable criteria (Supplemental Table S2). However, this

should be interpreted cautiously rather than as an absence of bias, because important differences remained across studies in exposure assessment, lag specification, and adjustment for key confounders such as temperature, seasonality, and co-pollutants, which are not comprehensively addressed by the NHLBI tool.

The quality of evidence assessment was conducted using the GRADE approach and is shown in Supplemental Tables S3-S18. Among the 16 meta-analyses conducted, 10 were deemed to be of low quality and 6 were of very low quality. The top reasons for downgrading included inconsistency (n = 3) and publication bias (n = 4).

Hemorrhagic stroke risk outcomes

Table 2 shows a summary of the risk outcomes for air pollution and hemorrhagic stroke. This review showed that there is an increased risk of hemorrhagic stroke per 10 μg/m^3 increase in NO_2 exposure (RR, 1.0142; 95% confidence interval [CI], 1.0000-1.0286; P = 0.05) and CO exposure (OR, 1.0008; 95% CI, 1.0000-1.0016; P = 0.05). The other air pollutants had a statistically insignificant (P > 0.05) increase in risk as follows: $PM_{2.5}$ (OR, 1.0172; RR, 1.0002), PM_{10} (OR, 1.0076; RR, 1.0008), SO_2 (RR, 1.0060), O_3 (OR, 1.0024; RR, 1.0017), CO (OR, 1.0008; RR, 1.0001). With the exception of SO_2, the risk outcomes for 10 ppb exposure increments also had a statistically insignificant increase in risk: NO_2 (OR, 1.0634), CO (OR, 1.0017), SO_2 (OR, 0.9928), and O_3 (OR, 1.0131).

$PM_{2.5}$ - Risk Ratio (10 μg/m^3 exposure interval). Ten studies (n = 413,578) reported RR for a 10 μg/m^3 exposure interval, with Guo et al.,[30] Liu et al.,[31] Liu et al.,[32] Lv et al.,[33] Wu et al.,[34] and Zhao et al.,[35] who reported an increased risk of hemorrhagic stroke, and Ban et al.,[36] Jin et al.,[37] and Weng et al.,[38] who reported a reduced risk. Liu et al.[39] reported a null effect. There was an overall increased risk of hemorrhagic stroke (RR, 1.00; 95% CI, 0.9985-1.0018; I^2 = 20%), but it was not statistically significant (P = 0.85; Supplemental Fig. S1). The quality of evidence was rated low on the GRADE scale (Supplemental Table S3).

PM_{10} - Risk Ratio (10 μg/m^3 exposure interval). Ten studies (n = 336,687) reported RR for a 10 μg/m^3 exposure interval, with Czernych et al.,[40] Han et al.,[41] Han et al.,[42] Liu et al.,[43] Liu et al.,[31] Lv et al.,[33] Weng et al.,[38] Wu et al.,[34] and Zhao et al.,[35] who reported an increased risk of hemorrhagic stroke, and Liu et al.,[43] who reported a reduced risk. There was an overall increased risk of hemorrhagic stroke (RR, 1.0008; 95% CI, 0.9990-1.0025; I^2 = 49%), but it was not statistically significant (P = 0.39; Supplemental Fig. S2). The quality of evidence was rated very low on the GRADE scale because of publication bias (Supplemental Table S4).

NO_2 - Risk Ratio (10 μg/m^3 exposure interval). Seven studies (n = 122,602) reported RR for a 10 μg/m^3 exposure interval: Czernych et al.,[40] Guo et al.,[30] Han et al.,[41] Liu et al.,[43] Liu et al.,[32] and Lv et al.,[33] who reported an increased risk of hemorrhagic stroke, and Weng et al.[38] who reported a decreased risk. There was an overall increased risk of hemorrhagic stroke (RR, 1.0142; 95% CI, 1.0000-1.0286; I^2 = 71%), and it was statistically significant (P = 0.05; Fig. 2). The quality of evidence was rated low on the GRADE scale (Supplemental Table S5).

CO - Risk Ratio (10 μg/m^3 exposure interval). Four studies (n = 107,500) reported RR for a 10 μg/m^3 exposure interval, with Czernych et al.,[39] Liu et al.,[32] and Lv et al.,[33] who report an increased risk of hemorrhagic stroke, and Liu et al.,[43] who reported a reduced risk. There was an overall increased risk of hemorrhagic stroke (RR, 1.0001; 95% CI, 0.9997-1.0005; I^2 = 62%), but it was not statistically significant (P = 0.53; Supplemental Fig. S3). The quality of evidence was rated low on the GRADE scale (Supplemental Table S6).

SO_2 - Risk Ratio (10 μg/m^3 exposure interval). Six studies (n = 119,555) reported RR for a 10 μg/m^3 exposure interval, with Czernych et al.,[40] Liu et al.,[43] Liu et al.,[32] Lv et al.,[33] and Shen et al.,[27] who reported an increased risk of hemorrhagic stroke, and Weng et al.,[38] who reported a reduced risk. There was an overall increased risk of hemorrhagic stroke (RR, 1.0060; 95% CI, 0.9983-1.0138; I^2 = 43%), but it was not statistically significant (P = 0.13; Supplemental Fig. S4). The quality of evidence was rated low on the GRADE scale (Supplemental Table S7).

