Stroke

TOPICAL REVIEW

Section Editors: Mitchell S.V. Elkind, MD, and Graeme J. Hankey, MBBS, MD

Ambient Air Pollution and Stroke: An Updated Review

Erin R. Kulick, PhD, MPH; Joel D. Kaufman, MD, MPH; Coralynn Sack, MD, MPH

ABSTRACT: Despite recent advances in treatment and prevention, stroke remains a leading cause of morbidity and mortality. There is a critical need to identify novel modifiable risk factors for disease, including environmental agents. A body of evidence has accumulated suggesting that elevated levels of ambient air pollutants may not only trigger cerebrovascular events in susceptible people (short-term exposures) but also increase the risk of future events (long-term average exposures). This review assesses the updated evidence for both short and long-term exposure to ambient air pollution as a risk factor for stroke incidence and outcomes. It discusses the potential pathophysiologic mechanisms and makes recommendations to mitigate exposure on a personal and community level. The evidence indicates that reduction in air pollutant concentrations represent a significant population-level opportunity to reduce risk of cerebrovascular disease.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: air pollution ■ lung ■ nitric oxide ■ nitrogen dioxide ■ particulate matter ■ smoke ■ stroke

Despite recent advances in treatment and prevention, stroke remains the second leading cause of death and third leading cause of death and serious long-term disability combined.[1,2] Conventional cardiovascular risk factors such as hypertension, diabetes, sedentary behavior, and smoking do not account for all of the variations in stroke risk.[3,4] In addition, traditional risk factors are primarily associated with long-term risk and do not account for short-term risk or a triggering event (ie, the reason why an event occurs at a particular point in time, despite risk factors being present for years).

In the search for novel modifiable risk factors, there is growing interest in the adverse health effects of environmental agents; among the most pervasive is ambient air pollution. Over 99% of the world's population lives in areas where pollution levels exceed the World Health Organization Global Air Quality Guidelines.[5] Ambient particulate matter (PM) air pollution is a leading cause of global disability and accounts for an estimated 2.9 million deaths per year.[2] Accumulating evidence demonstrates that both short-term (hours to days) and long-term (months to years) exposure to air pollution is a risk factor for cerebrovascular disease. An earlier analysis by Global Burden of Disease Investigators reported that ambient air pollution was a leading cause of global stroke-related disability-adjusted life-years, accounting for an estimated 16% of all stroke-related disability-adjusted life-years.[3]

This review provides an overview of the sources of air pollution, assesses the updated evidence for the association between air pollution and stroke, and discusses potential pathophysiologic mechanisms. Finally, potential strategies for risk mitigation in both the personal and clinical settings are discussed.

AMBIENT AIR POLLUTION

Ambient air pollution consists of a mixture of solid, liquid, and gaseous components, including over 40 toxic substances from a variety of man-made and natural sources. There are 6 principal air pollutants regulated explicitly under the Clean Air Act (Table 1).[6,7] Often considered the most widespread threat is PM, itself a mixture of solid and liquid aerosol from fossil fuel combustion, transportation, industry, resuspended material, and episodic sources such as wildfire smoke and volcanic eruptions.[6] PM is categorized by the mean

Correspondence to: Erin R. Kulick, PhD, MPH, Temple University College of Public Health, 1301 Cecil B Moore Ave, Ritter Annex 904, Philadelphia, PA 19122. Email erin.kulick@temple.edu

For Sources of Funding and Disclosures, see page 890.

Stroke is available at www.ahajournals.org/journal/str

Table 1. Sources of Air Pollution and Evidence for Its Effect on Stroke

Pollutant	EPA standard	Averaging time	Dominant sources	Evidence for short-term effect on stroke incidence	Evidence for long-term effect on stroke incidence	Known effect on stroke risk factors
$PM_{2.5}$	35 μg/m³ 12 μg/m³	24 h Annual	• Fuel combustion from automobiles • Industrial processes • Power plants • Wood burning • Diesel-powered vehicles	Overall: ++++ Ischemic: +++ Hemorrhagic: ++	Overall: ++++ Ischemic: +++ Hemorrhagic: ++	• Accelerated atherosclerosis • Elevated blood pressure • Hypertension • Arrhythmias • Diabetes • Congestive heart failure
PM_{10}	150 μg/m³	24 h	• Coal and Petroleum Combustion • Vehicles • Industry • Surface dust suspension	+++	++	• Exacerbation of ischemic heart disease
Nitrogen dioxide (NO_2)	100 ppb 53 ppb	1 h Annual	• Motor vehicles • Coal and petroleum combustion • Industry	++	++	
Ozone (O_3)	0.07 ppm	8 h	• Secondary formation from NO_2 and hydrocarbons	++	++	

EPA indicates Environmental Protection Agency; and PM, particulate matter.
++++Causal relationship: Pollutant has been shown to result in health effects at relevant exposure based on multiple lines of evidence.
+++Suggestive of, but not sufficient to infer: Evidence is generally supportive but not entirely consistent or is limited overall.
++Inadequate to infer the presence or absence of causal influence: Insufficient quantity, quality, consistency, or statistical power of results.
+Not likely to be causal: Studies consistently show no effect.

