Air Pollution and Ischaemic Stroke

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Abstract

Air pollution is a significant contributor of cardiovascular diseases, including ischaemic stroke (IS), with substantial mortality and morbidity. However, associations between air pollution and IS remain unclear. Limited data are available on the relationship between IS and individual air pollutants. In this systematic review, we present an overview of the current literature about various individual ambient air pollutants that are believed to contribute towards incidence of hospitalization and mortality related to IS.

Keywords: Air pollutant, air pollution, cerebrovascular accident, environmental epidemiology, environmental health, haze, ischemic stroke

INTRODUCTION

Over the past decades, air pollution has been increasingly shown to be a major global concern to human health. According to the World Health Organization (WHO), air pollution causes the about 7 million deaths globally every year, largely due to increased mortality from cardiovascular diseases, chronic respiratory diseases, lung cancer and acute respiratory infections, which is on par with other major health risks such as tobacco smoking. The WHO air quality guidelines propose recommendations on the acceptable levels of air pollutants, which has been lowered in the 2021 update to reflect recent research on the adverse health effects at lower levels of air pollution. It is estimated that 99% of the world population live with air pollution above the levels recommended by WHO, who are vulnerable to the increased risk of non-communicable diseases such as stroke and ischaemic heart disease.

Globally, stroke is the second leading cause of death and third leading cause of death and disability combined. The yearly incidence of stroke is 12 million patients and is responsible for 143 million disability-adjusted life years (DALYs). Despite falling age-standardised mortality and DALY rates, the annual number of stroke and deaths increased substantially from 1990 to 2019, especially in low-income countries due to their urbanization and industrialization. In 2019, the Global Burden of Disease study found that air pollution accounted for 28.7 million stroke-related DALYs and was one of the five leading risk factors for stroke.

In this review, we explored the impact of air pollution on ischemic stroke, and summarised the evidence of short-term and long-term exposure to individual pollutants. The potential mechanisms behind the association and potential interventions or future research directions are discussed.

AIR POLLUTANTS

The major air pollutants reported by the WHO are particulate matter (PM), and gaseous pollutants such as ozone (O₃), carbon monoxide (CO), nitrogen dioxide (NO₂) and sulphur dioxide (SO₂). The levels of outdoor pollution levels have been declining over the last few decades in high income countries, particularly in North America and Europe. However, levels of air pollution in developing nations in Asia, Africa and South America remains consistently high.

Particulate matter

PM is a complex mixture of solid and liquid particles of organic and inorganic substances and is thought to be the air pollutant with strong association with increased mortality. Coarse particles with a diameter of ≤10 μm (PM₁₀) from resuspension of soil and dust by wind or industrial activity generally remain in the upper bronchus, but fine particles with a diameter of ≤2.5 μm (PM₂.₅) produced from fossil fuel combustion can enter the bronchioles, alveoli and blood stream, causing systemic damage. Due to the harmful effects of PM, the WHO recommends an air quality guideline (AQG) PM₂.₅ level of <5 μg/m³ in the 2021 update, a decrease from 10 μg/m³ in the previous version.

Ozone

Ozone is a strong oxidant and can cause biological damage. Ground level ozone causes photochemical smog and is generated from a chemical reaction between nitrogen oxides and volatile organic compounds from vehicles and industry.
emissions. The concentration of ozone increases in warm weather due to sunlight exposure, increasing the rate of photochemical reactions. Inhaled ozone can penetrate deeply into the lungs, causing respiratory and cardiac deaths.

**Carbon monoxide (CO)**
CO is a colourless, odourless gas produced from incomplete combustion of fossil fuels, for example from motor vehicles. Due to its higher affinity for haemoglobin than oxygen, CO can cause hypoxia and ischaemia related cardiovascular and cerebrovascular diseases.

**Nitrogen dioxide (NO₂)**
NO₂ is produced principally by combustion processes in road traffic, power generation and heating. It is a free radical that when inhaled, is absorbed by the respiratory tract and deposited in the lung peripheries, leading to increased respiratory diseases.

**Sulphur dioxide (SO₂)**
SO₂ is a colourless gas with sharp odour, produced from fossil fuel burning and smelting of mineral ores containing sulphur. As an irritant, SO₂ causes bronchitis, bronchospasm and has been associated with worsening of cardiovascular diseases.

It is also associated with acid rain, leading to deforestation and environmental damage.

**Short-term Air Pollution and Stroke**

Short-term exposure to air pollution is associated with increased risk of stroke and related mortality, which may have a lag of several days. Studies from countries across all continents except Antarctica found the strongest short-term association of PM with stroke. CO, SO₂, NO₂ and O₃ were also associated with cerebrovascular disease. The results of recent meta-analyses are presented in Table 1.

**Stroke incidence**
The incidence of stroke is associated with PM₂.₅, PM₁₀, SO₂, NO₂, CO and O₃ in several meta-analysis and cohort studies. Across 3 meta-analyses, every 10 μm/m³ increase in PM₂.₅ was significantly associated with increased incidence and admission with stroke (HR 1.008-1.012). This was consistently observed in time-series analysis and case-crossover studies based in Europe, Asia, North and South America, especially in studies on ischaemic stroke. Similarly, two meta-analyses of 15 and 21 studies each found a significant association of PM₁₀ with incidence or admission with stroke (HR 1.004-1.006 per 10 μm/m³ increase). The Asian dust storm events, mainly driven by PM₁₀, were significantly associated with stroke admission in Taiwan.

In Korea, a national study on 13,535 patients found that PM₁₀ and SO₂ were independently associated with cardioembolic stroke when compared to large artery atherosclerosis and non-cardioembolic stroke. Another study in Italy found an association of PM₁₀ with lacunar stroke. Other studies in China, US, UK and Italy confirmed the relationship between PM₁₀ and stroke incidence or admission.