O_3 - Risk Ratio (10 μg/m^3 exposure interval). Five studies (n = 117,261) reported RR for a 10 μg/m^3 exposure interval, with Guo et al.,[30] Liu et al.,[43] and Weng et al.,[38] who reported an increased risk of hemorrhagic stroke, and Liu et al.[32] and Lv et al.,[33] who reported a reduced risk. There was an overall increased risk of hemorrhagic stroke (RR, 1.0017; 95% CI, 0.9975-1.0060; I^2 = 31%), but it was not statistically significant (P = 0.43; Supplemental Fig. S5). The quality of evidence was rated low on the GRADE scale (Supplemental Table S8).

$PM_{2.5}$ - Odds Ratio (10 μg/m^3 exposure interval). Ten studies (n = 99,780) reported ORs for a 10 μg/m^3 exposure interval, with Chiu et al.,[24] Huang et al.,[44] Huang et al.,[25] and Sun et al.,[45] who reported an increased risk of hemorrhagic stroke, and Fisher et al.,[46] Li et al.,[47] Villeneuve et al.,[48] Wang et al.,[49] Wang et al.,[50] and Zheng et al.,[51] who reported a reduced risk. Overall, there was a statistically insignificant increase in the risk of hemorrhagic stroke (OR, 1.0172; 95% CI, 0.9918-1.0431; P = 0.19; I^2 = 90%; Supplemental Fig. S6). The quality of evidence was rated very low on the GRADE scale because of inconsistency (Supplemental Table S9).

PM_{10} - Odds Ratio (10 μg/m^3 exposure interval). Twelve studies (n = 98,750) reported ORs for a 10 μg/m^3 exposure interval, with Huang et al.,[44] Sun et al.,[45] Tsai et al.,[28] Villeneuve et al.,[48] and Zhong et al.,[29] who reported an increased risk of hemorrhagic stroke, and Fisher et al.,[46] Kim et al.,[26] Li et al.,[47] Wang et al.,[49] Wang et al.,[50] Xiang et al.,[52] and Zheng et al.,[51] who reported a reduced risk. Overall, there was a statistically insignificant increase in the risk of hemorrhagic stroke (OR, 1.0076; 95% CI, 0.9957-1.0196; P = 0.21; I^2 = 82%;