aerodynamic diameter of particles into PM_{10} (aerodynamic diameter, <10 μm); coarse particles ($PM_{2.5-10}$, aerodynamic diameter between 2.5 and 10 μm); fine particles ($PM_{2.5}$, aerodynamic diameter <2.5 μm); and ultrafine particles (aerodynamic diameter <100 nm). Although all sizes of PM are considered harmful, particles <2.5 μm are more likely to penetrate deep into the lung, where they may deposit, interact with host defense mechanisms, or pass directly into the circulatory system and be distributed throughout the body.[8,9] Oxides of nitrogen (collectively "NO_x") including nitric oxide (NO) and nitrogen dioxide ($NO_{2)}$ are generated from the combustion of fossil fuels and increase exponentially on major roadways in urban areas. NO is rapidly oxidized to nitrogen dioxide (NO_2), and both NO_2 and NO_x are often considered when assessing traffic-related air pollution.[6,10] Ozone is created through a series of chemical reactions involving chemical reactions of volatile organic chemicals and nitrogen oxides and solar UV irradiation. Ozone is of particular health concern when air is stagnant for several days, as often occurs in areas surrounded by mountains like Los Angeles and Mexico City.[6] Although concentrations of many components of air pollution have decreased due to regulatory successes, ground ozone levels continue to increase.[10]

Although the health effects of these individual pollutant components are often reported seperately, exposure to ambient air pollution in the real world is mixed. Pollutant components may interact to either augment or counteract disease processes. This can make disentangling the effect of isolated pollutants difficult, particularly in epidemiologic studies.

EPIDEMIOLOGIC STUDIES

Short-Term Exposure to Ambient Air Pollution and Stroke

The first studies of the impact of air pollution on stroke focused on the short-term or triggering effects of exposure, with an increasing number of studies being published over the last 10 years. The bulk of evidence demonstrates that short-term pollution exposure is a significant risk factor for stroke hospitalization and mortality. There is still some ambiguity regarding which specific pollutants trigger stroke, critical lag times between exposure and stroke onset, and magnitude of risk (Table 1).[11–14] In particular, studies of the association between short-term pollution exposure and stroke mortality may be limited by significant exposure misclassification, as well as misclassification of the timing of the stroke event. In comparison with other acute outcomes, such as incident acute coronary syndrome, the time between stroke onset and mortality may have significant variability, ranging from minutes to days or months. This makes identifying the correct window of short-term pollution exposure difficult.

A large meta-analysis by Shah et al of over 94 studies and 6.2 million events found small but significant associations between exposure to a wide range of air pollutants and a combined outcome of stroke hospitalization and mortality.[13] Increased concentrations of pollutants over periods encompassing the week prior to event were associated with increased risk of admission to hospital for stroke, or mortality from stroke for $PM_{2.5}$ (relative risk [RR], 1.011 per 10 μg/m³; [95% CI, 1.011–1.012]), carbon monoxide (RR, 1.015 per 1 ppm; [95% CI, 1.004–1.026]), sulfur

dioxide (RR, 1.019 per 10 ppb; [95% CI, 1.011–1.027]), and NO_2 (RR, 1.014 per 10 ppb; [95% CI, 1.009–1.019]). Most of the included studies were based in higher income countries, such as Europe and the United States, where pollutant levels are substantially lower than the rest of the world. The associations were stronger in low- and middle-income countries than high-income countries for NO_2 but not for the other pollutants.

Several recent studies have focused on countries with higher pollutant concentrations. In particular, recent independent studies out of China have shown a significant relationship between a wide range of pollutants including $PM_{2.5}$, PM_{10}, SO_2, NO_2, and ozone, and risk of all-cause stroke hospitalization in the first 3 days after exposure.[15–18] On days of high $PM_{2.5}$ pollution in Beijing, China ($PM_{2.5}$ concentration > 150 μg/m^3), the odds of hospitalization for ischemic stroke were 7.1% higher (OR, 1.071; [95% CI, 1.053–1.090]) than on days with lower $PM_{2.5}$ levels.[19] In Shenyang, China, significant associations were found between $PM_{2.5}$ (RR per 10 μg/m^3 1.012; [95% CI, 1.003–1.096]), PM_{10} (RR per 10 μg/m^3 1.02; [95% CI, 1.002–1.083]), ozone (RR per 10 μg/m^3 1.178; [95% CI, 1.014–1.352]) and risk of all-cause stroke hospitalizations in the first 3 days after exposure.[16]

In contrast, several recent studies based in the United States found no significant associations between PM[20] or traffic-related air pollutants ($PM_{2.5}$, NO_x, and black carbon)[21] and all-cause stroke mortality. A study from Vietnam also found no consistent associations between pollutant exposure and stroke hospitalizations.[22,23] Another meta-analysis incorporating all studies of ambient PM and stroke events from 1966 to 2014 showed no evidence of an association between PM and stroke hospitalization, but did find positive trends with stroke mortality ($RR_{PM2.5}$, 1.014; [95% CI, 0.9–1.9%], and RR_{PM10}, 1.005; [95% CI, 0.3–0.7%]) per 10 μg/m^3 increase in pollution.[14]

It is unclear whether the inconsistencies between these studies are due to variability in pollution exposure, differences in sample size, or misclassification of the time between pollutant exposure and the outcome. Estimates from meta-analyses may also mask important heterogeneity between studies. This highlights the importance of individual, well-designed observational studies when interpreting the evidence for an association between pollution exposure and stroke incidence.

