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# Short term exposure to air pollution and stroke: systematic review and meta-analysis

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## ABSTRACT

### OBJECTIVE

To review the evidence for the short term association between air pollution and stroke.

### DESIGN

Systematic review and meta-analysis of observational studies

### DATA SOURCES

Medline, Embase, Global Health, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science searched to January 2014 with no language restrictions.

### ELIGIBILITY CRITERIA

Studies investigating the short term associations (up to lag of seven days) between daily increases in gaseous pollutants (carbon monoxide, sulphur dioxide, nitrogen dioxide, ozone) and particulate matter (<2.5 µm or <10 µm diameter (PM<sub>2.5</sub> and PM<sub>10</sub>)), and admission to hospital for stroke or mortality.

### MAIN OUTCOME MEASURES

Admission to hospital and mortality from stroke.

### RESULTS

From 2748 articles, 238 were reviewed in depth with 103 satisfying our inclusion criteria and 94 contributing to our meta-estimates. This provided a total of 6.2 million events across 28 countries. Admission to hospital for stroke or mortality from stroke was associated with an increase in concentrations of carbon monoxide (relative risk 1.015 per 1 ppm, 95% confidence interval 1.004 to 1.026), sulphur dioxide (1.019 per 10 ppb, 1.011 to 1.027), and nitrogen dioxide (1.014 per 10 ppb, 1.009 to 1.019). Increases in PM<sub>2.5</sub> and PM<sub>10</sub> concentration were also associated with admission and mortality (1.011 per 10 µg/m<sup>3</sup> (1.011 to 1.012) and 1.003 per 10 µg/m<sup>3</sup> (1.002 to 1.004), respectively). The weakest association was seen with ozone (1.001 per 10 ppb, 1.000 to 1.002).

Strongest associations were observed on the day of exposure with more persistent effects observed for PM<sub>2-5</sub>.

### CONCLUSION

Gaseous and particulate air pollutants have a marked and close temporal association with admissions to hospital for stroke or mortality from stroke. Public and environmental health policies to reduce air pollution could reduce the burden of stroke.

### SYSTEMATIC REVIEW REGISTRATION

PROSPERO-CRD42014009225.

## Introduction

Outdoor air pollution is an important risk factor for cardiovascular disease throughout the world, with particulate air pollution alone responsible for over three million deaths each year.<sup>1,2</sup> Increases in concentrations of daily air pollution are associated with acute myocardial infarction<sup>3</sup> and admission to hospital or death from heart failure.<sup>4</sup> These associations could be mediated through direct and indirect effects of exposure to air pollutants on vascular tone, endothelial function, thrombosis, and myocardial ischaemia.<sup>5-8</sup>

Stroke accounts for five million deaths each year and is a major cause of disability.<sup>9</sup> The incidence of stroke is increasing, particularly in low and middle income countries, where two thirds of all strokes occur.<sup>10</sup> The global burden of stroke related disability is therefore high and continues to rise. This has been primarily attributed to an ageing population in high income countries and the accumulation of risk factors for stroke, such as smoking, hypertension, and obesity, in low and middle income countries.<sup>11,12</sup> The impact of environmental factors on morbidity and mortality from stroke, however, might be important and is less certain.<sup>13-15</sup> Given similarities in the pathophysiology of acute coronary syndrome and ischaemic stroke, it is plausible that air pollution is also an important and modifiable risk factor.<sup>3,4</sup>

To provide global policy makers with the best estimates of the effect of short term exposure to air pollution on risk of stroke, we systematically reviewed studies examining the association between air pollution and admission to hospital for stroke or mortality from stroke.

## Methods

### Databases, sources, and searches

We searched Medline and Embase (from 1948 to 21 January 2014), Global Health, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science with detailed search terms for: “stroke”, “cerebrovascular

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Stroke is a major cause of disability worldwide with an increasing incidence, particularly in low and middle income countries

While exposure to outdoor air pollution is strongly associated with acute cardiac events, the relation between air pollution and stroke is less clear

## WHAT THIS STUDY ADDS

Our findings suggest a strong association between short term exposure to both gaseous (except ozone) and particulate air pollution, and admission to hospital for stroke and mortality from stroke

These associations were strongest in low and middle income countries, suggesting the need for policy changes to reduce personal exposure to air pollutants especially in highly polluted regions

disease”, “air pollution”, “carbon monoxide”, “sulphur dioxide”, “nitrogen dioxide”, “ozone”, and “particulate matter” (see appendix 1 for detailed search strategy). We also hand searched the bibliographies of all the included studies and relevant review articles to identify any remaining studies.

### Selection of articles and extraction of data

Original studies were included if they evaluated short term associations (up to a lag of seven days) between carbon monoxide, sulphur dioxide, nitrogen dioxide, ozone, and particulate matter PM<sub>2.5</sub> (fine particles <2.5 µm in size) or PM<sub>10</sub> (coarse particles <10 µm in size) and admission to hospital for stroke or mortality from stroke (appendix 2). Admission or mortality had to be recorded as an end point. Our search criteria imposed no language restrictions. We did not include studies that evaluated association of long term exposure to air pollution and stroke (appendix 2) or abstracts, but we did include short reports.

