

Air Pollution and Stroke

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The adverse health effects of air pollution have long been recognised; however, there is less awareness that the majority of the morbidity and mortality caused by air pollution is due to its effects on the cardiovascular system. Evidence from epidemiological studies have demonstrated a strong association between air pollution and cardiovascular diseases including stroke. Although the relative risk is small at an individual level, the ubiquitous nature of exposure to air pollution means that the absolute risk at a population level is on a par with "traditional" risk factors for cardiovascular disease. Of particular concern are findings that the strength of this association is stronger in low and middle income countries where air pollution is projected to rise as a result of rapid industrialisation. The underlying biological mechanisms through which air pollutants exert their effect on the vasculature are still an area of intense discussion. A greater understanding of the effect size and mechanisms is necessary to develop effective strategies at individual and policy levels to mitigate the adverse cardiovascular effects of air pollution.

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Introduction

Exposure to air pollution is now increasingly recognised as a major public health issue and is one of the leading causes of mortality and morbidity, contributing to 6.5 million deaths and 167.3 million disability-adjusted life years (DALYs; a measure of time spent in ill health, disability or premature death) in 2015.¹ More importantly it ranks within the top five risk factors for mortality in emerging economies such as India and China (Figure 1).¹ It was estimated that 99% of deaths attributed to household air pollution and 89% of deaths attributed to ambient air pollution occurred in low and medium income countries (LMICs).²

Although exacerbation of respiratory conditions is intuitively linked with air pollution, over the last two decades evidence has emerged linking air pollution and cardiovascular mortality and morbidity.^{3,4} Recently both epidemiological and mechanistic studies have shown robust associations between air pollu-

tion and atherosclerotic cardiovascular diseases, including myocardial infarction³ and stroke.⁵ The Global Burden of Diseases study estimated that in 2015, air pollution accounted for 19% of all cardiovascular death, 21% of deaths due to stroke and 24% deaths due to ischaemic heart disease.⁶

Stroke remains one of the leading causes of morbidity and mortality worldwide, accounting for over 118.6 million DALYs and 6.3 million deaths in 2015.⁷ It is important to note that this burden of disease varies significantly across different parts of the world. Over the past 20 years, high income countries have experienced a significant decline in age-standardized mortality and DALY rates of approximately 20% to 40%.^{7,8} Conversely, the vast majority of strokes (approximately 85%) now occur in LMICs where incidence, deaths and DALYs have increased significantly over this period.⁷ It is also in LMICs where air pollution is projected to increase significantly over the next few decades due to rapid industrialisation.^{9,10}