An additional explanation for differences in study findings may be attributable to the lumping of stroke into a single outcome. Stroke is an etiologically diverse disease, and air pollution may have a differential effect on stroke subtypes. As highlighted in a recent review article, most of the studies that have examined the effect of ambient air pollution on stroke subtypes report stronger associations between air pollution and ischemic rather than hemorrhagic stroke.[15,24–33]

Hemorrhagic stroke was more strongly associated with $PM_{2.5}$ in only 1 study,[34] whereas there were numerous studies that saw no association between ambient air pollution and hemorrhagic stroke risk, including several large studies in Europe.[35,36] These findings speak to the need to further investigate potential mechanisms behind the impact of short-term spikes in air pollution and triggering of stroke subtypes.

Long-Term Exposure to Ambient Air Pollution and Stroke

A growing body of literature demonstrates that long-term exposure to ambient air pollution, measured over months to years, is also a risk factor for cerebrovascular events. Similar to the evidence regarding short-term exposure to pollution, results of studies looking at the association between long-term exposure to ambient air pollution and stroke events are somewhat mixed. Despite some null studies,[11,37] the preponderance of evidence supports a causal association between long-term exposure to pollutants, stroke incidence, and mortality.

A meta-analysis of 20 studies,, including over 10 million people, found a significant association between PM (PM_{10} and $PM_{2.5}$) (hazard ratio [HR] per 10 μg/m^3, 1.061; [95% CI, 1.018–1.105]) and overall stroke events, and a positive but not significant association between PM and stroke mortality (HR, 1.080; [95% CI, 0.992, 1.177]). When stratified by continent, they found stronger associations between PM_{10} and stroke events in studies done in North America and Europe when compared with that in Asia.[37] A more recent meta-analysis limited to $PM_{2.5}$ studies confirmed these findings, reporting a 13% increased risk for incident stroke per 10 μg/m^3 (95% CI, 11–15%), and a 24% for cerebrovascular mortality (95% CI, 13–36%).[38]

Large cohort studies in North America,[39–43] Europe,[44–50] and Asia[51–54] have provided updated evidence around the relationship between long-term exposure to ambient air pollution and stroke mortality and incidence. One of the largest studies to date, the European ESCAPE study (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) of 22 pooled cohorts found increased risk of cerebrovascular disease deaths with exposure to higher levels of $PM_{2.5}$ (HR, 1.21 per 5 μg/m^3; [95% CI, 0.87–1.69]), PM_{10} (HR per 10 μg/m^3 1.22; [95% CI, 0.91–1.63]), and coarse PM (HR 1.17 per 5 μg/m^3; [95% CI, 0.90–1.52]).[48] In the multinational PURE study, the largest prospective cohort study on this topic to date, which included participants from low-, middle-, and high-income countries, the authors found a HR for incident stroke of 1.07 (95% CI, 1.05, 1.10) per 10 μg/m^3 increase in ambient fine particles ($PM_{2.5}$).[55] When results of the PURE study (Prospective Urban and Rural Epidemiological) were limited only to low- and middle-income countries with high concentrations of $PM_{2.5}$ (>35 μg/m^3), the effects of $PM_{2.5}$ on incident stroke were similar.[55]

 Stroke. 2023;54:882–893. DOI: 10.1161/STROKEAHA.122.035498

Recent studies have begun to look at the effects of long-term exposure to ambient air pollution on different stroke subtypes to untangle the contrasting results between studies assessing all-cause stroke risk. In most studies, the strongest effects of long-term exposure to pollution were seen on incident ischemic stroke.[45,52,56] In the Danish Nurses Cohort, a nationwide sample of over 23,000 nurses, $PM_{2.5}$ (per IQR) was more strongly associated with incident ischemic stroke (HR, 1.13; [95% CI, 1.01–1.26]) than incident hemorrhagic stroke (HR, 1.07; [95% CI, 0.80–1.44]).[45] A similar pattern of results was seen in a pooled sample of cohorts from Norway and the UK,[56] and the Danish Diet, Cancer, and Health Cohort.[49] The results of these studies of long-term exposure are similar to the studies assessing the effects of short-term spikes in air pollution, with stronger and more consistent associations observed in ischemic than in hemorrhagic stroke.[15,24,26–29,51,57] It should be noted that despite these findings being compelling, the results of studies that have tried to look at hemorrhagic versus ischemic stroke have not been entirely consistent, though at least some of this is due to weakness in outcome classification in research, especially that which relies on administrative sources of data.

PATHOPHYSIOLOGICAL MECHANISMS OF AIR-POLLUTION–ASSOCIATED STROKE

The precise pathophysiologic mechanisms that link ambient air pollution to stroke are still unknown. Extensive research across in vitro, animal, and human studies demonstrates that exposure to air pollution induces processes with a central role in triggering acute cerebrovascular stroke such as systemic inflammation, enhanced thrombogenicity, atherosclerotic plaque vulnerability, vasoconstriction, and alteration in cardiac rhythm.[58,59] In addition, there is robust evidence showing that chronic pollution exposure is associated with traditional risk factors for stroke, including accelerated atherosclerosis, diabetes, high-density lipoprotein dysfunction, hypertension, endothelial dysfunction, and cardiac arrhythmias.[59] Emerging literature also suggests that some pollutants may directly cause neurotoxicity and neuronal damage.[60] Through these interconnected mechanisms, acute exposure to pollution may trigger the molecular and cellular pathways that precipitate stroke onset, while chronic exposure to pollutants may contribute to a predisposition to cerebrovascular accidents (Figure 1).