One investigator (ASVS) performed the initial screening of titles and abstracts. A second investigator (KKL) assessed a random sample of 200 initial titles and abstracts during the initial screening process, and no cases of disagreement were found. Two investigators (ASVS and KKL) were involved in the examination of the full text reports for eligibility of studies according to our prespecified review protocol (PROSPERO registration CRD42014009225). The inter-rater agreement for eligibility of studies was 0.95 (95% confidence interval 0.91 to 0.99). ASVS and KKL independently extracted the required parameters of each study, and conflicts were adjudicated by a third author (AH). We contacted authors for additional data or clarification for our meta-analysis where these were not presented.

### Study design

We included both case crossover and time series studies (appendix 3). The case crossover design uses conditional logistic regression to compare exposure in a case period when the event occurred with exposure in specified control periods, with adjustment for individual characteristics such as age, sex, and comorbidity as well as secular trends and seasonal patterns with a time stratified approach. It assumes that short term time varying risk factors (such as smoking) are constant within reference periods<sup>4 16 17</sup> and therefore do not confound rapidly fluctuating parameters such as concentrations of air pollution and other meteorological parameters.

Time series studies measure the association between exposure and outcome with regression analysis to adjust for confounding factors, such as meteorological variables, but are less effective at controlling for secular trends such as seasonality.<sup>18</sup>

### Data synthesis

We pooled relative risks for a standardised increment in pollutant concentration as follows: 10  $\mu\text{g}/\text{m}^3$  for PM<sub>2.5</sub> and PM<sub>10</sub>, 10 ppb (parts per billion) for nitrogen dioxide (NO<sub>2</sub>), sulphur dioxide (SO<sub>2</sub>), and ozone (O<sub>3</sub>),

and 1 ppm (parts per million) for carbon monoxide (CO). These increments were used in most studies and in previous meta-analysis.<sup>3 4</sup> We calculated standardised risk estimates for each study using the following formula:

Five studies reported natural log of relative risk and the corresponding *t* statistic value or standard error of mean.<sup>19–23</sup> Studies that expressed substratified risk estimates by age, location, season, sex, and type of stroke rather than an overall risk estimate were pooled separately.

### Additional analysis

We used the shortest lag presented to derive the overall estimates consistent with previous studies.<sup>3 4</sup> The temporal association between air pollution and admission to hospital for stroke or mortality from stroke were further stratified according to time lags. Summary estimates for lag 0 (days) refer to the risk of an event per increment in air pollution on the day of the event. Lag 1 refers to risk estimates per increment in air pollution concentrations one day before the event. Most studies presented single lag analysis but only a few studies explicitly reported use of distributed lag models (appendix 4). We were therefore unable to further stratify studies reporting single lag analysis using distributed lag models. Several studies reported data based on pollutant concentrations over cumulative lags (for example lag 0–1 or lag 0–2) and were not suitable for pooling in single lag analysis.

We performed additional prespecified analysis stratified by study design, age, sex, outcome, and type of stroke. For nitrogen dioxide and PM<sub>10</sub> we further provided pooled estimates stratified by the nation's income status as defined by the World Bank using the gross national income per capita.<sup>24</sup> We provided pooled estimates for stratified variables where at least three or more estimates were available.

### Risk of bias

We assessed each individual study for risk of bias across three parameters: selection bias, assessment of exposure, and adjustment for confounders. We then carried out sensitivity analysis eliminating those studies with high risk of bias.

### Selection bias

We did not have access to primary data and therefore were reliant on the case definitions used by the authors of the individual studies. Most studies (83%, 86/103 studies), however, used ICD-9 (international classification of diseases, ninth revision) codes 430–438 and ICD-10 (international classification of diseases, 10th revision) codes I60–I69 (appendix 4). Studies that used all clinical information, including brain imaging, to define stroke or those that used an inclusive definition of stroke (ICD-9 codes 430–437 and ICD-10 codes I60–I68) were considered to be at low risk of selection bias. Studies that used a less inclusive definition were considered to be at increased risk of selection bias.

### Exposure assessment

Accuracy of the measurement of exposure was difficult to assess because of variable reporting in the primary studies. The frequency of measurement (daily or intermittent monitoring), however, was reported to a high standard, and we considered studies that used daily measurement to be at low risk of bias.

### Adjustment of confounders

Adjustment for meteorological parameters, time trends, seasonality, and influenza outbreaks are summarised in the data supplement (appendix 4). Studies that adjusted for at least three confounders were considered to be at low risk of bias.