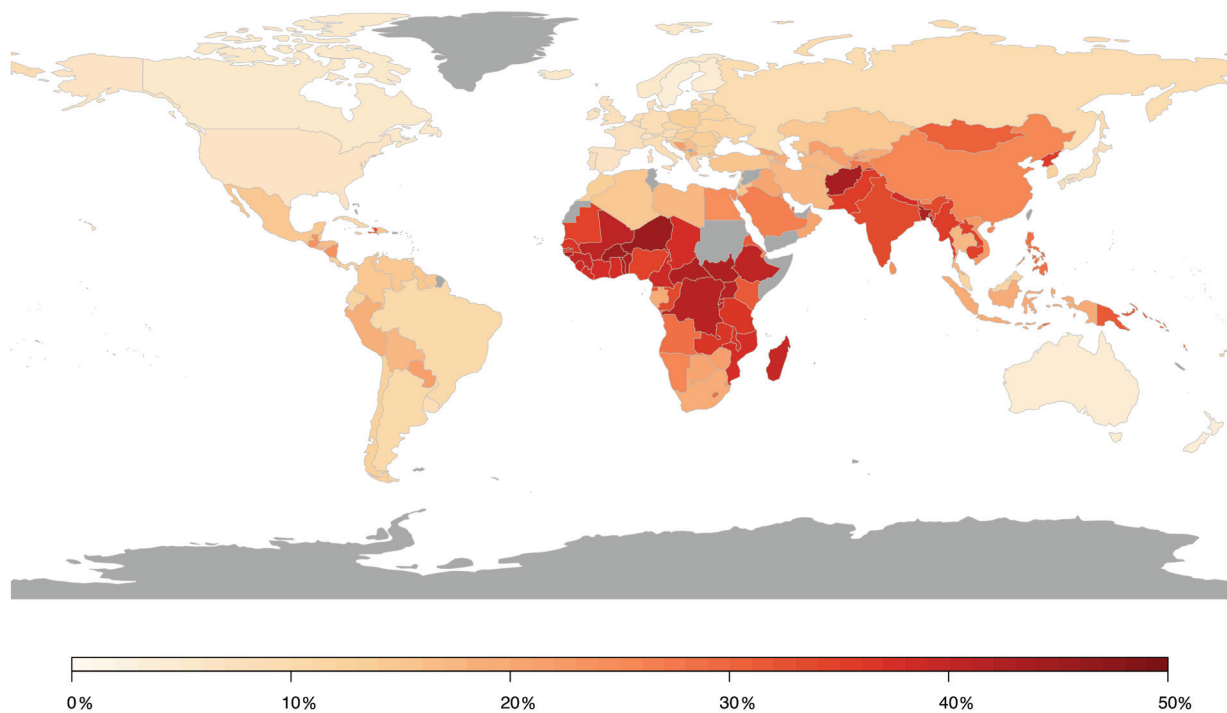


Figure 1. Population attributable risk of cerebrovascular disease associated with air pollution worldwide. Estimates from Institute for Health Metrics and Evaluation (IHME).

In this review, we describe the epidemiological evidence for the association between air pollution and stroke, and the proposed pathophysiological pathways linking air pollutants to atherothrombosis that underlies a significant proportion of cerebrovascular disease.

What is air pollution?

Air pollution is an expansive term consisting of a complex mixture of thousands of components from a wide range of different sources. The main pollutants currently recognised to pose risk to health include airborne particulate matter (PM) and gaseous pollutants such as ozone (O₃), sulphur dioxide (SO₂), carbon monoxide (CO), and nitrogen oxides including nitrogen dioxide (NO₂) and nitrogen oxide (NO_x).

Particulate matter

Airborne PM is classified by the size of the particles into coarse particles or PM₁₀ (diameter of 10 µm or less), fine particles or PM_{2.5} (diameter of 2.5 µm or less) and ultrafine particles or nanoparticles (diameter smaller than 0.1 µm). The size and composition of particles primarily depend on its source. Airborne PM₁₀ is chiefly a result of resuspension of soil, road dust

by wind and moving vehicles, construction work and industrial emissions. PM_{2.5} is mainly derived from the combustion of fossil fuel, including motorized road traffic, power plants, industrial and residential heating using oil, coal, or wood. Particles formed in this way are commonly composed of carbon, transitional metals, complex organic molecules, sulphate, and nitrates. Vehicle engine exhaust (especially diesel exhaust) is particularly rich in nanoparticles, which, while contributing only a very small fraction of the total mass of PM_{2.5}, have a greater reactive surface area for a given mass.

Gaseous pollution

The gaseous pollutants predominantly consist of SO₂, NO_x, CO, and O₃. SO₂ is mainly produced in fossil fuel power plants, whilst NO_x mainly originates from motorised road traffic, residential heating, power generation and industrial sources. Besides their own inherent toxicity, SO₂ and NO_x can contribute in atmospheric photochemical reactions resulting in complex secondary particles composed of inorganic and organic compounds. Ground level O₃ is a form of secondary gaseous pollutant made as a result of photochemical reactions of NO₂ with volatile hydrocarbons in the presence of sunlight and is a major constituent of photochemical smog.

Global variation in air pollution concentrations

In LMICs, biomass fuel, agriculture related burning, open fires and forest burning are more prevalent. In rural communities, as well as deprived populations in urban regions, exposure to household air pollution is intimately linked with poverty. This is primarily due to the dependence on biomass fuel, firewood and charcoal as a means for cooking and heating with traditional stoves. For example in sub-Saharan Africa and most of South Asia, firewood remains the main source of fuel.¹¹ The nature of air pollution is expected to change significantly as LMICs industrialise and reliance on biomass fuel decreases.¹² Over the past few decades, household air pollution associated with poverty and traditional lifestyles has decreased worldwide but remains an important risk factor.¹³ On the contrary ambient air pollution is increasing significantly in LMICs as these regions become more industrialized.¹⁴