Initiating Pathways

Inhaled pollutants are hypothesized to cause damage through 3 initial pathways of injury. The inflammatory pathway is one of the key mechanisms of injury, resulting from localized oxidative stress and inflammation in the respiratory tract with spillover effects into systemic circulation.[59] Inhaled particulates are avidly phagocytized by macrophages, which causes an inflammatory cascade with release of leukocytes, TNF-α, interleukin-6, c-reactive protein, fibrinogen, and other pro-inflammatory markers. Both surface markers on particulates and oxidant gases generate reactive oxygen species, which deplete antioxidant defenses and stimulate intracellular mediators of inflammation. These initial responses are further enhanced through epigenetic mechanisms, such as DNA methylation and histone modification of noncoding DNA-mediated gene regulation.[61] Activation of inflammatory and reactive oxygen species-mediated pathways have diverse tissue responses, which promote coagulation, vascular dysfunction, atherogenesis, metabolic derangements, and hypertension.

Inhaled pollutants also activate sensory receptors in the lung to disrupt autonomic nervous system homeostasis and activate the hypothalamic-pituitary axis. The stimulation of nocioceptive and noradrenergic receptors leads to rapid release of catecholamines, increased sympathetic tone, and upregulation of vasoconstrictor pathways. Autonomic nervous system dysfunction is thought to be responsible for the acute rise in systemic blood pressure, increased vascular resistance, and cardiac autonomic dysfunction that has been repeatedly demonstrated in human controlled exposure studies of diesel exhaust and other pollutants.[62,63] Autonomic nervous system–mediated changes to heart rate parameters and cardiac blood flow also precipitate cardiac arrhythmias or ischemia, a dominant mechanism in ischemic strokes due to cardio-embolism. The acute activation of vasoconstrictor pathways may be of more importance in hemorrhagic strokes or ischemic strokes due to small vessel occlusion.

Due to their small size, ultrafine particles, and nanoparticles can directly translocate across epithelial border, enter the systemic circulation, and impact remote sites. Ultrafine particles have been shown to upregulate adhesion molecules, such as intercellular adhesion molecule-1 and vascular adhesion protein-1, on endothelial cells which promotes perivascular migration of monocytes and is the initiating step of atherosclerosis.[64] There is growing evidence that some ultrafine particles also directly reach the central nervous system, by altering the blood brain barrier permeability or passing through the olfactory epithelium and olfactory bulb.[65] Once in the brain, particles may accumulate in areas of vascular inflammation and have direct neurotoxicity. The link between stroke risk and whether particles themselves reach the brain remains rather uncertain, though evidence is accumulating that pollutant-related neuroinflammation can combine with vascular insults to create white matter injury.[66]

Subclinical Manifestations

Chronic or repeated stimulation of these initial pathways is associated with the development and progression of atherosclerosis, endothelial dysfunction, hypertension,