### Statistical analysis

Based on our previous analysis,<sup>4</sup> we anticipated a larger degree of variation and heterogeneity in the overall effect estimates between studies because of different study designs, methods of analysis, different exposure lags, and geographical and population differences. As we did not assume that the “true effect” estimate would be the same across all studies, we used a prespecified random effects model (maximum likelihood approach)

for our analysis to account for heterogeneity both within and between studies.<sup>25</sup> We conducted prespecified subgroup analysis by study design, age, sex, outcome, and type of stroke to explore any underlying source for heterogeneity.

We constructed funnel plots to examine publication bias (appendix 5) and assessed them for asymmetry using Egger's regression test.<sup>26</sup> We then corrected for asymmetry using the trim and fill method, with adjusted relative risks and the number of studies adjusted presented for each pollutant.<sup>27</sup>

Summary statistics are presented as relative risk per given increment in pollutant concentration. The analysis was performed with comprehensive meta-analysis (Biostat, Englewood, NJ) and RStudio (RStudio 2013, version 0.98.501). Significance for pooled estimates was taken as a two sided  $P < 0.05$ .

### Results

We assessed the abstracts of 2748 articles and reviewed 238 relevant studies in depth. Of these, we identified 103 that fulfilled the inclusion criteria (appendix 2 and 3).<sup>13 14 20–23 28–35 61–149</sup> Sixty nine studies used a time series design, 33 used a case crossover design, and one used both study designs incorporating over 6.2 million events across 28 countries (appendix 3). Twenty five (24%) studies presented analyses stratified by type of stroke (haemorrhagic and ischaemic), though only a minority of studies reported on haemorrhagic strokes (15 studies, 15%). Most studies presented risk estimates for stroke defined from administrative databases using the ICD-9 and ICD-10 codes (appendix 4). Most studies adjusted for other meteorological parameters including time trends, seasonality, and temperature (appendix 4). Not all studies provided risk estimates across all pollutants (appendix 3).

Of the 103 studies that met the inclusion criteria, we excluded nine studies from meta-analysis. Of these nine studies, five presented estimates as a subset of the parent study and therefore only estimates from the parent study were included.<sup>28–32</sup> Four studies were excluded as risks were presented per category of pollutant concentration rather than per unit increment, the increment was not defined, or the effect estimates were not presented as either relative risks or odds ratios.<sup>21 33–35</sup>

There was a positive association between all gaseous and particulate air pollutants and admission to hospital for stroke or mortality from stroke, with the weakest association seen for ozone (fig 1). Individual forest plots for each of the pollutants are presented in appendix 6.

### Particulate pollutants

Both  $PM_{2.5}$  and  $PM_{10}$  were positively associated with admission to hospital for stroke or mortality from stroke, with a stronger association for  $PM_{2.5}$ . The increase in relative risk was 1.011 (95% confidence interval 1.011 to 1.012) per  $10 \mu g/m^3$  increase in  $PM_{2.5}$  concentration (fig 1). The association between  $PM_{2.5}$  and stroke was evident on the day of the event (lag 0) and was present for up to two days (lag 2) before the event.

These associations persisted when we stratified by outcome (admission or death), sex, age ( $>65$ ), or study design