For gaseous pollutants, NO₃ is most associated with stroke incidence and admission. Meta-analysis of 15 studies by Niu et al. and 24 studies by Yang et al. found a 2.2-2.3% increase in stroke with every 10 μm/m³ increase in NO₃ concentration. The study of lag effect showed that the association was the strongest on the day of stroke (lag 0) and diminishes with increasing lag. The relationship between O₃ and stroke is inconsistent, with the meta-analysis by Niu et al. and Yang et al. who reported a significant association, which was not seen in the meta-analysis by Shah et al. O₃ was associated with stroke in several studies in China, Korea, Iran, US, France and Iceland. The effect of air pollution on stroke appeared higher in Asian countries than European or North American countries, which could be due to the higher prevalence of low- or middle-income countries in Asia. However, the geographical variation could have contributed to the high heterogeneity between studies.

Integrated markers of air pollution are also associated with stroke incidence. In Singapore, a city-state with seasonal exposure to the Southeast Asian haze, the Pollution Standards Index (PSI) was associated with stroke occurrence, and the escalated risk persisted up to lag 5. Furthermore, in Canada, the Air Quality Health Index, CO and NO were positively associated with emergency department presentations with ischaemic stroke.

**Stroke survival**
The meta-analysis of 94 studies by Shah et al. found that air pollution was positively associated with a combined outcome of stroke admission and mortality. Several recent meta-analysis reported that short-term concentration of PM₂.₅ (HR 1.008-1.020), PM₁₀ (HR 1.006-1.007), SO₂ (HR 1.006-1.025), NO₂ (HR 1.009-1.015), CO (HR 1.045-1.078), and O₃ (HR 1.005-1.014) were associated with stroke mortality. Studies on PM₂.₅ were performed across different continents, including China, Korea, Japan, US, Italy, Finland and Brazil, which found consistent associations with stroke mortality across different levels of air pollution. Interestingly, PM may affect stroke outcomes post revascularisation. Cappellari et al. found that in stroke patients who underwent intravenous thrombolysis, increased exposure to PM₂.₅, PM₁₀ and NO₂ 3 days and 4 weeks prior to the stroke were independently associated with 3-month mortality.

Short-term exposure to SO₂, NO₂, and CO increases stroke mortality. Two previous meta-analysis showed 0.6-2.5% increase in risk of stroke mortality with every 10 μm/m³ of SO2 and a 0.9-1.5% increase with NO2. CO was significant associated with stroke mortality in a meta-analysis of 16 studies by Yang et al. but not in the meta-analysis of 5 studies by Niu et al. However, O₃ was consistently shown to be not associated with stroke mortality by Niu et al., Yang et al. and Shah et al. Studies on CO and O₃ were mostly performed in Asia, particularly in China and Korea, with few studies from other regions such as Iran and Finland. There
was significant heterogeneity for all gaseous pollutants,\textsuperscript{[15]} and significant publication bias with the literature on O\textsubscript{3}~\textsuperscript{[14]} suggesting that more research is needed on the association of short-term exposure to gaseous pollutants and stroke mortality.

**LONG-TERM AIR POLLUTION AND STROKE**

Long-term exposure to air pollution, often measured as the mean annual concentration, is also associated with stroke incidence and mortality in previous studies\textsuperscript{[13,43,44]} The results of meta-analysis on this relationship is presented in Table 2.

**Stroke incidence**

PM\textsubscript{2.5} is the most investigated air pollutant, whereas long-term exposure to PM\textsubscript{2.5} remains most strong association with stroke incidence or admission. Three meta-analysis were performed between 2019 and 2021, which showed that long-term 10 m\textsuperscript{m/m\textsuperscript{3}} increase in PM\textsubscript{2.5} was associated with 2-13\% increase in stroke.\textsuperscript{[13,43,44]} They included large population-based cohorts in China,\textsuperscript{[6]} US,\textsuperscript{[45]} Canada\textsuperscript{[46]} and Europe.\textsuperscript{[47]} Ischaemic-stroke specific analysis confirmed the relationship between PM\textsubscript{2.5} and stroke incidence in a cohort of 115,575 patients, with an almost linear exposure-response relationship.\textsuperscript{[6]} In Ontario, Canada, interquartile range increments in 5-year mean concentrations of PM\textsubscript{2.5}, NO\textsubscript{2} and O\textsubscript{3} were associated with atrial fibrillation (AF) and stroke incidence.\textsuperscript{[48]} A study of 11 cohorts in Europe found that both PM\textsubscript{2.5} and PM\textsubscript{10} were associated with incident stroke, and 5 m\textsuperscript{m/m\textsuperscript{3}} increase in PM\textsubscript{2.5} was linked to a 19\% increase in stroke, even at low levels <25 m\textsuperscript{m/m\textsuperscript{3}}.\textsuperscript{[3,47]} Long-term exposure to PM\textsubscript{10} was also associated with stroke in Israel,\textsuperscript{[49]} Sweden,\textsuperscript{[50]} Germany\textsuperscript{[51]} and UK,\textsuperscript{[52]} however, studies in low- and middle-income countries are lacking. Annual mean traffic-related PM\textsubscript{10} was associated with stroke in Stockholm, Sweden,\textsuperscript{[50]} and both exhaust and non-exhaust PM\textsubscript{10} were associated with total anterior circulation infarcts in South London.\textsuperscript{[52]}