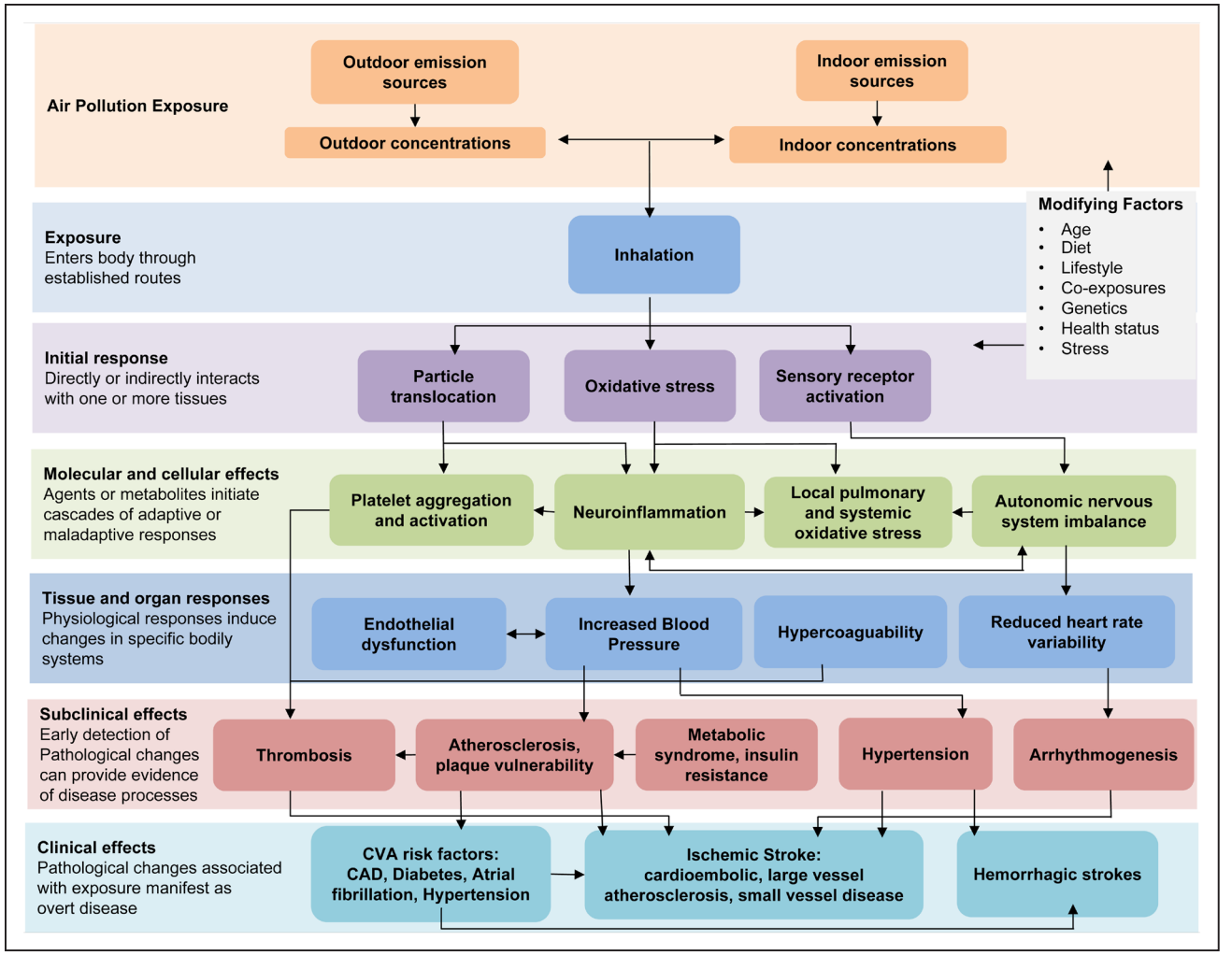

Figure 1. Pathophysiologic mechanisms of exposure to air pollution.
CAD indicates coronary artery disease; and CVA, cerebrovascular accident.

metabolic derangements, and cardiac arrhythmias. These subclinical manifestations are well-described intermediaries in the development of cerebrovascular disease and may represent the underlying mechanisms for the observed association between air pollution and stroke.

The association between air pollution and stroke may be partially ascribed to hypertension and altered vascular resistance, a common risk factor for most cerebrovascular subtypes. The vascular dysfunction related to pollution exposure is thought to be driven by autonomic nervous system activation with release of vasoconstrictors, reactive oxygen species, and pro-inflammatory markers. Air pollution has repeatedly been shown to cause short-term elevations in blood pressure, even in young and healthy individuals.[62] In older adults, short-term $PM_{2.5}$ exposure is associated with higher cerebrovascular resistance and lower cerebral blood flow.[67] These acute changes in hemodynamics might contribute to cerebral hypoperfusion and subsequent cerebrovascular events, particularly in susceptible individuals with underlying disease. Repeated exposure may result in chronic elevation of systemic arterial blood pressure, with structural maladaptation of the microvasculature. Systemic reviews and meta-analyses have shown a consistent association between long-term exposure to pollution and chronic elevation in blood pressure, with increased prevalence and incidence of hypertension.[13,68] Animal studies suggest that chronic exposure to PM leads to an observed increase in systolic blood pressure, systemic inflammation, and increased incidence of cerebral microbleeds.[69]

Atherosclerosis is one of the major causes of ischemic stroke and a well-established outcome of pollutant exposure. Pollution can contribute to the formation, progression, and rupture of atherosclerotic plaques through oxidative stress and inflammatory pathways. Pollutant-induced vascular injury and endothelial activation stimulates perivascular migration of monocytes, the initiating step in atherosclerotic plaque formation. Chronic exposure to pollution is associated with increased plaque instability through the accumulation of oxidized lipids and weakening of the fibrinous cap.[70] In particular, the identification of ultrafine particles in atherosclerotic lesions suggest that particles may contribute to plaque inflammation and instability. Studies in mice with metabolic disorders show

that long-term exposure to $PM_{2.5}$ in contrast to filtered air is associated with increased atherosclerotic plaque, lipid content, vascular inflammation, and oxidant stress.[71] One recent study using Sprague-Dawley rats demonstrated that the pro-atherogenic effects of pollutants extend to the cerebral vasculature and also cause worsening of intracranial atherosclerosis.[72] Epidemiologic studies further confirm these findings from toxicologic and animal studies: cross-sectional and longitudinal studies demonstrate that chronic pollutant exposure is associated with progression of atherosclerosis as assessed by carotid intimal medial thickness, coronary and abdominal aortic calcium scores.[73,74]

Pollutant-induced cardiac arrhythmias have been proposed as another important cause of cerebrovascular accidents, and specifically atrial fibrillation-related strokes. Heart-rate variability, cardiac electrical instability, and repolarization abnormalities have been reported in association with pollutant exposure with mixed results. Mechanistic studies implicate autonomic nervous system dysregulation and systemic inflammation as the primary drivers of these associations. Vascular dysfunction and hypercoagulability can lead to transient occlusion of coronary arteries with accompanying myocardial ischemia and arrhythmogenic potential. Epidemiologic studies show a modest association between pollution exposure and new onset of atrial fibrillation,[75] with a parallel increase in stroke admission.[39] In addition, by increasing the risk of decompensated heart failure, exposure to air pollution may further augment the risk of a cardioembolic event.