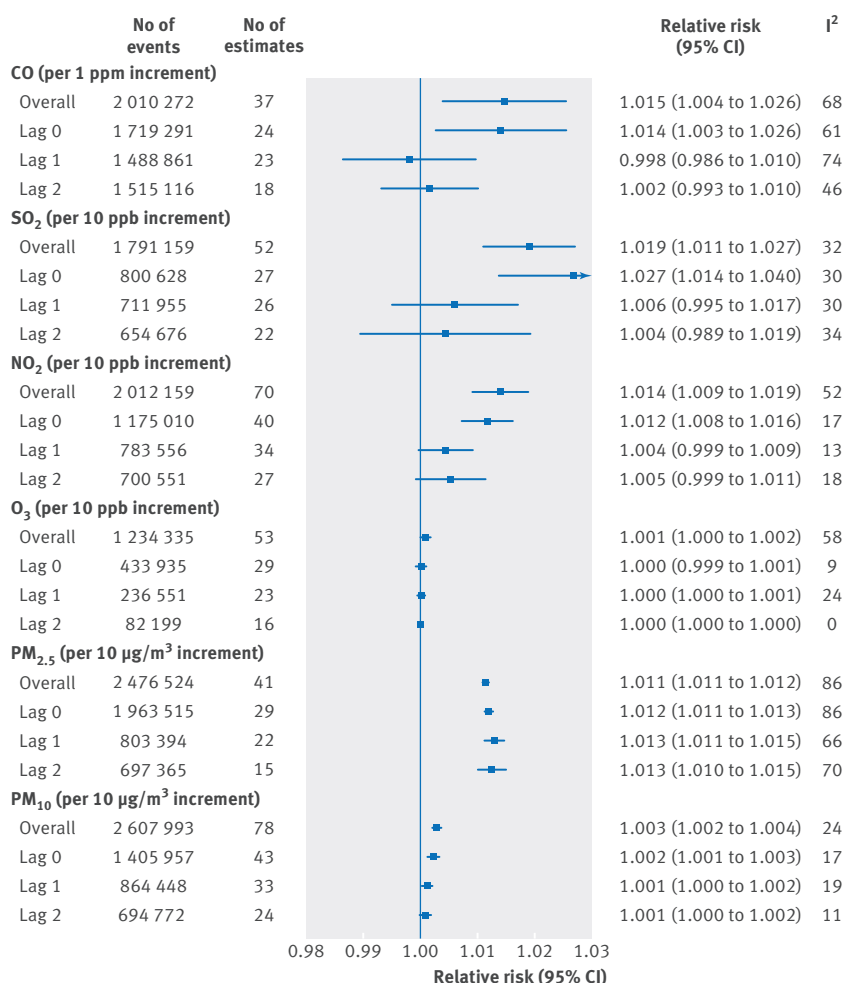


Fig 1 | Association between gaseous and particulate air pollutants and admission for stroke or mortality from stroke stratified by time lag (days)

(fig 2 and appendix 7) for either PM<sub>2.5</sub> or PM<sub>10</sub>. Few studies reported summary estimates by type of stroke, but when they were reported, the association for PM<sub>2.5</sub> was 1.010 (95% confidence interval 1.008 to 1.011; I<sup>2</sup>=69%) for ischaemic stroke and 1.004 (0.978 to 1.029; I<sup>2</sup>=14%) for haemorrhagic stroke (appendix 7). Risks for ischaemic stroke and haemorrhagic stroke associated with PM<sub>10</sub> exposure were comparable (1.002 (0.999 to 1.004; I<sup>2</sup>=23%) and 1.002 (0.997 to 1.006; I<sup>2</sup>=0%), respectively).

### Gaseous pollutants

Nitrogen dioxide was the most commonly measured gaseous pollutant, with a 1.014 (95% confidence interval 1.009 to 1.019) relative increase in risk of admission

to hospital for stroke or mortality from stroke per 10 ppb increment across two million events (fig 1). Both sulphur dioxide (1.019 (1.011 to 1.027) per 10 ppb) and carbon monoxide (1.015 (1.004 to 1.026) per 1 ppm) were also positively associated with admission and mortality. Ozone however, showed only a weak association (1.001 (1.000 to 1.002) per 10 ppb; fig 1).

These associations persisted when we stratified by outcome, age, and study design. All gaseous pollutants except ozone showed a positive and consistent relation with ischaemic stroke (appendix 7). Nitrogen dioxide exposure showed a consistent association with both ischaemic and haemorrhagic stroke (1.024 (95% confidence interval 1.010 to 1.038, I<sup>2</sup>=56%) and 1.024 (1.003 to 1.045; I<sup>2</sup>=42%), respectively; see appendix 7).

The association between gaseous pollutants and stroke was related to lag in exposure (days), with the strongest associations evident for pollutant concentrations on the day of the event (lag 0) and diminishing with longer lag periods (fig 1).

### Stratification by category of national income

Most studies (80%) originated from high income countries, with only 21 (20%) originating from low or middle income countries. Both nitrogen dioxide and particulate matter (PM<sub>10</sub>) were commonly measured across high and low to middle income countries. Studies for these pollutants originated from Latin America (including Brazil, Chile, and Mexico), South Africa, China, Thailand, Iran, and South Africa (fig 3). Most studies from low and middle income countries originated from mainland China (14 studies).

Pooled estimates from studies originating in low and middle income countries showed a stronger association than high income countries for nitrogen dioxide (1.019 (95% confidence interval 1.011 to 1.027) v 1.012 (1.006 to 1.017)) and PM<sub>10</sub> (1.004 (1.002 to 1.006) v 1.002 (1.001 to 1.003)) (fig 3). The median pollutant concentrations for nitrogen dioxide and PM<sub>10</sub> were higher in low and middle income countries (median pollutant concentration 27.6 ppb (interquartile range 23.8–29.6 ppb) for nitrogen dioxide and 50.2 µg/m<sup>3</sup> (32.6–65.7 µg/m<sup>3</sup>) for PM<sub>10</sub>) than in high income countries (median pollutant concentration 22.6 ppb (19.4–28.3 ppb) for nitrogen dioxide and 25.3 µg/m<sup>3</sup> (23.8–29.6 µg/m<sup>3</sup>) for PM<sub>10</sub>).

### Bias and heterogeneity

There was no difference in our overall effect estimates when we removed studies at increased risk of bias (appendix 8). Publication bias (Egger's test for asymmetry P<0.05) was observed for all pollutants except sulphur dioxide and PM<sub>2.5</sub> (table; appendix 4). Adjustment for asymmetry with the trim and fill method did not alter the effect direction but, as expected, did attenuate the effect size. We observed heterogeneity across all pollutants, and this was most evident with PM<sub>2.5</sub> (I<sup>2</sup>=86%) and least evident with PM<sub>10</sub> (I<sup>2</sup>=24%).