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**Table 1: Meta-analysis of short-term exposure to air pollutants and stroke**

| Author | Year | Database | Number of studies | Pollutant | HR (95\% CI) | I\textsuperscript{2} |
|--------|------|----------|------------------|-----------|--------------|----------------|
| **Incidence or admission** | | | | | | |
| Niu et al. | 2021 | Pubmed, Embase, Web of Science | 19 | PM2.5 | 1.008 (1.005-1.011) | 96.6\% |
| | | | 15 | PM10 | 1.004 (1.001-1.006) | 92.7\% |
| | | | 13 | SO2 | 1.013 (1.007-1.020) | 94.5\% |
| | | | 15 | NO2 | 1.023 (1.015-1.030) | 92.6\% |
| | | | 8 | CO | 1.000 (1.000-1.001) | 92.7\% |
| | | | 15 | O3 | 1.002 (1.000-1.003) | 80.2\% |
| Fu et al. | 2019 | Pubmed | 54 | PM2.5 | 1.01 (1.01-1.02) | 94.1\% |
| Yang et al. | 2014 | Pubmed, Embase, Web of Science | 8 | PM2.5 | 1.012 (1.002-1.022) | 38.2\% |
| | | | 21 | PM10 | 1.006 (1.003-1.009) | 76.2\% |
| | | | 22 | SO2 | 1.015 (1.007-1.024) | 74.0\% |
| | | | 16 | CO | 1.030 (1.007-1.053) | 76.0\% |
| | | | 24 | NO2 | 1.022 (1.012-1.033) | 82.6\% |
| | | | 20 | O3 | 1.005 (1.000-1.010) | 66.2\% |
| **Admission and mortality** | | | | | | |
| Shah et al. | 2015 | Medline, Embase, CINAHL, Web of Science | 41 | PM2.5 | 1.011 (1.011-1.012) | 86\% |
| | | | 78 | PM10 | 1.003 (1.002-1.004) | 24\% |
| | | | 52 | SO2 | 1.019 (1.011-1.027) | 32\% |
| | | | 70 | NO2 | 1.014 (1.009-1.019) | 52\% |
| | | | 37 | CO | 1.015 (1.004-1.026) | 68\% |
| | | | 53 | O3 | 1.001 (1.000-1.002) | 58\% |
| **Mortality** | | | | | | |
| Niu et al. | 2021 | Pubmed, Embase, Web of Science | 12 | PM2.5 | 1.008 (1.005-1.012) | 89.2\% |
| | | | 10 | PM10 | 1.006 (1.003-1.010) | 83.3\% |
| | | | 6 | SO2 | 1.006 (1.005-1.008) | 45.8\% |
| | | | 10 | NO2 | 1.009 (1.003-1.016) | 70.1\% |
| | | | 5 | CO | 1.045 (0.980-1.115) | 50.6\% |
| | | | 6 | O3 | 1.005 (0.999-1.010) | 84.8\% |
| Fu et al. | 2019 | Pubmed | 9 | PM2.5 | 1.02 (1.01-1.04) | 92.13\% |
| Yang et al. | 2014 | Pubmed, Embase, Web of Science | 8 | PM2.5 | 1.013 (1.003-1.024) | 38.2\% |
| | | | 21 | PM10 | 1.007 (1.005-1.008) | 76.2\% |
| | | | 22 | SO2 | 1.025 (1.018-1.031) | 74.0\% |
| | | | 16 | CO | 1.078 (1.05-1.116) | 76.0\% |
| | | | 24 | NO2 | 1.015 (1.004-1.026) | 82.6\% |
| | | | 20 | O3 | 1.014 (0.995-1.032) | 66.2\% |
Several studies investigated long-term exposure to gaseous air pollutants with stroke incidence, but no meta-analysis has been published so far. A population-based cohort of 5 million residents in Ontario, Canada found a significant association of interquartile increase in NO\(_2\) (HR 1.04) and O\(_3\) (HR 1.05) with stroke.\(^{49}\) On a follow-up of 9.8 years, interquartile increase in NO\(_2\) was associated with ischaemic stroke and severe stroke followed by death within 30 days.\(^{51}\) However, studies in Korea and Stockholm did not find a significant relationship between long-term NO\(_2\) levels and ischaemic stroke.\(^{54,55}\) Long-term exposure to ambient air pollution determined by distance to a roadway was not associated with subclinical cerebrovascular disease on magnetic resonance imaging.\(^{45}\) Due to the differences in measurement of pollutant concentration (e.g., annual mean, monthly mean, proxy by distance to roadway) comparisons between studies and therefore meta-analysis is challenging. Future research should develop consistent methods to measure exposure and standardise reporting.

### Stroke survival

Similar to stroke incidence, PM\(_{2.5}\) is most investigated and most strongly associated with stroke survival.\(^{13,43,44}\) Three meta-analysis of 17 studies, 13 studies and 6 studies, respectively, reported a 3%–24% increase in stroke mortality associated with an increase in long-term PM\(_{2.5}\) concentration by 10 \(\mu\)g/m\(^3\).\(^{3,13,43,44}\) In China, PM\(_{2.5}\) and PM\(_{10}\) (ultrafine particles) were associated with 1-year mortality after ischaemic stroke but not with PM\(_{10}\) or NO\(_2\).\(^{56}\) Similarly, studies in the US\(^{57,58}\) and UK\(^{59}\) found significant associations of PM\(_{2.5}\) with stroke mortality. In contrast, the study in Australia found no significant association between PM\(_{2.5}\) and NO\(_2\) with stroke mortality, which was attributed to the low pollutant level and baseline incidence of stroke in Australia.\(^{60}\) PM\(_{10}\) and CO was associated with stroke mortality in the UK\(^{25}\) and NO\(_2\) was shown to be associated with stroke mortality in Denmark\(^{53}\) and UK.\(^{25}\) Studies on long-term SO\(_2\) and O\(_3\) with stroke mortality are lacking, and further research is needed to explore this potential relationship.