REDUCING RISK OF STROKE BY REDUCING AIR POLLUTANT EXPOSURES

With increasingly compelling evidence that air pollution exposure increases stroke risk, the focus for clinicians and policy makers needs to shift toward effective strategies to mitigate risk. Although the modification in an individual's risk of disease may be small, a decrease in pollutant levels may represent a large opportunity for stroke reduction when applied over the entire population. Furthermore, as no level of pollutant exposure has yet been shown to be without risk, the impact of intervention may be beneficial across a wide range of settings, including areas where pollutant levels are regularly below regulatory standards.

There are multiple approaches to pollution reduction, from policy-level interventions targeting emissions to personal strategies aimed at decreasing individual exposure (Table 2). Although improvement in community-wide air quality is the goal, personal-level interventions can be particularly important and effective for susceptible individuals or during high pollutant events, such as wildfires. There is a paucity of studies and specifically, clinical trials examining the efficacy of pollutant reduction on stroke incidence; however, several review articles have examined the strength of evidence for cardiovascular and respiratory end points, and these can be assumed to be applicable to stroke as well.[76–79] Experts argue that although the evidence for substantial efficacy may be lacking, recommendations for intervention should still be made based on "the precautionary principle" to err on the side of health protection even when uncertainty exists, particularly when the proposed interventions have reasonable costs and pose no additional health risks.[77]

Personal-level interventions typically include an awareness of pollution alerts and a change in behavior in response to predicted poor air quality. The Air Quality Index (AQI) is the primary communication tool used by governmental agencies to illustrate current pollutant levels based on national air quality standards. The AQI is color coded into 6 categories, which represent increasing levels

Table 2. Personal Strategies to Mitigate Effects of Air Pollution Exposure

Intervention	Examples	Comments
Monitor local air forecast	• Automated air pollution networks that provide warnings (eg, AirNow) • Personal pollution monitors	• May be particularly helpful for susceptible populations
Activity modification to reduce exposure to pollutants	• Stay indoors during high pollutant events • Reduce exercise in areas with high pollutants • Select transportation routes to avoid high pollutant zones	• Consider variable infiltration of outdoor pollutants into buildings • Trade-off between health benefits of physical exercise and adverse health effects of pollution
Clean indoor air	• Portable air filters, such as high efficiency particulate air purifiers • Central air cleaning systems	• Must be appropriately sized for room • Filters must be maintained • Can be expensive
Personal protective equipment	• Negative pressure APR, such as N95 • Positive pressure APR	• Must have correct filter • Negative pressure APR must have appropriate seal/fit to be effective • May be uncomfortable or difficult for individuals with chronic cardiopulmonary disease to wear
Medications or dietary supplements	• Antioxidants • Omega 3-fatty acids • Targeted therapy to proposed pathophysiology	• Mixed evidence of benefit • Not currently recommended

APR indicates air-purifying respirators; and N95, respirator that can reduce 95% of particles.

of health concern: levels below 50 indicate good air quality, and levels over 300 correspond to hazardous air quality. Of note, the AQI has many limitations, which may restrict its usefulness in accurately predicting health risk. The AQI is a threshold metric based on a single pollutant-level that may not reflect levels of other, important co-pollutants. Because the AQI has typically been assigned based on measurements at a small number of regulatory monitors, it also may not accurately reflect exposures at an individual's residential address, during their commute, in their indoor office, or in other places that define the microenvironment. Furthermore, although the AQI is widely used, different countries set their own level of concern based on their own regulatory standards; thus, a level that is considered "unhealthy" in one country, may be considered acceptable in another. Better communication tools are needed that incorporate increased exposure data at a finer scale, with uniform consistent messaging and recommendations.[77] That said, public health authorities typically make behavioral recommendations based on the AQI, and we advise health providers to reinforce those recommendations when communicating with their patients.

Behavior changes aimed at reducing the amount of time and activity spent in polluted areas are commonly recommended by public health groups, such as local health agencies and the Environmental Protection Agency.[80] Examples of behavior changes include reducing exercise in more polluted urban areas, selecting travel routes that minimize near-road environments, or staying indoors during high, acute pollutant events. Although many of these interventions are low-cost and simple to implement, it is important to qualify recommendations in consideration of the burden, trade-offs, and efficacy of these modifications. For instance, while physical activity may increase the inhaled pollutant load by increasing the rate and depth of inhalation, exercise also has well-recognized protective effects against cardiovascular disease, including stroke incidence. A recent nationwide cohort study from Korea demonstrated that moderate to vigorous physical activity decreased the risk of stroke in groups with both high and low pollutant exposure.[81] Thus, for most people, the benefits of physical activity are likely to outweigh the risks of increased pollutant exposure except during extreme air pollution conditions.[79]

There is also accumulating evidence for the use of technological interventions, such as filters to clean indoor air in buildings, vehicles, and residential homes, as a means to reduce adverse pollutant-related outcomes. While pollutant levels are typically higher outdoors, indoor levels may vary widely depending on building structure, indoor sources of pollution, weatherproofing and ventilation. As most people, especially older individuals at the highest risk of stroke, spend most of their time indoors, it is particularly important to limit exposure to pollution in the indoor environment. High efficiency particulate air filters mechanically remove >99.9% of particles with a diameter of 0.3 μm from filtered air, and have been shown in well-designed studies to reduce PM concentrations between 40% and 70%.[79] These filters can be used in portable air purifiers to clean individual rooms or placed in preexisting heating, ventilation, and air conditioning systems. Importantly, while many agencies recommend the use of high efficiency particulate air filters, they caution against the use of ionizers or other ozone-generating air cleaners. Ozone generators intentionally produce ozone and should never be used as an air cleaner in occupied rooms. Ion generators and some electronic air cleaners, use electrostatic forces to capture particles and may produce ozone as a byproduct.