### Discussion

In this systematic review and meta-analysis, we evaluated the effects of short term exposure to gaseous and

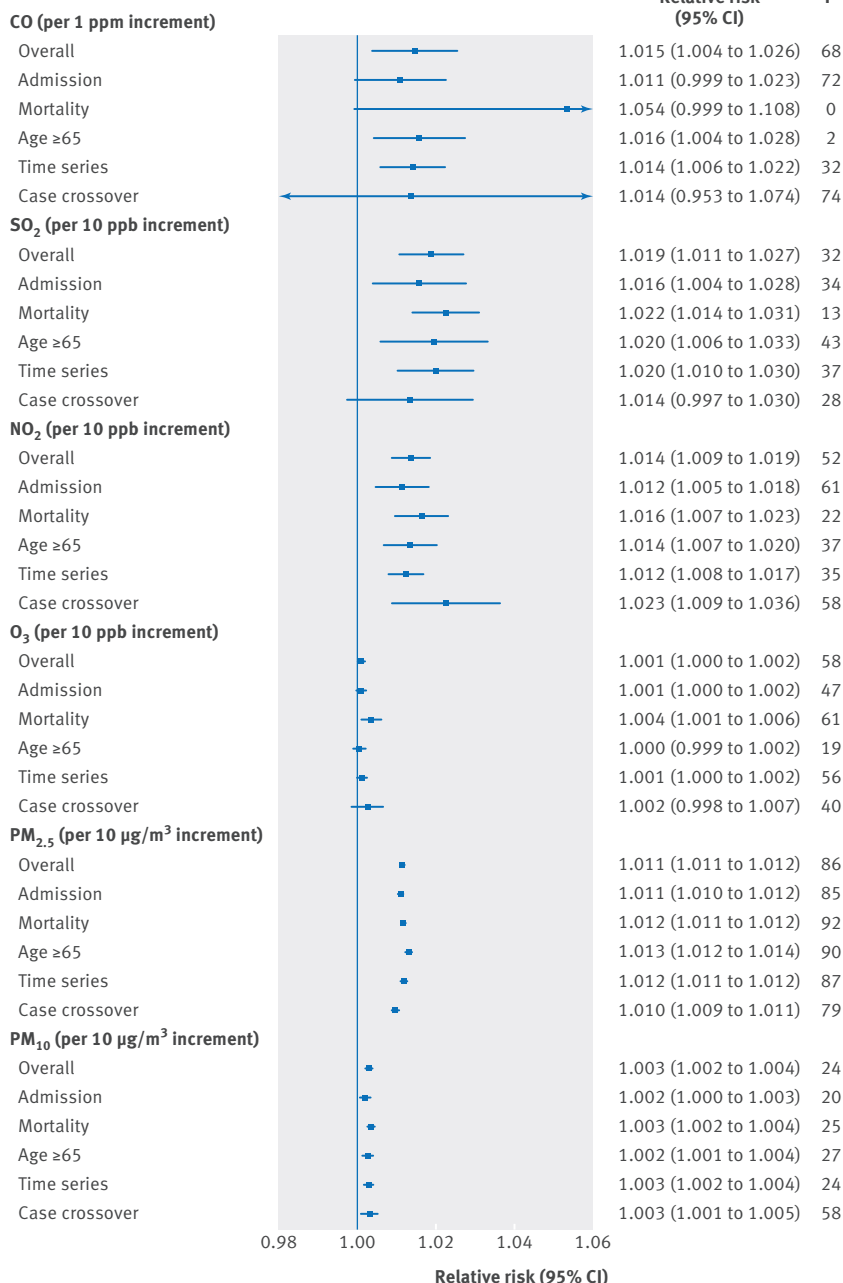


Fig 2 | Associations across all gaseous and particulate air pollutants stratified by outcome, age, and study design