### Effect Modification of Air Pollution-Associated Stroke

Consistently high heterogeneity in the effect sizes of the impact of air pollution on stroke incidence or mortality suggest variable susceptibility to air pollution-induced stroke in the general population. Previous studies have studied subgroups and effect modifiers that may increase the vulnerability to adverse health effects of air pollution.

### Socioeconomic status and income

At the country level, national income may affect the impact of air pollution on stroke. The meta-analysis performed by Shah et al.\(^{12}\) in 2015 found that pooled estimates from studies performed in middle- or low-income countries, a majority of which from China, showed stronger associations between NO\(_2\) and PM\(_{10}\) and stroke than studies from high-income countries. The mean concentrations of NO\(_2\) and PM\(_{10}\) were higher in middle- and low-income countries than high-income countries, which may explain the stronger association.\(^{12}\) There is a paucity of studies from Africa and the Indian subcontinent, and with the increasing stroke incidence and mortality in developing nations, research in these areas is needed.

Individual socioeconomic status may also modify the effect of air pollution on stroke. In the US, higher levels of PM\(_{2.5}\) were associated with higher odds of severe stroke in those with higher disadvantage scores than those from lower disadvantage areas.\(^{61}\) In another study performed in the US, PM\(_{2.5}\) was no longer significantly associated with stroke risk after accounting for socioeconomic status. In Canada, the long-term average NO\(_2\) and CO levels were associated with higher stroke risk, but this was strongly attenuated by household income levels.\(^{60}\) The reasons underlying this is unclear, and qualitative research to identify root causes for the increased air pollution-associated stroke in areas with lower socioeconomic status may be useful to inform targeted interventions in these areas.

### Demographic characteristics

Age, sex and ethnicity have been explored as effect modifiers in previous studies on stroke and air pollution. A majority of studies with subgroup analysis based on age found that older age was associated with increased vulnerability to air pollution-associated stroke. This included studies performed in large cities in China,\(^{34,62}\) Singapore,\(^{32}\) UK,\(^{63}\) Spain,\(^{84}\) 11 cohorts in Europe\(^{47}\) and Canada.\(^{31}\) In contrast, one study in Chongqing, China, on O\(_3\) and NO\(_2\) contrasted this and found a higher risk in those age <60 years.\(^{65}\) which might be due to behavioural differences where older individuals were more
likely to stay at home when air quality was poor. The effect of gender is not well-established. Some studies found a stronger association in women,[32,42,60] whereas others found a stronger association with men.[63,67,68] Ethnic differences were suggested by a study in the US, which found that \( O_3 \) was associated with greater odds of ischaemic stroke for Mexican Americans than non-Hispanic Whites.[69] However, another study investigating \( O_3 \) did not find any differences between African American and European Americans with regards to ischaemic stroke.[70]

**Recurrent stroke**

Patients with previous stroke may be more vulnerable to air pollution-associated stroke. An interquartile range increase in PM \(_{10}\) concentration was associated with 2.3% increase in ischaemic stroke events in those with previous stroke, but not in those without any previous stroke.[70] This was also observed with short-term \( O_3 \) in a study performed in France, where there was a linear relationship with recurrent stroke and large artery stroke only.[71] The association of short-term \( NO_2 \) with ischaemic stroke was stronger in those with a history of stroke in a Canadian study.[72] In contrast, the study on patients with recurrent ischaemic stroke found no association with PM \(_{2.5}\) and \( O_3 \), but the study may be underpowered due to a limited variability in exposure levels in Corpus Christi, Texas, US.[73]

**Cardiovascular risk factors**

Diabetes mellitus was associated with increased stroke associated with PSI, PM \(_{2.5}\), PM \(_{10}\), and nitrogen oxides in several studies, for both short- and long-term exposures.[32,68,74-76] Stroke admission associated with \( NO_2 \), CO, \( SO_2 \) was also increased in patients with hypertension and heart disease.[77] Hypertension was found to be a possible mediator between PM \(_{10}\) and stroke,[77] and was also seen in stroke associated with PSI.[72] Similarly, obesity was also associated with increased air pollution-associated stroke.[77,66,68] However, studies on hyperlipidaemia are conflicting.[32,77-79] Necessitating better designed and powered studies to evaluate the association. Interestingly, non-smokers seemed more vulnerable to air pollution-associated stroke, which was shown in a study on PM \(_{2.5}\) and PM \(_{10}\).[79] Pre-existing cardiac disease was also associated with increased air pollution-associated stroke in two studies on short-term exposure to \( NO_2 \), CO, \( SO_2 \), \( O_3 \) and PM.[77,80]

**Mechanisms Mediating the Association of Air Pollution and Stroke**

Acute exposure to air pollutants can promote stroke through a variety of proposed mechanisms that can largely be divided into two main categories, including activation of the thrombosis pathway and systemic vascular dysfunction. On the contrary, atherosclerosis progression, peripheral artery disease and systemic vascular dysfunction are thought to be the main underlying mechanisms during chronic exposure to air pollutants.

**Hypercoagulopathy and thrombosis**

Independent studies performed in patients with chronic obstructive pulmonary disease collectively found short-term exposure to a range of air pollutants (\( NO_2 \), CO and PM \(_{10}\)) to correlate with increased plasma fibrinogen.[81,82] Others have found elevated ambient \( NO_2 \) or CO in the previous day of blood sampling to be associated with a 1.5% increase in plasma fibrinogen in a population based study.[83] Similarly, acute exposure to ambient air pollution is associated with elevated plasma levels of plasminogen activator inhibitor-1 (PAI-1) and soluble platelet selectin (sP-selectin), which is a marker associated with platelet activation.[85] Studies conducted around the 2008 Beijing Olympic Games, where there was a decrease in air pollution due to strict restriction policies, found plasma sP-selectin and von Willebrand factor (vWF) to be reduced in relation to improved air quality.[86,87] A prothrombotic state through elevated plasma levels of prothrombotic factors and direct platelet activation have been associated with increased stroke incidence and mortality,[88-90] providing a potential mechanistic link between air pollution and stroke.