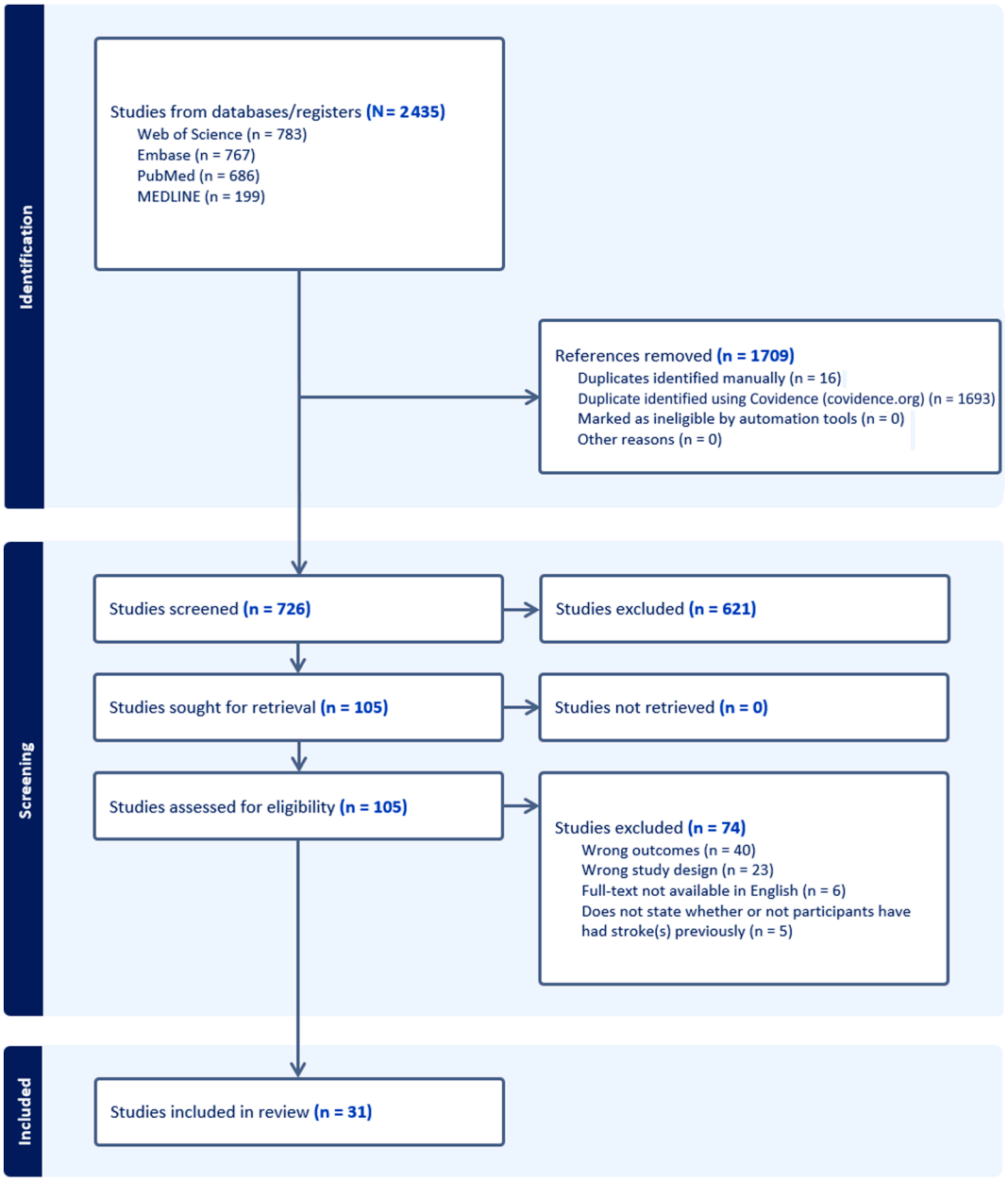


Figure 1. **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) flow diagram.

Supplemental Fig. S7). The quality of evidence was rated very low on the GRADE scale because of inconsistency (Supplemental Table S10).

NO_2 - Odds Ratio (10 μg/m^3 exposure interval). Five studies (n = 44,297) reported ORs for a 10 μg/m^3 exposure interval, with Zhong et al.,[29] who reported an increased risk of hemorrhagic stroke, and Li et al.,[47] Wang et al.,[49] Wang et al.,[50] and Xiang et al.,[52] who reported a reduced risk. Overall, there was a reduced risk of hemorrhagic stroke (OR, 0.9853; 95% CI, 0.9685-1.0024; I^2 = 4%), but this was not statistically significant (P = 0.09; Supplemental Fig. S8). The quality of evidence was rated low on the GRADE scale (Supplemental Table S11).

CO - Odds Ratio (10 μg/m^3 exposure interval). Three studies (n = 41,651) reported ORs for a 10 μg/m^3 exposure interval, with Li et al.,[47] who reported an increased risk of hemorrhagic stroke, and Wang et al.[49] and Wang et al.,[50] who reported a reduced risk. Overall, there was an increased risk of hemorrhagic stroke (OR, 1.0008; 95% CI, 1.0000-1.0016; I^2 = 0%), and it was statistically significant (P = 0.05; Fig. 3). The quality of evidence was rated low on the GRADE scale (Supplemental Table S12).

SO_2 - Odds Ratio (10 μg/m^3 exposure interval). Five studies (n = 44,297) reported ORs for a 10 μg/m^3 exposure interval, with Wang et al.[49] and Zhong et al.,[29] who reported an increased risk of hemorrhagic stroke, and Li et al.,[47] Wang