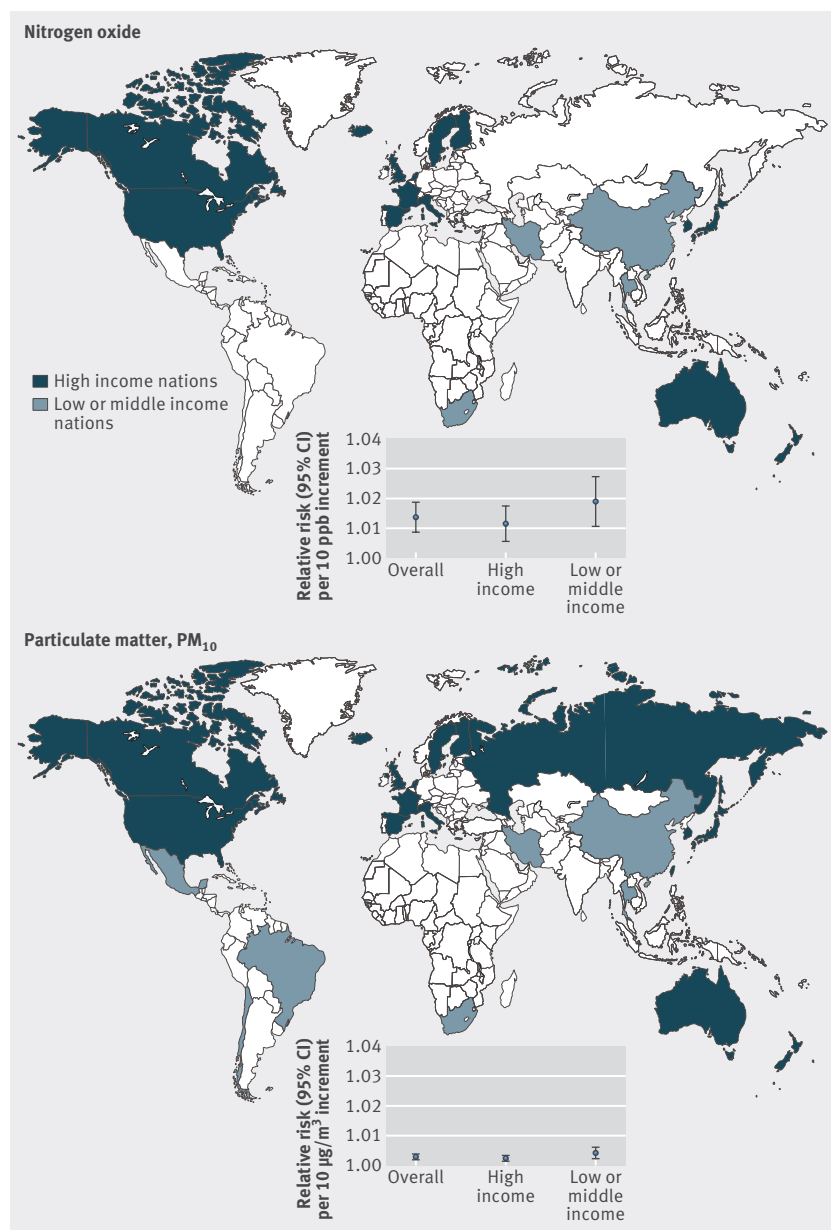


Fig 3 | Cartogram identifying association between nitrogen dioxide and particulate matter (PM<sub>10</sub>) and admission to hospital for stroke or mortality from stroke in countries stratified as high and low to middle income

particulate air pollution on admission to hospital for stroke or mortality from stroke. We made several important observations. Firstly, in over 6.2 million events across 28 countries throughout the world, our pooled analysis showed robust and clear associations between both gaseous and particulate air pollution and stroke admission or mortality. Secondly, the strongest associations between air pollution and admission or mortality were observed from studies originating in low to middle income countries. Thirdly, these associations persisted when we stratified our pooled analyses by study design, age, or outcome. Thus, we have shown that gaseous and particulate air pollutants have a robust and close temporal association with admission to hospital for stroke or stroke death. We

suggest that improvements in air quality could reduce the burden of stroke.

### Evidence of short term exposure to air pollution and stroke

Over the past three decades, epidemiological studies including pooled analyses have shown that cardiac, rather than pulmonary, disease is the primary cause of morbidity and mortality associated with exposure to air pollution.<sup>36</sup> Long term exposure studies have already shown strong associations between air pollution and stroke.<sup>37–39</sup> While the short term effects of air pollution on cardiac disease, including heart failure and myocardial infarction, have received much attention, it is less certain whether acute exposure to air pollution is a trigger for cerebrovascular disease, especially stroke.<sup>3,4,11</sup> This is partly because the results of many short term exposure studies evaluating the effect of air pollution on stroke have been inconclusive, reflecting both the nature of the condition and the size of individual studies.<sup>36</sup> Recently meta-analyses, including 12 and 45 studies, reported an association between particulate air pollution and stroke.<sup>40–43</sup> To our knowledge, our study is the first comprehensive prespecified pooled analysis to examine the short term effects after exposure to gaseous or particulate air pollution and admission to hospital for stroke or mortality from stroke across both time series and case crossover study designs.

Particulate matter and gaseous pollutants both showed a strong temporal relation with mortality from stroke and admission to hospital for stroke. The lag effects of exposure and stroke have to be interpreted with caution. Unlike other cardiac conditions such as acute myocardial infarction, decompensated heart failure, and sudden cardiac death, the timing of onset of stroke symptoms and subsequent admission to hospital or mortality might differ substantially.<sup>44</sup> Lokken and colleagues showed that in cases of acute ischaemic stroke, onset of symptoms occurred at a median of one calendar day before admission, and this delay in presentation is likely to underestimate the overall association between exposure to pollutant and stroke.<sup>44</sup>