Air pollutant levels have substantial temporal and spatial variation. Temporal variation of daily average air pollutant concentrations is often related to weather conditions affecting the dispersion of pollutants. These include wind direction, speed, and atmospheric stability. Temperature and sunlight are crucial in the formation of O₃; therefore, concentrations are typically highest during the warmest, high-intensity sunlight hours of the day. Consequently, O₃ levels peak between noon and 9:00 PM during the time when individuals are outdoors, resulting in significant human exposure. Traffic-related pollution such as soot, ultrafine particles and combustion-derived gaseous pollutants often peak during the morning and evening rush hours, resulting in high exposure for people commuting to work.

Spatial variation is related to local and regional sources. For example, PM_{2.5} concentration has been found to be significantly higher in traffic sites compared to urban background sites.¹⁵ PM_{2.5} can travel large distances (>100 km) resulting in high background concentrations over wide areas. In West Africa, satellite data indicate that wind-blown dust from the Sahara Desert causes increased PM_{2.5} air pollution that is believed to result in a significant burden of disease in one of the most densely populated regions in Africa and beyond.¹⁶

Air pollution and stroke: epidemiological evidence

Patients with cardiovascular disease share many risk factors such as obesity, hyperlipidaemia, hypertension, smoking, poor diet, and inactive lifestyle. Crucially, air pollution differs from other modifiable risk factors because exposure to air pollution, for the large majority of people, is unavoidable. Therefore, even though the individual risk estimates for exposure to air pollu-

tion are relatively small compared to the other cardiovascular risk factors, since exposure to (some form of) air pollution is ubiquitous, the overall population attributable risk and subsequent burden is significant.¹⁷

Long-term exposure

Most studies of long-term exposure use air pollution levels at residential addresses over months to years as a proxy for long-term accumulated individual exposure. Individual exposure is estimated using residential distance to major roadways, measurements from nearby fixed air quality monitoring stations or advanced modelling using land-use databases, meteorological data, traffic density, and emissions database. The majority of studies looking at the long-term effects of air pollution on cardiovascular disease have been on PM_{2.5}. A 2013 meta-analysis reported that PM_{2.5} was associated with a pooled excess risk of 6% (95% confidence interval [CI], 4% to 8%) for all-cause mortality and 11% (95% CI, 5% to 16%) for cardiovascular mortality¹⁸ for every 10 µg/m³ increment. Similar associations have been found for certain gaseous co-pollutants, with a 2014 meta-analysis reported a 13% (95% CI, 9% to 18%) increase in cardiovascular mortality per 10 µg/m³ increase in NO₂ concentration.¹⁹ We summarize several key longitudinal studies in Table 1.²⁰⁻²⁵ Associations with cerebrovascular disease was found to be stronger in LMICs where air pollutant levels were greater.²⁰ Interestingly, increased risk was also observed in regions where PM_{2.5} met European Union air quality standard of 25 µg/m³.²¹ Carotid artery stenosis, a known precursor to ischaemic strokes, was recently reported to be independently associated with PM_{2.5} concentration even after adjusting for known cardiovascular risk factors.²⁶

Short-term exposure

In the early 1980s, a study in England and Wales investigating the association between fluctuations in meteorological variables and cerebrovascular mortality found an unexpectedly strong correlation with atmospheric particulate air pollution levels.²⁷ Several years later, a study in China found indoor coal fumes to be a risk factor for stroke, independent of age, blood pressure, and cigarette smoking.²⁸ In the United States, a study published in 1994 reported a weak but significant association between daily PM pollution and cerebrovascular mortality (relative risk of 1.15) using cause of death data between 1973 and 1980.²⁹ Since then, there has been a large number of ecological studies investigating the short-term effects of air pollution (>100).⁵ Of note, Dominici et al.³⁰ reported a 0.81% (95% CI, 0.30% to 1.32%) increase in hospital admission due to cerebrovascular disease per 10 µg/m³ increment in same-day PM_{2.5}

Table 1. Selected studies of the association between long-term exposure to air pollution and cerebrovascular disease