Although there have been no studies with specific stroke-related outcomes, several studies have demonstrated that the use of high efficiency particulate air filters is associated with a reduction in arterial blood pressure and inflammatory and thrombogenic biomarkers in young, healthy adults.[82,83] In addition, modeling studies have estimated that the use of portable air cleaners during wildfire smoke events in California would be a cost-effective intervention in reducing mortality-related costs, particularly if the elderly population is targeted.[84]

Personal protective equipment, such as masks, is another commonly used method of reducing pollutant exposure that has been variably adopted in many parts of the world. Cloth and surgical masks are not recommended due to the lack of an airtight seal and uncertain filtering ability depending on mask material.[76] Although negative pressure respirators, such as N95s (defined as being able to reduce 95% of particles <0.3 μm) and N99s (defined as being able to reduce 99% of particles <0.3 μm), can effectively reduce PM exposure, they are not effective against hazardous gases, such as ozone. In addition, they must have a tight-fitting seal, may be uncomfortable to wear (particularly in extreme heat), and may increase work of breathing for individuals with chronic cardiorespiratory disease. There have been no studies of respirator use in the prevention of stroke-related outcomes.

Various pharmacotherapy, vitamin supplementation, and dietary modification have also been proposed to decrease pollutant-related adverse health outcomes. These interventions target the hypothesized pathophysiologic mechanisms, such as pollutant-mediated oxidative stress and inflammation. Clinical trial of antioxidant supplementation with vitamin C and N-acetylcysteine have been mixed, with some studies even suggesting augmented pollutant-mediated vascular dysfunction.[85] Until more conclusive evidence of benefit is found, pharmacologic intervention to prevent pollutant health effects should not be routinely recommended.

Clinical Implications and Guidelines

Although many agencies have produced risk communication and public health recommendations synthesizing

Stroke. 2023;54:882–893. DOI: 10.1161/STROKEAHA.122.035498

these pollution interventions, there is little clinical guidance to help healthcare providers counsel patients. The American Heart Association recently published a "clinical framework" to address this need (Figure 2).[77] This algorithm incorporates both the patient's health risks (susceptibility factors) and the patient's acute and chronic exposure to pollution (vulnerability factors). Patients who may be at a higher risk for pollution-attributable stroke includes individuals with advanced age, established atherosclerotic cardiovascular disease, diabetes, or chronic kidney disease with one additional traditional cardiac risk factors. The authors recommend personal-level interventions to reduce pollutant exposure in high-risk patients when $PM_{2.5}$ levels acutely exceed 35 μg/m^3 or chronically exceed 12 μg/m^3, which corresponds to an AQI of 50.[77]

SUMMARY AND CONCLUSIONS

The current epidemiologic evidence suggests that exposure to higher levels of ambient air pollution will increase the risk of stroke and stroke mortality, but inconsistencies in the research remain, and future research is needed.

In much of the research assessing the impact of air pollution on stroke, stroke is considered a composite end point that includes strokes of different event types (hospitalization, mortality) and subtypes (ischemic, hemorrhagic). This broad categorization of events may be masking considerable differences in true associations across both stroke subtype and event type.

Several large studies showed associations between air pollution and stroke mortality, but not stroke hospitalizations.[37,38] This could be related to methodologic limitations such as misclassification of stroke hospitalizations because of diagnostic or coding errors or incorrect temporal classification of initial stroke onset and hospitalization compared with death.[86] These factors are likely not associated with exposure to air pollution; therefore, it is expected that these limitations are biasing estimates toward the null. Because stroke severity is the largest determinant of mortality, it is also reasonable to consider mortality as a proxy for severity, potentially implicating that exposure to air pollution may lead to more severe cerebrovascular outcomes. Future studies should take into consideration stroke severity when assessing the impact of air pollution on stroke events in order to understand whether exposure is more strongly related to stroke incidence or severity.