**Endothelial dysfunction and blood pressure**

Exposure to air pollution can result in systemic vascular dysfunction due to vasoconstriction and increasing blood pressure. Critically, hypertension is a key risk factor associated with increased incidence and worse outcomes in both ischaemic and haemorrhagic stroke.[91,92] Short-term exposure to PM \(_{2.5}\) and \( O_3 \) at ambient concentrations in healthy volunteers under experimental settings led to acute arterial vasoconstriction in a small study.[93] The endothelium plays key roles in modulating arterial tone, and endothelial dysfunction results in vasoconstriction due to reduced NO.[94] Episodic PM \(_{2.5}\) exposure in healthy adults correlated with endothelial cell apoptosis, along with increased circulating monocytes and CD4+ and CD8+ T cells, which is consistent with systemic inflammation.[95] Importantly, the pathogenic roles of T cells in stroke are well documented through a plethora of animal and human studies.[96,97] In addition, many studies have related both short and long term PM \(_{2.5}\) exposure to increased blood pressure.[98] A randomised crossover trial found that reduced short-term exposure to ambient air pollutants in Beijing through the use of facemasks resulted in significantly lower ambulatory blood pressure in patients with coronary artery disease.[99] Overall, although several studies identified air pollution exposure to be associated with a range of stroke risk factors, further mechanistic studies are required to better elucidate the mechanisms underlying air pollution and stroke predisposition.

**Atherosclerosis**

During chronic exposure to air pollutants, stroke predisposition is mainly thought to be due to progression of atherosclerosis. Using a variety of surrogates, including carotid intima-media thickness and coronary artery calcification, independent studies found PM \(_{2.5}\) and PM \(_{10}\) to be associated with atherosclerosis.[100-103] Residents that live in closer...
proximity to major roads with presumed increased exposure to traffic-related air pollution, have increased risk of atherosclerosis and peripheral artery disease as measured by arterial calcification, carotid-intima-media thickness and ankle brachial index.\cite{102,104,105} Finally, increased blood pressure due to air pollution exposure may facilitate subsequent plaque rupture, leading to thrombosis and stroke.\cite{106}

**Potential Interventions and Future Research Direction**

Behavioural factors may modify the effects of air pollution exposure on stroke, thus allowing means of intervention through education and enforced regulations. A recent study found the increase in blood pressure associated with long-term exposure to air pollution (PM$_{2.5}$, PM$_{10}$ or NO$_x$) is more pronounced in individuals who consume 75 g of more meat per day.\cite{107} On the contrary, daily consumption of 500 g or more vegetable and fruits did not affect risk of high blood pressure associated with air pollutants but these subjects had lower odds of stroke associated with PM$_{2.5}$.\cite{108} These results suggest that education and public health awareness may reduce the detrimental effects of air pollution on stroke, but more studies are needed to confirm these findings.

Reduction in ambient air pollution has measurable effects on stroke. This was evident when temporary reduction in air pollution during the Beijing 2008 Olympics, was associated with reduced plasma vWF\cite{86,87}, an important risk factor for stroke due to its prothrombotic functions.\cite{109,110} Implementation of public transport can also reduce air pollution and associated stroke risk. Residents living in surrounding areas of the light rail transit in Houston had significantly reduced daily stroke mortality, which mirrors the lower acetylene levels after LRT implementation.\cite{111}

Intriguingly, the contemporary COVID-19 pandemic provided a unique opportunity to study the potential effects of air pollution intervention on stroke. A modelling study found nationwide lockdown measures due to COVID-19 across China and Europe and the resultant 29.7% and 17.1% reduction in population-weighted PM$_{2.5}$, respectively, was associated with significantly reduced premature mortality related to multiple cardiovascular and respiratory conditions, including stroke.\cite{112} Similarly, a study in Pakistan found significantly improved air quality during the COVID-19 pandemic, to be associated with reduced stroke-related hospital admissions potentially due to reduced incidence.\cite{111} Finally, face coverings may reduce short-term exposure to ambient air pollution. Given the association of hypertension to stroke, facemask-wearing led to increased heart rate variability and reduced mean arterial blood pressure during prescribed walks in a randomised crossover trial.\cite{99} Altogether, these observations suggest that interventions against air pollution may be effective in reducing stroke risk or mortality.

There are several limitations to the methodology of the current literature. The date of admission to hospital or presentation to emergency department is often used as the date of onset of stroke, and a study by Lokken et al.\cite{116} found that assessing exposure based on hospitalization date could underestimate the strength of associations compared to date of presentation. There are also concerns that the date of onset of stroke may differ from date of presentation, and there may be significant recall bias. However, in a study that compared using the date of onset as reported by the patient and the date of presentation, more than 70% of patients experienced stroke onset on the same day as presentation to hospital, and this was an unlikely source of error.\cite{115} Many studies also used ICD 9 or ICD 10 to identify patients who had a stroke from large databases, and although the change from ICD 9 to ICD 10 may not significantly affect the effects of air pollution,\cite{116} the use of coding systems may cause an over- or under-capture of cases.\cite{117} There is also a lack of clinical detail associated, increasing the challenge of identifying relationships with stroke subtypes.