Location of study, author	Study design	Exposure measurement	Significant findings
USA (36 cities) Miller et al. (2007) ²²	65,893 Postmenopausal women Median follow-up of 6 years	Per 10 µg/m ³ increase in mean PM _{2.5} concentration	Stroke incidence increased by 35% (95% CI, 8%–68%) Stroke deaths increased by 83% (95% CI, 11%–200%)
California, USA Lipsett et al. (2011) ²³	124,614 Current and former public school professionals Median follow-up of 5.6 years	Per 10 µg/m ³ increase in PM _{2.5}	Stroke incidence increased by 19% (95% CI, 2%–38%)
England, UK Atkinson et al. (2013) ²⁴	836,557 Patients registered with 205 English general practices Median follow-up of 5 years	Per interquartile change in SO ₂ (2.2 µg/m ³)	Stroke incidence increased by 4% (95% CI, 2%–6%)
New-England region, USA Kloog et al. (2012) ²⁵	24,066 Hospital admissions of medicare recipients aged 65 years or older between years 2000–2006	Per 10 µg/m ³ increase in PM _{2.5}	Stroke hospitalisation increased by 3.49% (95% CI, 0.09%–5.18%)
Shenyang, China Zhang et al. (2011) ²⁰	9,941 Residents followed up from 1998–2009	Per 10 µg/m ³ increase in PM ₁₀ and NO ₂	Stroke mortality increased by 49% (95% CI, 45%–53%) for PM ₁₀ and 144% (95% CI, 127%–162%) for NO ₂
Europe (multiple countries) Stafoggia et al. (2014) ²¹	99,446 People enrolled across 11 cohorts from 1997–2007 Mean follow-up of 11.5 years	Per 5 µg/m ³ increase in PM _{2.5}	Overall stroke incidence increased by 19% (95% CI, –12% to 62%). Increased risk was observed even at concentrations that met the European Union standard of 25 µg/m ³ (33% increase [95% CI, 1%–77%])

PM_{2.5}, particulate matter diameter of 2.5 µm or less; CI, confidence interval; SO₂, sulphur dioxide; PM₁₀, particulate matter diameter of 10 µm or less; NO₂, nitrogen dioxide.

across 204 United States counties. In contrast, a study in Chile, where mean PM_{2.5} concentrations are over twice as high at 31 µg/m³, hospitalisations for cerebrovascular disease increased by 1.29% (95% CI, 0.55% to 2.03%) for every 10 µg/m³ increment.³¹ In Edmonton, Canada, the association between NO₂ and ischaemic stroke were found to be significantly stronger for individuals with a history of stroke, heart disease, and diabetes (odds ratio [OR], 2.31 [95% CI, 1.39 to 3.83]; OR, 1.99 [95% CI, 1.20 to 3.28]; and OR, 2.03 [95% CI, 1.14 to 3.59], respectively).³²

A recent systematic review and meta-analysis reported that gaseous and PM air pollutants have a temporal association with hospital admissions and mortality due to stroke (Figure 2).⁵ Both PM_{2.5} and PM₁₀ were associated with admission to hospital for stroke and mortality from stroke, with a stronger association with PM_{2.5} with a relative risk of 1.011 (95% CI, 1.011 to 1.012) per 10 µg/m³ increment. NO₂ was the most studied pollutant with a 1.014 (95% CI, 1.009 to 1.019) relative increase in hospital admission or mortality due to stroke per 10 parts per billion (ppb) increment. Both SO₂ and CO were significantly associated with admission or mortality with relative risks of 1.019 (95% CI, 1.011 to 1.027) per 10 ppb increment and 1.015 (95% CI, 1.004 to 1.026) per 1 part per million (ppm) increment respectively. O₃ only had a weak association with relative risk of 1.001 (95% CI, 1.000 to 1.002) per 10 ppb increment. The pooled analysis of over 6.2 million stroke events