Table 1. Summary of study characteristics

Reference	Study design	Air pollutant	Exposure (increments in $\mu g/m^3$)	Lag (time delay)	Risk scale (ie, RR or OR)	Country	Sample size, n	Male sex, n (%)
Ban et al.[36]	Case-crossover	$PM_{2.5}$	10 $\mu g/m^3$	Lag0 (same day)	RR	China	19,100	10,254 (53.7%)
Chiu et al.[24]	Case-crossover	$PM_{2.5}$	IQR, 17.46 $\mu g/m^3$	Lag0-2 (3-day average)	OR	Taiwan	12,520	NR
Czernych et al.[40]	Time series	NO_2	IQR, 14.62 $\mu g/m^3$	Lag0 (same day)	RR	Poland	4542	2767 (61%)
		CO	IQR, 164.04 $\mu g/m^3$					
		SO_2	IQR, 3.65 $\mu g/m^3$					
		PM_{10}	IQR, 16.76 $\mu g/m^3$					
Fisher et al.[46]	Case-crossover	$PM_{2.5}$	IQR, 8.91 $\mu g/m^3$	Lag0 (same day)	OR	United States	122	122 (100%)
		PM_{10}	IQR, 14.46 $\mu g/m^3$					
Guo et al.[30]	Time series	$PM_{2.5}$	10 $\mu g/m^3$	Lag0-3 (4-day average)	RR	China	11,415	7071 (61.9%)
		NO_2	10 $\mu g/m^3$					
		O_3	10 $\mu g/m^3$					
Han et al.[41]	Cohort	PM_{10}	10 $\mu g/m^3$	Lag0-month end (monthly average)	RR	South Korea	799	495 (62.0%)
		NO_2	10 $\mu g/m^3$					
Han et al.[42]	Time series	PM_{10}	10 $\mu g/m^3$	Lag0-month end (monthly average)	RR	South Korea	1477	801 (54.2%)
		NO_2	10 ppb					
		O_3	10 ppb					
Huang 2016[44]	Case-crossover	$PM_{2.5}$	IQR, 82.0 $\mu g/m^3$	Lag0 (same day)	OR	China	16,880	10,349 (61.3%)
		PM_{10}	IQR, 93.5 $\mu g/m^3$					
Huang et al.[25]	Case-crossover	$PM_{2.5}$	10 $\mu g/m^3$	Lag2 (2-day delay)	OR	China	99	NR
Jin et al.[37]	Case-crossover	$PM_{2.5}$	10 $\mu g/m^3$	Lag0 (same day)	RR	China	36,850	22,647 (61.5%)
Kim et al.[26]	Cohort	SO_2	0.01 ppm	Lag0-7 (8-day average)	OR	South Korea	4404	NR
		NO_2	0.1 ppm					
		O_3	0.01 ppm					
		CO	1 ppm					
		PM_{10}	10 $\mu g/m^3$					
Li et al.[47]	Case-crossover	$PM_{2.5}$	IQR, 27 $\mu g/m^3$	Lag0-1 (2-day average)	OR	China	39,732	24,926 (62.7%)
		PM_{10}	IQR, 37 $\mu g/m^3$					
		SO_2	IQR, 10.8 $\mu g/m^3$					
		NO_2	IQR, 11.2 $\mu g/m^3$					
		O_3	IQR, 38.6 $\mu g/m^3$					
		CO	IQR, 0.32 mg/m^3					
Liu et al.[39]	Case-crossover	$PM_{2.5}$	IQR, 47.5 $\mu g/m^3$	Lag0 (same day)	RR	China	69,399	47,179 (68.0%)
		PM_{10}	IQR, 76.9 $\mu g/m^3$					
Liu et al.[43]	Case-crossover	PM_{10}	IQR, 85.7 $\mu g/m^3$	Lag0-5 (6-day average)	RR	China	41,746	28,223 (67.6%)
		NO_2	IQR, 25.4 $\mu g/m^3$					
		SO_2	IQR, 38.3 $\mu g/m^3$					
		CO	IQR, 0.81 mg/m^3					
		O_3	IQR, 67 $\mu g/m^3$					
Liu et al.[31]	Time series	$PM_{2.5}$	10 $\mu g/m^3$	Lag0 (same day)	RR	China	9541	5692 (60.0%)
		PM_{10}	10 $\mu g/m^3$					
Liu et al.[32]	Case-crossover	$PM_{2.5}$	10 $\mu g/m^3$	Lag0-1 (2-day average)	RR	China	58,090	31,378 (54.0%)
		NO_2	10 $\mu g/m^3$					
		O_3	10 $\mu g/m^3$					
		CO	10 $\mu g/m^3$					
		SO_2	10 $\mu g/m^3$					
Lv et al.[33]	Case-crossover	$PM_{2.5}$	10 $\mu g/m^3$	Lag0 (0-2 hour average)	RR	China	3122	1658 (53.1%)
		PM_{10}	10 $\mu g/m^3$					
		NO_2	10 $\mu g/m^3$					
		SO_2	10 $\mu g/m^3$					
		O_3	10 $\mu g/m^3$					
		CO	1 mg/m^3					
Montresor-López et al.[54]	Case-crossover	O_3	10 ppb	Lag0 (same day)	OR	United States	2582	1153 (44.7%)
Shen et al.[27]	Time series	SO_2	10 $\mu g/m^3$	Lag0 (same day)	RR	China	9167	NR

Continued

Table 1. Continued.