**Conclusion**

There is strong evidence that short- and long-term exposure to air pollution is linked to increased stroke incidence and mortality. The mechanism behind the association of air pollution and stroke may be related to hypercoagulopathy, endothelial dysfunction, increased blood pressure and atherosclerosis. Although the incidence of stroke and levels of air pollution are decreasing in developed countries, the stroke burden and air pollution is constant or increasing in developing countries. Further research from middle- and low-income countries is needed, especially regarding long-term exposure to air pollutants. It is important to reduce levels of air pollution globally, to reduce the associated adverse health effects.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. WHO. Ambient (outdoor) air pollution. Available from: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health. [2019, Last accessed on 2021 Dec 15].
2. WHO. WHO global air quality guidelines: Particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. 2021. Available from: https://www.who.int/publications/i/item/9789240034228. [Last accessed on 2021 Dec 15].
3. Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, et al. Global, regional, and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the global burden of disease study 2019. Lancet Neurol 2021;20:795-820.
4. Verhoeven JJ, Allach Y, Vaartjes ICH, Klijn CJM, de Leeuw FE. Ambient air pollution and the risk of ischaemic and haemorrhagic stroke. Lancet Planet Health 2021;5:e542-52.
5. Shaddick G, Thomas ML, Mudu P, Ruggeri G, Guny S. Half the world’s population are exposed to increasing air pollution. npj Clim Atmos Sci 2020;3:23. doi: 10.1038/s41612-020-0124-2.
6. Huang K, Liang F, Yang X, Liu F, Li J, Xiao Q, et al. Long term exposure to ambient fine particulate matter and incidence of stroke: Prospective cohort study from the China-PAR project. BMJ 2019;367:l6720. doi: 10.1136/bmj.l6720.
7. Hatch GE, Slade R, Harris LP, McDonnell WF, Devlin RB, Koren HS, et al. Ozone dose and effect in humans and rats. A comparison using oxygen-18 labeling and bronchoalveolar lavage. Am J Respir Crit Care Med 1994;150:676-83.

8. Liu C, Yin P, Chen R, Meng X, Wang L, Niu Y, et al. Ambient carbon monoxide and cardiovascular mortality: A nationwide time-series analysis in 272 cities in China. Lancet Planet Health 2018;2:e12-8.

9. Bell ML, Peng RD, Dominici F, Samet JM. Emergency hospital admissions for cardiovascular diseases and ambient levels of carbon monoxide: Results for 126 United States urban counties, 1999-2005. Circulation 2008;117:949-55.

10. Lanzara U, Gerdes S, Baur X. Effects of nitrogen dioxide on human health: Systematic review of experimental and epidemiological studies conducted between 2002 and 2006. Int J Hyg Environ Health 2009;212:271-87.

11. Sunyer J, Ballester F, Tertre AL, Atkinson R, Ayres JG, Forastiere F, et al. The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (The AirPoll-study). Eur Heart J 2003;24:752-60.

12. Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, et al. Short term exposure to air pollution and stroke: Systematic review and meta-analysis. BMJ 2015;350:h1295. doi: 10.1136/bmj.h1295.

13. Fu P, Guo X, Cheung FMH, Yong KKL. The association between PM (2.5) exposure and neurological disorders: A systematic review and meta-analysis. Sci Total Environ 2019;655:1240-8.

14. Niu Z, Liu F, Yu H, Wu S, Xiang H. Association between exposure to ambient air pollution and hospital admission, incidence, and mortality of stroke: An updated systematic review and meta-analysis of more than 23 million participants. Environ Health Prev Med 2021;26:15. doi: 10.1186/s12949-021-00937-1.

15. Yang WS, Wang X, Deng Q, Fan WY, Wang WY. An evidence-based appraisal of global association between air pollution and risk of stroke. Int J Cardiol 2014;175:307-13.

16. Byrne CP, Bennett KE, Hickie A, Kavanagh P, Broderick B, O’Mahony M, et al. Short-term air pollution as a risk for stroke admission: A time-series analysis. Cerebrovasc Dis 2020;49:404-11.

17. Gu J, Shi Y, Chen N, Wang H, Chen T. Ambient fine particulate matter and hospital admissions for ischemic and hemorrhagic strokes and transient ischemic attack in 248 Chinese cities. Sci Total Environ 2020;715:136896. doi: 10.1016/j.scitotenv.2020.136896.

18. Leiva GM, Santibañez DA, Ibarra ES, Matus CP, Seguel R. A five-year study of particulate matter (PM2.5) and cerebrovascular diseases. Environ Pollut 2013;181:1-6. doi: 10.1016/j.envpol.2013.05.057.

19. Tian Y, Xiang T, Wu Y, Cao Y, Song J, Sun K, et al. Fine particulate air pollution and first hospital admissions for ischemic stroke in Beijing, China. Sci Rep 2017;7:3897. doi: 10.1038/s41598-017-04312-5.

20. Kang JH, Liu TC, Kellar J, Lin HC. Asian dust storm events are associated with an acute increase in stroke hospitalization. J Epidemiol Community Health 2013;67:125-31.

21. Chung JW, Bang OY, Ahn K, Park SS, Park TH, Kim JG, et al. Air pollution is associated with ischemic stroke via cardioembolic embolism. Stroke 2017;48:17-23.

22. Corea F, Silvestrelli G, Bucarello A, Giua A, Previdi P, Siliprandi G, et al. Airborne pollutants and lacunar stroke: A case cross-over analysis on stroke unit admissions. Neurol Int 2012;4:e11. doi: 10.4081/ni.2012.e11.

23. Liu H, Tian Y, Xu Y, Haung Z, Haung C, Hu Y, et al. Association between ambient air pollution and hospitalization for ischemic and hemorrhagic stroke in China: A multicity case-crossover study. Environ Pollut 2017;230:234-41.

24. Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Kourtakis P, et al. Ambient air pollution and the risk of acute ischemic stroke. Arch Intern Med 2012;172:229-34.

25. Maheshwaran R, Haining RP, Brindle P, Law J, Pearson T, Fryers PR, et al. Outdoor air pollution and stroke in Sheffield, United Kingdom: A small-area level geographical study. Stroke 2005;36:239-43.