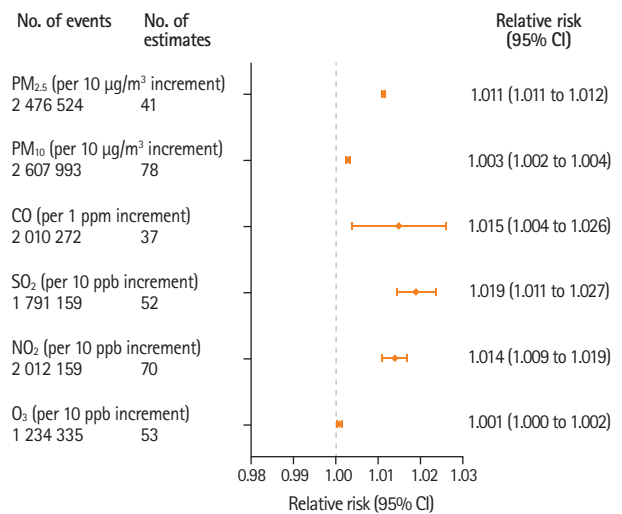


Figure 2. Association between air pollutants and hospitalisation or mortality from stroke. Adapted from Shah et al.⁵ CI, confidence interval; PM_{2.5}, particulate matter diameter of 2.5 µm or less; PM₁₀, particulate matter diameter of 10 µm or less; CO, carbon monoxide; ppm, part per million; SO₂, sulphur dioxide; ppb, part per billion; NO₂, nitrogen dioxide; O₃, ozone.

across 28 countries worldwide, demonstrated that associations persists even after stratification by study design, age and hospitalisation or mortality outcome. Pooled estimates demonstrated stronger associations in LMICs than high income countries for NO₂ (relative risks of 1.019 [95% CI, 1.011 to 1.027] vs. 1.012 [95% CI, 1.006 to 1.017]) and PM₁₀ (1.004 [95% CI,

1.002 to 1.006] vs. 1.002 [95% CI, 1.001 to 1.003]).

Limitations of epidemiological studies

Most epidemiological studies are performed in high income countries; however, it is in the LMICs where the effects of air pollution are most marked and the incidence of stroke is continuing to rise significantly. In most outdoor air pollution epidemiological studies, individual exposures are extrapolated from ambient air pollutant concentrations reported at a regional level or recorded by the nearest fixed air quality monitor. This approach assumes a uniform exposure across the area without precisely accounting for within-region variability or variations in personal exposure of the individual. Unlike other acute conditions, the time of onset may precede mortality due to stroke by days or weeks, leading to significant exposure misclassification. Furthermore, many studies did not adjust for 'traditional' risk factors for cardiovascular disease such as diabetes, hypertension, smoking, and socioeconomic deprivation which may confound the association between air pollution and stroke. Whilst the associations reported in epidemiological studies are significant, proving a causal relationship between the different air pollutants and stroke is more challenging. Experimental and clinical data are therefore crucial in establishing the biological plausibility of this relationship.

Experimental evidence for the association between air pollution and stroke

The potential for harm from air pollution is related to both exposure (e.g., the concentration, dose and period of exposure, and the ability of the body to clear the pollutants) and toxicity of the pollutant (e.g., reactivity of the material, ability access different biological compartments). In regards to the latter, for PM pollution, the smaller the particle, the greater the potential for harm due to ability to penetrate deeper into the lung and larger reactive surface area available (for a given mass and composition). Consequently, association between PM_{2.5} and cardiovascular disease has been more marked and consistent than PM₁₀ in epidemiological studies.^{3,5} Smaller nanoparticles are able to penetrate the alveolar spaces of the lung and may even infiltrate the blood stream to reach systemic organs.³³ The chemical composition of particles is another crucial factor in determining its biological effects once it has gained access into the human body. Combustion-derived particles have a vast cocktail of surface chemicals, including reactive transition metals and organic hydrocarbons, which are thought to be significant drivers of inflammation and oxidative stress. Although

epidemiological studies have limitations in proving causality between air pollution exposure and cerebrovascular disease, several cellular, animal, controlled exposure, and longitudinal clinical studies have provided robust biologically plausible evidence underlying these associations.³⁴

The biological mechanisms by which pollutants could promote stroke are complex, and remained to be fully elucidated. In more simplified *in vitro* studies using cultures of neurons, astrocytes, and microglia have demonstrated increased susceptibility to oxygen and glucose deprivation,³⁵ alteration in synaptic function³⁶ and upregulation in inflammatory cytokines³⁷ when exposed to PM air pollutants. However, *in vitro* studies are frequently performed by directly exposing cells to very high concentrations of PM. Whether particles are able to translocate (pass from the lung into the blood) in sufficient concentration to cause these effects after inhalation *in vivo* is debatable, and other mechanistic pathways will undoubtedly play a role in the pathophysiology.