Reference	Study design	Air pollutant	Exposure (increments in μg/m^3)	Lag (time delay)	Risk scale (ie, RR or OR)	Country	Sample size, n	Male sex, n (%)
Sun et al.[45]	Case-crossover	$PM_{2.5}$	IQR, 8.2 μg/m^3	Lag0 (same day)	OR	United States	924	0 (0.0%)
		PM_{10}	IQR, 14.3 μg/m^3					
		NO_2	IQR, 10.2 ppb					
		SO_2	IQR, 2.5 ppb					
		O_3	IQR, 20.6 ppb					
Tsai et al.[28]	Case-crossover	PM_{10}	IQR, 66.33 μg/m^3	Lag0-1 (2-day average)	OR	Taiwan	4539	NR
		SO_2	IQR, 6.17 ppb					
		NO_2	IQR, 17.08 ppb					
		CO	IQR, 0.29 ppm					
		O_3	IQR, 21.20 ppb					
Turin et al.[53]	Case-crossover	SO_2	IQR, 2.2 ppb	Lag0 (same day)	OR	Japan	432	230 (53.1%)
		NO_2	IQR, 10.4 ppb					
Villeneuve et al.[48]	Case-crossover	SO_2	IQR, 3.0 ppb	Lag0 (same day)	OR	Canada	2329	1126 (48.3%)
		NO_2	IQR, 13.5 ppb					
		CO	IQR, 0.5 ppm					
		O_3	IQR, 18.0 ppm					
		$PM_{2.5}$	IQR, 6.3 μg/m^3					
		PM_{10}	IQR, 16.0 μg/m^3					
Wang et al.[49]	Case-crossover	$PM_{2.5}$	10 μg/m^3	Lag0 (same day)	OR	China	1052	693 (65.9%)
		PM_{10}	10 μg/m^3					
		SO_2	1 μg/m^3					
		NO_2	10 μg/m^3					
		CO	0.1 mg/m^3					
		O_3	10 μg/m^3					
Wang et al.[50]	Case-crossover	$PM_{2.5}$	10 μg/m^3	Lag0 (same day)	OR	China	867	572 (66.0%)
		PM_{10}	10 μg/m^3					
		SO_2	1 μg/m^3					
		NO_2	10 μg/m^3					
		CO	0.1 mg/m^3					
		O_3	10 μg/m^3					
Weng et al.[38]	Time series	$PM_{2.5}$	10 μg/m^3	Lag0 (same day)	RR	China	2888	1807 (62.5%)
		PM_{10}	10 μg/m^3					
		NO_2	10 μg/m^3					
		SO_2	10 μg/m^3					
		O_3	10 μg/m^3					
Wu et al.[34]	Case-crossover	$PM_{2.5}$	10 μg/m^3	Lag0-4 (5-day average)	RR	China	160,264	89,185 (55.6%)
		PM_{10}	10 μg/m^3					
Xiang et al.[52]	Case-crossover	PM_{10}	10 μg/m^3	Lag0 (same day)	OR	China	2225	1358 (61%)
		NO_2	10 μg/m^3					
		SO_2	10 μg/m^3					
Zhao et al.[35]	Time series	$PM_{2.5}$	10 μg/m^3	Lag0 (same day)	RR	China	42,909	27,351 (63.74%)
		PM_{10}	10 μg/m^3					
Zheng et al.[51]	Case-crossover	$PM_{2.5}$	10 μg/m^3	Lag0 (same day)	OR	China	25,255	15,107 (59.8%)
		PM_{10}	10 μg/m^3					
		$PM_{2.5}$	IQR, 22.6 μg/m^3					
		PM_{10}	IQR, 29.8 μg/m^3					
Zhong et al.[29]	Case-crossover	SO_2	10 μg/m^3	Lag2 (2-day delay)	OR	China	421	NR
		NO_2	10 μg/m^3	Lag1 (1-day delay)				
		PM_{10}	10 μg/m^3	Lag2 (2-day delay)				

CO, carbon monoxide; IQR, interquartile range; NO_2, nitrogen dioxide; NR, not reported; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter ≤ 2.5 μm in diameter; PM_{10}, particulate matter ≤ 10 μm in diameter; ppb, parts per billion; ppm, parts per million; RR, risk ratio; SO_2, sulfur dioxide.

et al.,[50] and Xiang et al.,[52] who reported a reduced risk. An overall reduction in hemorrhagic stroke risk was observed (OR, 0.9982; 95% CI, 0.9805-1.0163; $I^2 = 9\%$), but it was not statistically significant ($P = 0.85$; Supplemental Fig. S9). The quality of evidence was rated low on the GRADE scale (Supplemental Table S13).

O_3 - Odds Ratio (10 μg/m^3 exposure interval). Three studies (n = 41,651) reported ORs for a 10 μg/m^3 exposure interval, with Wang et al.,[50] who reported an increased risk of hemorrhagic stroke, and Li et al.[47] and Wang et al.,[49] who reported a reduced risk. There was an overall increased risk of hemorrhagic stroke (OR, 1.0024; 95% CI, 0.9814-1.0239; $I^2 = 61\%$), but it was not statistically significant ($P = 0.82$; Supplemental Fig. S10). The quality of evidence was rated low on the GRADE scale (Supplemental Table S14).

NO_2 - Odds Ratio (10 ppb exposure interval). Five studies (n = 12,628) reported ORs for a 10-ppb exposure interval, with Sun et al.,[45] Tsai et al.,[28] Turin et al.,[53] and Villeneuve et al.,[48] who reported an increased risk of hemorrhagic stroke, and Kim et al.,[26] who reported a reduced risk. Overall, an increased risk of hemorrhagic stroke was apparent (OR, 1.0634; 95% CI, 0.9623-1.1751; $I^2 = 86\%$), although not statistically significant ($P = 0.23$; Supplemental Fig. S11). The quality of evidence was rated very low on the GRADE scale because of inconsistency and publication bias (Supplemental Table S15).

CO - Odds Ratio (10 ppb exposure interval). Three studies (n = 11,272) reported ORs for a 10-ppb exposure interval, with Kim et al.,[26] Tsai et al.,[28] and Villeneuve et al.,[48] who reported an increased risk of hemorrhagic stroke. Although an overall increased risk of hemorrhagic stroke was evident (OR, 1.0017; 95% CI, 0.9988-1.0046; $I^2 = 83\%$), it was not statistically significant ($P = 0.26$; Supplemental Fig. S12). The quality of evidence was rated very low on the GRADE scale because of inconsistency (Supplemental Table S16).