26. Vidale S, Bonanomi A, Guidotti M, Arnaboldi M, Sterzi R. Air pollution positively correlates with daily stroke admission and in hospital mortality: A study in the urban area of Como, Italy. Neurot Sci 2010;31:179-82.
term exposure to ambient air pollution and the incidence of stroke in Edmonton, Alberta, Canada. Stroke 2010;41:1319-25.

47. Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: Results from 11 European cohorts within the ESCAPE project. Environ Health Perspect 2014;122:919-25.

48. Shin S, Burnett RT, Kwong JC, Hystad P, van Donkelaar A, Brook JR, et al. Ambient air pollution and the risk of atrial fibrillation and stroke: A population-based cohort study. Environ Health Perspect 2019;127:87009. doi: 10.1289/EHP4883.

49. Yitshak Sade M, Novack Y, Ifgarne G, Horev A, Klooq L. Air pollution and ischemic stroke in young adults. Stroke 2015;46:3348-53.

50. Korek MJ, Bellander TD, Lind T, Bottai M, Eneroth KM, Caracciolo B, et al. Traffic-related air pollution exposure and incidence of stroke in four cohorts from Stockholm. J Exp Sci Environ Epidemiol 2015;25:517-23.

51. Hoffmann B, Weinmayr G, Hennig F, Fuks K, Moebus S, Weimar C, et al. Air quality, stroke, and coronary events: results of the Heinz Nixdorf recall study from the Ruhr region. Dtsch Arztebl Int 2015;112:195-201.

52. Crichton S, Barratt B, Spiridou A, Hoang U, Liang SF, Kovalchuk Y, et al. Associations between exhaust and non-exhaust particulate matter and stroke incidence by stroke subtype in South London. Sci Total Environ 2016;568:278-84.

53. Andersen ZJ, Kristiansen LC, Andersen KK, Olsen TS, Hvidberg M, Jensen SS, et al. Stroke and long-term exposure to outdoor air pollution from nitrogen dioxide: A cohort study. Stroke 2012;43:320-5.

54. Oudin A, Stroh E, Strömbärg U, Jakobsson K, Björk J. Long-term exposure to ambient air pollution and incidence of stroke. Int Arch Occup Environ Health 2021;94:69-76.

55. Guan T, Xue T, Liu Y, Zheng Y, Fan S, He K, et al. Differential susceptibility in ambient particle-related risk of first-ever stroke: Findings from a national case-crossover study. Am J Epidemiol 2018;187:1001-9.

56. Qin XD, Qian Z, Vaughn MG, Trevathan E, Emo B, Paul G, et al. Gender-specific differences of interaction between obesity and air pollution on stroke and cardiovascular diseases in Chinese adults from a high pollution range area: A large population based cross sectional study. Sci Total Environ 2015;529:243-8.

57. Xu X, Sun Y, Ha S, Talbott EO, Lissaker CT. Association between ozone exposure and onset of stroke in Allegheny County, Pennsylvania, USA, 1994-2000. Neuroepidemiology 2013;41:2-6.

58. Guan T, Xue T, Liu Y, Zheng Y, Fan S, He K, et al. Differential susceptibility in ambient particle-related risk of first-ever stroke: Findings from a national case-crossover study. Am J Epidemiol 2018;187:1001-9.

59. Wing JJ, Adar SD, Sánchez BN, Morgenstern LB, Smith MA, Lisabeth LD. Ethnic differences in ambient air pollution and risk of acute ischemic stroke. Environ Res 2015;143:62-7.

60. Oudin A, Forsberg B, Jakobsson K. Air pollution and stroke. Epidemiology 2012;23:505-6.

61. Sissa L, Fortier M, Lachaude S, Staccini P, Mahagne MH. Ozone air pollution and ischaemic stroke occurrence: A case-crossover study in Nice, France. BMJ Open 2013;3:e004060. doi: 10.1136/bmjopen-2013-004060.

62. Villeneuve PJ, Johnson JY, Pasichnyk D, Lowes J, Kirkland S, Rowe BH. Short-term effects of ambient air pollution on stroke: Who is most vulnerable? Sci Total Environ 2012;430:193-201.

63. Wing JJ, Adar SD, Sánchez BN, Morgenstern LB, Smith MA, Lisabeth LD, et al. Short-term exposures to ambient air pollution and risk of recurrent stroke. Environ Res 2017;152:304-7.

64. O’Donnell MJ, Fang J, Mittleman MA, Kapral MK, Wellenius GA. Environmental air pollution and acute cerebrovascular complications: An ecologic study in Tehran, Iran. Int J Prev Med 2012;3:723-9.

65. Qi X, Wang Z, Guo X, Xia X, Xue J, Jiang G, et al. Short-term effects of outdoor air pollution on acute ischaemic stroke occurrence: A case-crossover study in Tianjin, China. Occup Environ Med 2020;77:862-7.

66. Fisher JA, Puett RC, Laden F, Wellenius GA, Sapkota A, Liao D, et al. Case-crossover analysis of short-term particulate matter exposures and stroke in the health professionals follow-up study. Environ Int 2019;124:153-60.

67. Qian Y, Zhu M, Cai B, Yang Q, Kan H, Song G, et al. Epidemiological evidence on association between ambient air pollution and stroke mortality. J Epidemiol Community Health 2013;67:635-40.

68. Bianca B, Pauwin C, De Luz T, Benoit F, Benfield P, et al. Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients. Eur Respir J 2014;44:603-13.