Several animal models have been used to investigate the effects of air pollution on stroke. Intra-tracheal instillation of combustion-derived PM in healthy versus stroke-prone spontaneously hypertensive rats showed increase in cardiac and pulmonary oxidative stress markers.³⁸ Interleukin-6 and other pro-inflammatory molecules released after diesel exhaust inhalation in mice are associated with platelet activation, increased fibrinogen, factor VIII, and tissue factor release.³⁹ Exposure to vehicle exhaust was also demonstrated to alter blood-brain barrier function in apolipoprotein-E knockout mice.⁴⁰ In China, rats treated with PM₁₀ from a coal-burning city were reported to have changes consistent with cerebral ischaemia (i.e., endothelial dysfunction, inflammation, and neuro-functional impairment) on electron microscopic analysis of brain slices.³⁵

Controlled exposure studies in human subjects have also provided important insight. In healthy adults, diesel exhaust exposure increased platelet activation and thrombus formation at damaged blood vessels *ex vivo*.⁴¹ In patients with coronary artery disease, it was demonstrated that endogenous fibrinolytic capacity is inhibited due to a reduction in acute tissue plasminogen activator release.⁴² Air pollution may also reduce endothelial function through increased endothelial cell apoptosis⁴³ and decreased circulating levels of endothelial progenitor cells.⁴⁴ In a community of elderly community-dwelling individuals, PM_{2.5} was associated with higher resting cerebrovascular resistance and lower cerebral blood flow velocity using transcranial Doppler ultrasound measurements.⁴⁵

Mechanisms: inflammation, oxidative stress, and lipid modification

Cellular, animal, and clinical studies have led to several hypotheses to explain the adverse cardiovascular effects of ambient PM. It is likely that the relative contribution of each pathway depends on the physicochemical property of the particular pollutant and individual susceptibility.^{46,47} The classical "inflammation" hypothesis is that particles inhaled into the lungs are ingested by macrophages, activating a local inflammatory response within the lung. Inflammatory mediators then "spill-over" into the systemic circulation leading to "indirect" effects on the cardiovascular system.⁴⁸ Exposure to urban PM has been shown to cause pulmonary inflammation and elevated circulating levels of leucocytes and inflammatory cytokines such as tumour necrosis factor alpha, interleukin-1, interleukin-6, and acute phase reactants such as C-reactive protein and fibrinogen.⁴⁹⁻⁵¹ Inflammatory pathways also act in concert with oxidative stress, potentially amplifying the pathophysiological actions of pollutants. Generation of oxidative stress in the vascular endothelium will decrease the availability of NO, a key regulator of vascular tone and blood pressure. Exposure to diesel exhaust led to impaired endothelium-dependent mediated vasodilation and decreased endothelial NO bioavailability.⁵² Oxidative stress also leads to alteration in circulating lipids. Diesel exhaust particles have been shown to oxidise low-density lipoprotein generation and stimulate the release of other highly oxidised phospholipids.⁵³ Ambient particles are associated with an increase in plasma lipoprotein-associated phospholipase A2, an independent risk factor for stroke.⁵⁴ These proatherogenic molecules diffuse into subendothelial cells and cause further endothelial dysfunction.

Mechanisms: translocation of nanoparticles

More recently, discovery of the nanoparticle fraction of airborne PM pollution led to the hypothesis that due to the small size of these nanoparticles, they are able to traverse the alveolar-capillary barrier to enter systemic circulation and directly affect the vasculature and circulating blood cells.⁵⁵ *In vitro* studies have demonstrated that exposure to combustion-derived nanoparticles activate a proinflammatory response in endothelial cells.⁵⁶ Combustion-derived nanoparticles were also found to upregulate the expression of adhesion molecules, intercellular adhesion molecule-1, and vascular cell adhesion protein-1 on the surface of endothelial cells.^{57,58} This is a crucial step during the initiating events of atherosclerosis

which result in the retention of macrophages and monocytes in the subendothelial space. Diesel exhaust particles have been shown to increase endothelial cell permeability through downregulation of tight junction proteins, increased transendothelial resistance and redistribution of vascular endothelial cadherin from cell membrane intracellularly.⁵⁹⁻⁶¹ There is also evidence that particles may translocate to central regions at the level of the nasal passage, in particular the olfactory bulb where high doses of particles deposit due to route of air-flow. The particles could then penetrate the nasal respiratory epithelium into the rich blood capillary or neural network in the olfactory bulb.^{62,63} Translocation studies are challenging, especially in man, due to the small size and number of particles that will translocate, and the technical challenges in detecting carbon-based nanoparticles in biological tissue. However, recently, gold nanoparticles of a similar size to combustion derived nanoparticles have been shown to translocate rapidly from lungs into the circulation and accumulate in areas of vascular inflammation.³³