Table 2. Summary of risk outcomes for air pollution and hemorrhagic stroke

Air pollutant	Exposure interval	Risk value (95% CI)
$PM_{2.5}$	10 μg/m^3	RR, 1.0002 (0.9985-1.0018)
		OR, 1.0172 (0.9918-1.0431)
PM_{10}	10 μg/m^3	RR, 1.0008 (0.9990-1.0025)
		OR, 1.0076 (0.9957-1.0196)
NO_2	10 μg/m^3	RR, 1.0142 (1.0000-1.0286)*
		OR, 0.9853 (0.9685-1.0024)
	10 ppb	OR, 1.0634 (0.9623-1.1751)
CO	10 μg/m^3	RR, 1.0001 (0.9997-1.0005)
		OR, 1.0008 (1.0000-1.0016)*
	10 ppb	OR, 1.0017 (0.9988-1.0046)
SO_2	10 μg/m^3	RR, 1.0060 (0.9983-1.0138)
		OR, 0.9982 (0.9805-1.0163)
	10 ppb	OR, 0.9928 (0.8924-1.1046)
O_3	10 μg/m^3	RR, 1.0017 (0.9975-1.0060)
		OR, 1.0024 (0.9814-1.0239)
	10 ppb	OR, 1.0131 (0.9776-1.0499)

CI, confidence interval; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter ≤ 2.5μm in diameter; PM_{10}, particulate matter ≤ 10μm in diameter; ppb, parts per billion; RR, risk ratio; SO_2, sulfur dioxide.

* $P \leq 0.05$.

SO_2 - Odds Ratio (10 ppb exposure interval). Five studies (n = 12,628) reported ORs for a 10-ppb exposure interval, with Tsai et al.[28] and Turin et al.,[53] who reported an increased risk of hemorrhagic stroke, and Kim et al.,[26] Sun et al.,[45] and Villeneuve et al.,[48] who reported a reduced risk. Overall, there was a reduction in the risk of hemorrhagic stroke (OR, 0.9928; 95% CI, 0.8924-1.1046; $I^2 = 0\%$), but this was not statistically significant ($P = 0.89$; Supplemental Fig. S13). The quality of evidence was rated very low on the GRADE scale because of publication bias (Supplemental Table S17).

O_3 - Odds Ratio (10 ppb exposure interval). Five studies (n = 14,778) reported ORs for a 10-ppb exposure interval, with Kim et al.[26] and Tsai et al.,[28] who reported an increased risk of hemorrhagic stroke, Villeneuve et al.,[48] who reported a null effect, and Montressor-Lopez et al.[54] and Sun et al.,[45] who report a reduced risk. There was an overall increased risk of hemorrhagic stroke (OR, 1.0131; 95% CI, 0.9776-1.0499; $I^2 = 71\%$), but it was not statistically significant ($P = 0.47$; Supplemental Fig. S14). The quality of evidence was rated low on the GRADE scale (Supplemental Table S18).

Sensitivity analyses. To explore potential sources of heterogeneity, 3 sensitivity analyses were performed on lag structure, region, and study design, respectively.

The first sensitivity analysis was performed to account for potential heterogeneity stemming from lag differences. Nineteen of 31 studies (61.3%) reported risk on the basis of lag0 (same day exposure) and were analyzed separately to assess immediate, short-term outcomes. Sensitivity analysis revealed that NO_2 and hemorrhagic stroke showed a stronger, yet statistically insignificant association (RR, 1.0253; 95% CI, 0.9825-1.0700; $P = 0.25$; Supplemental Fig. S15). The RR outcome of CO and hemorrhagic stroke showed a mildly stronger association (RR, 1.0012; 95% CI,1.0003-1.0021) and was statistically significant ($P = 0.01$; Supplemental Fig. S16), whereas the OR outcome of CO and hemorrhagic stroke was no longer significant (OR, 0.9995; 95% CI, 0.9971-1.0019; $P = 0.70$; Supplemental Fig. S17). There were no other significant differences in this sensitivity analysis. Because of a lack of data, sensitivity analyses could not be performed for other lag intervals.

The second sensitivity analysis was performed to explore differences among regions. Twenty-six of 31 studies (83.9%) were conducted in Asia (with 20/31 studies [64.5%] from China) and were analyzed separately to assess outcomes from the same region. Sensitivity analysis showed that NO_2 and hemorrhagic stroke showed a weaker and statistically insignificant association (RR, 1.0091; 95% CI, 0.9955-1.0229; $P = 0.19$; Supplemental Fig. S18). CO OR risk outcomes remained unchanged and significant. Additionally, O_3 was associated with an increased risk of hemorrhagic stroke within the included Asian studies, as per a 10-ppb increase in exposure (RR, 1.0579; 95% CI, 1.0122-1.1057), and was statistically significant ($P = 0.01$; Supplemental Fig. S19). Not enough available data supported meaningful sensitivity analyses of other regions.