69. Hildebrandt K, Rückerl R, Koenig W, Schneider A, Pitz M, Heinrich J, et al. Air pollution and ischaemic stroke occurrence: A case-crossover study in Beijing, China, from 2014 to 2018. Ecotoxicol Environ Saf 2021;217:112201. doi: 10.1016/j.ecoenv.2021.112201.
and mechanisms. Environ Health Perspect 2009;117:1232-8.
86. Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, Zhu P, et al. Association between changes in air pollution levels during the beijing olympics and biomarkers of inflammation and thrombosis in healthy young adults. JAMA 2012;307:2068-78.
87. Yuan Z, Chen Y, Zhang Y, Liu H, Liu Q, Zhao J, et al. Changes of plasma vWF level in response to the improvement of air quality: An observation of 114 healthy young adults. Ann Hematol 2013;92:543-8.
88. Danesh J, Leowston S, Thompson SG, Lowe GD, Collins R, Kostis JB, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: An individual participant meta-analysis. JAMA 2005;294:1799-809.
89. Turaj W, Słowiak A, Dziedzic T, Pulyk R, Adamski M, Strojny J, et al. Increased plasma fibrinogen predicts one-year mortality in patients with acute ischemic stroke. J Neurol Sci 2006;246:13-9.
90. Tony AA, Tony EA, Mohammed WS, Kholef EF. Evaluation of plasma levels of neopterin and soluble CD40 ligand in patients with acute ischemic stroke in upper Egypt: Can they surroge the severity and functional outcome? Neuropsychiatr Dis Treat 2019;15:575-86.
91. Woo D, Haverbusch M, Sekar P, Khouria J, Schneider A, et al. Effect of untreated hypertension on hemorrhagic stroke. Stroke 2004;35:1703-8.
92. Wagjarten M, Silva GS. Hypertension and stroke: Update on treatment. Eur Cardiol 2019;14:111-5.
93. Brook RD, Brook JR, Urich B, Vincent R, Rajagopalan S, Silverman F. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. Circulation 2002;105:1534-6.
94. Yu B, Shahid M, Egorina EM, Sovershaev MA, Raher MJ, Lei C, et al. Endothelial dysfunction enhances vasoconstriction due to scavenging of nitric oxide by a hemoglobin-based oxygen carrier. Anesthesiology 2010;112:586-94.
95. Pope CA 3rd, Bhatnagar A, McCracken JP, Abplanalp W, Conklin DJ, Schwartz J, et al. Long-term exposure to black carbon and carotid intima-media thickness: The normative aging study. Environ Health Perspect 2013;121:1061-7.
96. Wajngarten M, Silva GS. Hypertension and stroke: Update on treatment. Eur Cardiol 2019;14:111-5.
97. Hoffmann B, Moebus S, Möhlenkamp S, Stang A, Lehmann N, Dragnano N, et al. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 2007;116:489-96.
98. Wilker EH, Mittleman MA, Coull BA, Gryparis A, Bots ML, Schwartz J, et al. Long-term exposure to black carbon and carotid intima-media thickness: The normative aging study. Environ Health Perspect 2013;121:1061-7.
99. Rohlfing L, Buxton OB, Dye C, Schnitzer ME, Kostis JB, et al. Residential exposure to urban air pollution, ankle-brachial index, and peripheral arterial disease. Epidemiology 2009;20:280-8.
100. Ho, et al.: Air pollution and stroke
101. Diez Roux AV, O’Toole T. Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation. Circ Res 2016;119:1204‑14.
102. Li N, Chen G, Liu F, Mao S, Liu Y, Liu S, et al. Associations between long-term exposure to air pollution and blood pressure and effect modifications by behavioral factors. Environ Res 2020;182:109109. doi: 10.1016/j.envres.2019.109109.
103. Wilker EH, Di Q, Zheng Y, Kowal P, Xiao J, et al. Ambient PM (2.5) and stroke: Effect modifiers and population attributable risk in six low- and middle-income countries. Stroke 2017;48:1191-7.
104. Meyer SFD, Stoll G, Wagner DD, Kleinschnittz C. von Willebrand factor and risk of ischemic stroke. Neurology 1997;49:1552-6.
105. Lin H, Guo Y, Di Q, Zheng Y, Kowal P, Xiao J, et al. Ambient PM (2.5) and stroke: Effect modifiers and population attributable risk in six low- and middle-income countries. Stroke 2017;48:1191-7.
106. Park ES, Sener IN. Impact of light rail transit on traffic-related pollution and stroke mortality. Int J Public Health 2017;62:721-8.
107. Giani P, Castruccio S, Anav A, Howard D, Hu W, Crippa P. Short-term and long-term health impacts of air pollution reductions from COVID-19 lockdowns in China and Europe: A modelling study. Lancet Planetary Health 2020;4:e474-82.
108. Hameed S, Khan M, Fatimi Z, Wasay M. Exploring the relationship between air quality and ischemic stroke admissions during the COVID-19 pandemic. J Stroke Cerebrovasc Dis 2021;30:105860. doi: 10.1016/j.jstrokecerebrovasdis.2021.105860.
109. Lokken RP, Wellenius GA, Coull BA, Burger MR, Schlaug G, Suh HH, et al. Air pollution and risk of stroke: Underestimation of effect due to missclassification of time of event onset. Epidemiology 2009;20:137-42.
110. Johnson JY, Villeneuve PJ, Pasichnyk D, Rowe BH. A retrospective cohort study of stroke onset: Implications for characterizing short term effects from ambient air pollution. Environ Health 2011;10:87. doi: 10.1186/1476-069x-10-87.
111. Qian Z, He Q, Lin HM, Kong L, Liao D, Gong J, et al. Exploring uncertainty of the change from ICD-9 to ICD-10 on acute mortality effects of air pollution. Environ Int 2008;34:248-53.
112. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using the international classification of diseases, revisions 9 and 10. Stroke 2005;36:1776-81.