Mechanisms: autonomic dysfunction

Inhaled particles, or the pulmonary inflammation caused by them, can stimulate neural sensory receptors on the alveolar surface which triggers changes in autonomic function leading to altered cardiovascular homeostasis.⁶⁴ There is extensive evidence demonstrating reductions in various parameters of heart rate variability (HRV) after exposure to PM_{2.5}.⁶⁵ Reduced HRV is a known marker of cardiac autonomic dysfunction, that has been linked to a worse prognosis in patients with heart disease and in the general population.^{66,67} Atrial fibrillation is a well-known risk factor for stroke. Several animal studies have shown that exposure to urban PM and diesel exhaust particles increases the incidence or susceptibility to arrhythmia.^{68,69} This mechanism could contribute to the observed association between air pollution and cardioembolic strokes.⁷⁰

Overall, a diverse range of pathophysiological mechanisms will contribute to the associations between air pollution and stroke (see Miller and Shah⁷¹ 2016 for further discussion). As well as lending further weight to the case for causality between air pollution and stroke, elucidation of these mechanisms will offer important insight in identifying the most detrimental pollutions and susceptible populations.

Possible interventions

Air pollution represents a considerable burden to human health, yet currently the vast majority of countries do not meet

accepted air quality standards.⁷² Nevertheless, the awareness of the health effects of air pollution has grown considerably over the last decade and the drive for interventions to tackle air pollution across the world should be a cause for optimism.

Measures to reduce air pollution will require policy changes at national, regional, and international levels. Burning of fossil fuels represents an important source of air pollution with well-recognised health consequences. Moving away from the use of fossil fuels, towards cleaner and more renewable energy sources such as solar and wind power could mitigate not just the adverse health effects from air pollution, but also climate change as a result of greenhouse gases. The transportation sector clearly has a major role to play by developing integrated public transportation systems and regulating emission standards for motor vehicles. City planners should be incentivised to take air pollution into account and build residential areas away from polluting industries such as power plants or heavily congested roads. National early warning systems with real-time PM_{2.5} concentrations throughout the country could also help inform people, especially those likely to be a particular risk to air pollution (e.g., children, the elderly and those with pre-existing cardiorespiratory disease) to avoid going outdoors during periods of poor air quality. In the case of rapidly industrialising LMICs, air pollution should not be seen as an inevitable side effect of modernisation. Through prudent leadership, air pollution can be decoupled from economic development using more sustainable models.

At an individual level, a number of simple measures could reduce personal exposure to air pollutants. Some of these measures include: commuting with public transport, cycling, or walking rather than using personal motor vehicles, limiting time spent outdoors during highly polluted periods, avoiding rush hour traffic or exercise near main traffic routes. Avoiding use of biomass fuel for domestic heating or cooking and improved domestic ventilation systems could have a large impact in LMICs. Individuals with pre-existing cardiorespiratory diseases, in particular, should be educated on the adverse cardiovascular risks posed by exposure to air pollution and advised to observe measures to reduce their exposure.

Conclusions

There is now substantial evidence linking air pollution and cardiovascular diseases including stroke. Epidemiological studies have demonstrated that both short- and long-term exposure to air pollution increases the risk of stroke. Controlled exposure studies in man and experimental studies have provided insight into the pathobiological mechanisms leading to the induction

of endothelial dysfunction, atherosclerosis, platelet activation, and propensity for coagulation. Air pollution should be recognised more widely as one of the most important modifiable risk factors for the prevention and management of cardiovascular disease. Healthcare professionals will have an important role in promoting the awareness of this evidence, not just to improve the care of individual patients, but also to place pressure on policy makers for air pollution to be a public health priority.

Disclosure

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