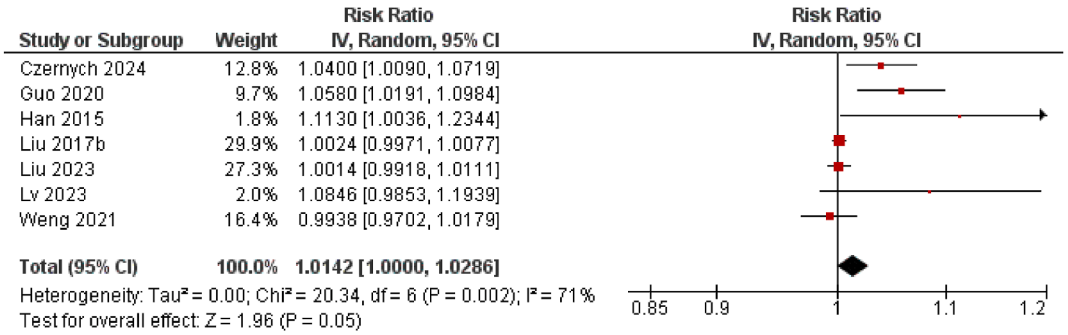


Figure 2. Relative risk of hemorrhagic stroke after a 10 μg/m^3 increase in nitrogen dioxide exposure.

The third sensitivity analysis was performed to explore differences in study design. Twenty-two of 31 studies (71.0%) had a case-crossover design and were analyzed separately to isolate studies with the same study design. Sensitivity analysis showed that NO_2 and hemorrhagic stroke had a weaker and statistically insignificant association (RR, 1.0024; 95% CI, 0.9958-1.0090; $P = 0.47$; Supplemental Fig. S20). OR risk outcomes for CO remained unchanged and significant. Not enough available data supported meaningful sensitivity analyses of other study designs.

Discussion

This study showed that short-term exposure to several ambient air pollutants is associated with an increased risk of developing hemorrhagic stroke. Risk measures of RR and OR were the outcomes of interest and they were stratified in this study because of varying literature on their interchangeability.[20] Statistically significant associations were found for NO_2 and CO. NO_2 was linked to a 1.42% relative increase in the risk of hemorrhagic stroke when risk was expressed per 10 μg/m^3 increment (RR, 1.0142; 95% CI, 1.0000-1.0286; $P = 0.05$). When risk was expressed as an OR per 10 μg/m^3 increase in CO, a statistically significant correlation was observed (OR, 1.0008; 95% CI, 1.0000-1.0016; $P = 0.05$). This might seem to be a small increase in risk, but it has large implications because it is derived from population-level data and hence affects millions of people. Additionally, considering that geographical areas can have exposure differences of several increments around the world rather than the standardized increment of 10 μg/m^3, it is appreciable that the risk of hemorrhagic stroke can starkly increase accordingly.

In contrast, across RR and OR scales, as well as across 10 μg/m^3 and 10 ppb exposure increments, particulate pollutants ($PM_{2.5}$ and PM_{10}), SO_2, and O_3 consistently showed very small effect sizes and confidence intervals crossed the null. Thus, altogether these results imply that NO_2 and CO might be more pertinent short-term triggers for hemorrhagic stroke compared with others.

Our findings are consistent with and further expand on reported patterns within previous literature on air pollutants and their correlation with cerebrovascular incidents.[43,47,55] Historically, the short-term effects of air pollution have been more transparent and consistent for total and ischemic stroke than for hemorrhagic stroke. However, the biological plausibility for hemorrhagic stroke might differ because hemorrhagic events are driven primarily by vessel rupture rather than thrombosis.[56] Accordingly, any effect of air pollutants on hemorrhagic stroke might be mediated more indirectly through acute blood pressure changes, vascular inflammation, endothelial dysfunction, and impaired vascular reactivity in susceptible vessels. In that context, Liu et al.[43] reported that NO_2 was the only pollutant, across 14 Chinese cities, that was significantly linked to admissions for hemorrhagic stroke, whereas associations for other pollutants were more erratic and imprecise. This is consistent with our finding of a higher risk per 10 μg/m^3 increase in NO_2. Similarly, Li et al.[47] reported that all 7 pollutants (particulate matter ≤ 1 μm in diameter, $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO) were linked to hospitalizations for ischemic stroke, but only CO was linked to hemorrhagic stroke. This is in line with our pooled estimate, which indicates a statistically significant increase in the risk of hemorrhagic stroke with short-term CO exposure. Moreover, our predominantly null pooled estimates for the risk of hemorrhagic stroke and particulate matter are in line with previous literature. Fisher et al.[46] reported no evidence of an increased risk of hemorrhagic stroke associated with short-term particulate matter exposure. Likewise, Wu et al.[34] and Zhang et al.[57] reported that particulate pollutants were