### Aetiology of stroke and exposure to air pollution

While our analysis showed consistent associations for ischaemic stroke and air pollution, the association for haemorrhagic stroke was more variable with larger imprecision. Our results were similar to those from a smaller meta-analysis that showed identical patterns with type of stroke and exposure to PM<sub>2.5</sub> and PM<sub>10</sub>.<sup>41</sup> While haemorrhagic and ischaemic stroke share similar risk factors and have a similar clinical presentation, they are different clinical entities.<sup>45</sup> Heterogeneity in the association between air pollution and stroke subtype might be caused by many factors. Firstly, the mechanisms linking exposure to air pollution and haemorrhagic stroke might differ for ischaemic stroke. Secondly, there were fewer estimates for haemorrhagic stroke, reflecting the lower incidence of this subtype, and therefore wider confidence intervals for these

Pollutant concentrations and assessment for publication bias stratified by gaseous and particulate air pollutants

	Gaseous pollutants				Particulate matter	
	Carbon monoxide (ppm)	Nitrogen dioxide (ppb)	Sulphur dioxide (ppb)	Ozone (ppb)	2.5 (µg/m³)	PM <sub>10</sub> (µg/m³)
Increment	1	10	10	10	10	10
No of estimates	37	70	52	53	41	78
Pollutant concentration:						
Median (IQR)	0.8 (0.7–1.3)	24.4 (17.0–30.1)	6.2 (2.6–10.1)	24.2 (18.9–31.7)	15.7 (8.7–23.6)	35.3 (25.6–51.6)
Range (min–max)	0.3–5.5	8.1–44.0	1.1–30.2	12.3–53.9	5.8–34.3	13–187.1
Publication bias:						
Egger regression test P value	0.070	0.036	0.098	0.014	0.670	<0.001
RR (95% CI)*	1.015 (1.004 to 1.026)	1.014 (1.009 to 1.019)	1.019 (1.011 to 1.027)	1.001 (1.000 to 1.002)	1.011 (1.011 to 1.012)	1.003 (1.002 to 1.004)
Adjusted RR (95% CI)†	1.015 (1.004 to 1.027)	1.014 (1.009 to 1.020)	1.017 (1.009 to 1.024)	1.001 (1.000 to 1.002)	1.011 (1.011 to 1.012)	1.001 (1.001 to 1.002)
No of studies adjusted	8	6	8	7	3	24

\*Relative risk derived from pooled analysis of studies.

†Relative risk adjusted for publication bias with trim and fill method.

ppm=parts per million; ppb=parts per billion.

estimates. Finally, misclassification of stroke subtype in those studies from countries with limited availability of medical imaging might have contributed to some of the observed heterogeneity.<sup>42 46</sup>

#### Particulate pollution and stroke

Exposure to PM<sub>10</sub> showed weaker associations with admission to hospital for stroke or mortality from stroke than PM<sub>2.5</sub>, consistent with observations from other meta-analyses for stroke<sup>42</sup> and acute myocardial infarction.<sup>3</sup> This could reflect differences in particle size, with larger particles more likely to exert local pulmonary effects whereas fine or ultrafine particles (PM<sub>2.5</sub>) or gaseous pollutants could cause additional systemic cardiovascular effects.<sup>36</sup> In contrast, the adverse effect of larger particles in patients with heart failure was more striking, possibly reflecting indirect biological pathways such as the adverse effect of sympathetic nervous activation on the failing heart.<sup>4 36</sup> We noticed greater heterogeneity for PM<sub>2.5</sub> than for PM<sub>10</sub>. These differences in heterogeneity persisted after subgroup analysis and could reflect variation in study design. We were able to meta-analyse twice as many estimates for PM<sub>10</sub> than for PM<sub>2.5</sub>, with an overall less marked but more consistent effect of exposure on stroke with PM<sub>10</sub>. There are several biologically plausible reasons for this. While there is a close correlation between PM<sub>2.5</sub> and PM<sub>10</sub> concentrations, epidemiological studies have shown that the association between PM<sub>10</sub> and acute cardiovascular events is primarily driven by the PM<sub>2.5</sub> fraction.<sup>47</sup> This fraction is enriched with ultrafine particles derived from the combustion of fossil fuels, which toxicology studies have suggested are the most potent component of particulate matter.<sup>48</sup> These particles are potentially small enough to translocate from the lungs into the circulation and are therefore perhaps more likely to trigger acute cardiovascular episodes.<sup>49</sup> Interestingly, all three gaseous pollutants derived from combustion (nitrogen dioxide, sulphur dioxide, and carbon monoxide) were associated with stroke, and this was consistent with reported associations with admission for heart failure and acute myocardial infarction.<sup>3 4 36</sup>