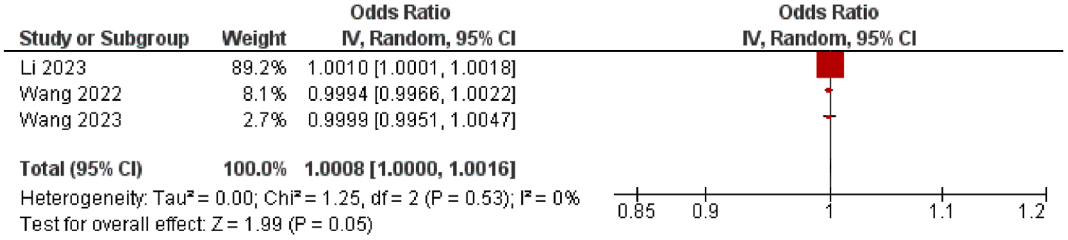


Figure 3. Odds ratio of hemorrhagic stroke after a 10 μg/m^3 increase in carbon monoxide exposure.

clearly associated with overall or ischemic stroke, but not with hemorrhagic stroke. However, research by Chiu et al.[24] showed positive correlations between fine particulate matter and hemorrhagic stroke in lag structures or in single-pollutant models. However, these estimates frequently lost statistical significance when co-pollutants were included. Overall, these studies supplement our review by indicating that short-term exposure to NO_2 and CO has the most consistent adverse effects on hemorrhagic stroke. In contrast, the evidence for particulate matter, SO_2, and O_3 remains inconsistent and context-dependent.

This review has several important limitations. First, the evidence base is primarily composed of observational time-series and case-crossover studies that used regional models or area-level concentrations from fixed-site monitors. These studies do not capture individual time-activity patterns and are likely to introduce nondifferential exposure misclassification, which would bias true effects toward the null. Second, studies differed considerably in terms of covariate adjustments such as temperature, seasonality, and co-pollutants. This limited comparability and prevented the pooling of certain pollutant-metric combinations. Additionally, many studies used data for hospital admissions for risk assessments and did not account for pre-hospital fatal cases. This limits the data in terms of providing a full picture of the adverse effects of short-term pollution exposure. Finally, generalizability to areas with different emission profiles, lower background pollution, and distinct hemorrhagic stroke epidemiology is uncertain, because most studies were conducted in China and other East Asian settings.

To explore these limitations, sensitivity analyses showed that when keeping the lag structure (lag0), region (Asia), or study design (case-crossover) constant, NO_2 RR outcomes no longer appeared significant. This demonstrated that the NO_2 result in the main analysis might have been influenced by these confounders. Although it is important to note that these insignificant results could be due to low power from a low number of studies remaining in the forest plot (for example, only 3 of 7 studies reported lag0 RR NO_2 risk outcomes). More research needs to be done in this area to determine whether this connection is true or not. In contrast, although CO risk outcomes were comparatively smaller than for NO_2, they remained consistent and statistically significant, which suggested that CO was less influenced by these potential confounders. Additionally, O_3 was shown to have an increased risk in hemorrhagic stroke in Asia. However, this result should be interpreted with caution because it is the result of only 2 included Asian studies. More research is warranted on O_3 pollution and hemorrhagic stroke in Asian regions to further test the extent of this association.

Despite the limitations, our findings provide valuable insight. Increases in NO_2 and CO RRs can result in a significant number of hemorrhagic stroke incidents at the population level. This is especially true when the population is already vulnerable because of previous strokes or a high baseline stroke incidence, and when the greater proportion is aging. From a policy standpoint, our findings encourage ongoing efforts to reduce emissions from combustion and traffic through stricter air quality regulations and to further develop and implement cleaner, alternative energy systems. Such interventions are likely to longitudinally help prevent hemorrhagic and ischemic strokes. Future research should prioritize high-quality studies in under-represented areas, improve exposure assessment, and include subtype-specific analyses that distinguish intracerebral from subarachnoid hemorrhage, alongside comprehensive data on comorbidities and medications.

Conclusions

The results of this meta-analysis showed an association of air pollution exposure with hemorrhagic stroke. More specifically, NO_2 and CO exposures per 10 $\mu g/m^3$ increment led to increases in hemorrhagic stroke risk; RR, 1.0142 and OR, 1.0008, respectively. Considering the context that the geographical distribution of air pollution can vary by several increments, this finding shows that the risk of hemorrhagic stroke can starkly increase with increased exposure. Because of the large burden of hemorrhagic stroke on cardiovascular health worldwide, it is imperative to consistently examine the effects of air pollution across multiple geographic regions to accurately inform environmental health policy, allocation of economic resources, and preventative measures. These strategies can aid in diminishing the burden of hemorrhagic stroke and other cardiovascular consequences caused by air pollution exposure.

Ethics Statement

This is a systematic review and meta-analysis of articles indexed on Embase, OVID Medline, Web of Science, and PubMed. An institutional review from the Ethics Board was not required.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This systematic review and meta-analysis did not involve direct patient participation or the use of identifiable patient information.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca/ and at https://doi.org/10.1016/j.cjca.2026.05.010.