#### Possible mechanisms explaining relation between stroke and air pollution

Several large cohort studies have shown a positive association between long term exposure to ambient air pollution and coronary and cerebrovascular events.<sup>50–52</sup> Staffoglia and colleagues showed that even in high income countries, where annual mean air pollution concentrations meet current international standards, small increases in PM<sub>2.5</sub> were associated with a 19% increase in the risk of cerebrovascular disease, including both ischaemic and haemorrhagic events.<sup>51</sup> Long term exposures to PM<sub>2.5</sub> accelerate carotid atherosclerosis.<sup>53</sup> The underlying pathophysiological mechanisms after acute exposure to air pollutants in triggering stroke, however, remain unclear and might differ for haemorrhagic and ischaemic stroke.<sup>12</sup> Previous controlled exposure studies have shown that air pollution can adversely affect the vascular endothelium and increase activity of the sympathetic nervous system, resulting in vasoconstriction, increases in blood pressure, ischaemia, and risk of thrombosis.<sup>5 8 54</sup> Indeed, even minor increases in PM<sub>2.5</sub> concentrations are associated with changes in cerebrovascular haemodynamics, including increased cerebrovascular resistance and reduced cerebral blood flow.<sup>55</sup> Another potentially important effect of air pollution that is pertinent to stroke is the risk of atrial arrhythmias, which could predispose to thromboembolic events. It is plausible that the association between short term exposure to air pollution and cerebrovascular events are a result of these important mechanistic pathways.

#### Air pollution and stroke by income of nation

Most of the studies used to derive our pooled estimates originated from high income countries. The smaller number of studies from low and middle income countries is probably a result of less cohesive policies on air quality, inadequate environmental monitoring, and less robust disease surveillance.<sup>56</sup> This is particularly concerning as it is these countries that bear a disproportionate burden of the global morbidity and mortality from stroke.<sup>12</sup> More concerning are the trends for cerebrovascular disease, where the incidence is falling by

12% in high income countries and increasing by 12% in low and middle income countries.<sup>10</sup> Urban cities in low and middle income countries not only experience high levels of ambient air pollution but also have larger daily fluctuations in levels.<sup>57 58</sup> Our pooled estimates stratified by region showed larger associations in low and middle income countries than in high income countries. Our estimates from low and middle income countries, however, predominantly come from East Asia, mainly mainland China followed by Latin America, South East Asia, and South Africa. There still remains a paucity of data from other highly populated regions including the Indian subcontinent and north and central Africa.

### Limitations

Several limitations of our study should be considered. Firstly, unlike other cardiac conditions such as myocardial infarction, case definition for stroke, especially when administrative data are used, might be less reliable.<sup>59 60</sup> Secondly, many studies measured concentrations of air pollution at remote monitoring sites, and it is therefore likely there will be some degree of misclassification of exposure. While there might be good correlations in measurements between pollutant concentrations at patient specific locations compared with those measured at remote stations, it is likely that highly urbanised city centres will not only experience higher concentrations but also greater fluctuations in concentrations. Therefore such ecological studies might underestimate the overall associations reported for stroke and air pollution. Thirdly, we did not have access to primary data and were not able to determine whether patients were included across multiple studies if there was partial temporal overlap between studies from the same geographical location. We did, however, exclude studies with complete geographical and temporal overlap during meta-analysis. Finally, we noticed significant heterogeneity (except for PM<sub>10</sub>) across all pollutants. This could be because of systemic differences in the baseline characteristics of the underlying population in addition to misclassification of both the measurement of pollutant and outcome. Our sensitivity analysis after exclusion of studies with a high risk of bias, however, showed similar results to the overall effect estimates.

### Conclusion

Stroke remains the second most common cause of death and third most important cause of disability worldwide. Over the past 20 years many environmental studies have evaluated the association between outdoor air pollution and stroke, with varying conclusions. Our pooled estimates now show a marked and close association between exposure to pollutants and adverse stroke outcomes. Only a few studies originated from low or middle income countries and yet these countries experience the highest levels of air pollution and bear a disproportionate burden of global stroke mortality and morbidity. Public and environmental health policies that aim to reduce air pollution levels might reduce the burden of stroke.

**Contributors:** ASVS and KKL contributed equally. ASVS conceived and designed the study. ASVS, KKL, and AH acquired the data. ASVS, KKL, DM, DEN, and NLM analysed and interpreted the data. ASVS, DEN, DM, and NLM drafted the initial manuscript. All authors made critical revisions of the manuscript for important intellectual content and approved the final version of the report. ASVS is guarantor.

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**Competing interests:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/col\\_disclosure.pdf](http://www.icmje.org/col_disclosure.pdf) and declare: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** Not required.

**Data sharing:** No additional data available.

**Transparency:** The lead author, (the manuscript's guarantor), affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix 1: Detailed search strategy

Appendix 2: Flow chart of included studies

Appendix 3: Contextual details of included studies: summary of study demographics and pollutants measured

Appendix 4: Contextual details of included studies: adjustment and assessment of bias

Appendix 5: Funnel plots

Appendix 6: Individual forest plots for each pollutant

Appendix 7: Overall and stratified risk estimates for incident stroke and stroke mortality

Appendix 8: Sensitivity analysis summarising associations between air pollution and stroke before and after removal of studies with increased risk of bias