Multiple pathophysiological pathways have been implicated in the association between air pollution and stroke and is likely that different pathophysiologic mechanisms are more important for different stroke subtypes. Exposure to air pollution results in systemic inflammation, enhanced thrombogenicity, atherosclerotic plaque instability, and vasoconstriction. Acutely, these cellular responses may trigger the onset of

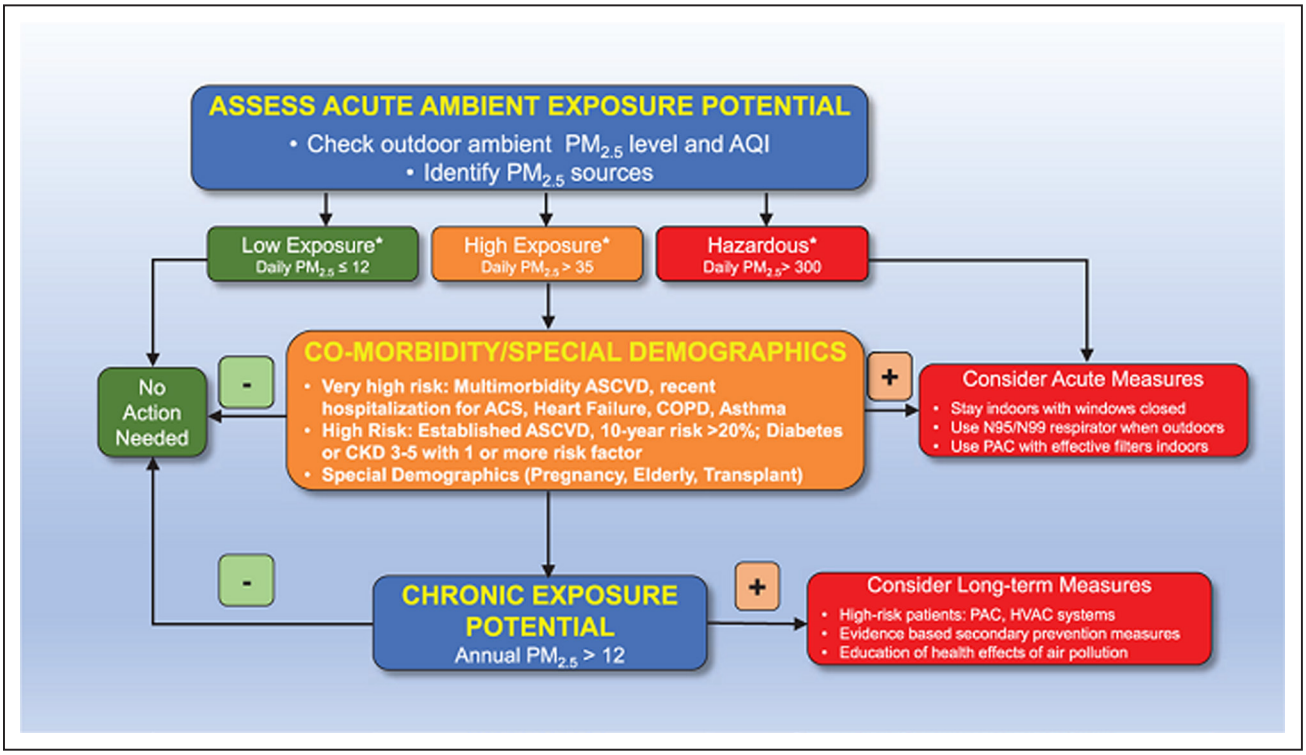

Figure 2. Framework for Personal-Level Protective Actions against Particulate Matter (PM) Air Pollution Exposure.
ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; AQI, The Air Quality Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; N95, respirator that can reduce 95% of particles; HVAC, heating, ventilation, and air conditioning; N99, negative pressure respirator that can reduce 99% of particles; and PAC, portable air cleaners. Reprinted from Rajagopalan et al[77] with permission. Copyright ©2020, the American Heart Association, Inc.

ischemic stroke, whereas chronically, they can contribute to the development of common risk factors for cerebrovascular disease, including diabetes, hypertension, cardiac arrhythmia, and accelerated atherosclerosis. As hemorrhagic stroke has a different pathogenesis, combining ischemic stroke and hemorrhagic stroke into 1 outcome may underestimate the true association between air pollution and ischemic stroke. Depending on the distribution of stroke type in a population, this could lead to much of the heterogeneity in results. Although these conclusions are informative, future research should focus on investigating specific pathogenic stroke subtypes, such as large artery atherosclerosis, small artery occlusion, or cardioembolic strokes.

Despite some remaining uncertainties in the scientific literature, attention needs to shift toward identifying effective ways to mitigate the impact of pollution exposure on stroke incidence and severity. Although policies that reduce emissions and improve air quality are the ultimate goal, interventions to reduce personal exposure to air pollution are important conjunctive measures, particularly when targeted at high-risk individuals. Although specific studies are lacking for stroke-related outcomes, there is growing evidence that individual interventions, such as activity modification, use of indoor air cleaners, and respiratory personal protection, can reduce air pollution exposure with measurable improvement in cardiopulmonary biomarkers. There is a need for a better framework for clinicians to help address the risk of air pollution exposure with their patients.

PUBLIC HEALTH AND POLICY IMPLICATIONS

The research continues to accumulate and support the role of ambient air pollutants in risk of cerebrovascular disease. These risks are associated with both short-term and long-term exposures. Mitigating these risks at an individual level, as by use of air cleaners, may be reasonable for patients at high risk of stroke from any cause.[77] However, the most effective route to lowering air pollution-related risk is through community- and society-level interventions to reduce the emissions that result in elevated air pollutant concentrations. Recent statements from the American Heart Association, along with other cardiovascular societies worldwide have endorsed the need for improved air quality as a path to reduced vascular disease.[87–89] Policy interventions that improve air quality can be expected to have numerous co-benefits; for example, a reduction in fossil fuel combustion will also reduce climate forcing agents. Policies that encourage active transport and increased use public transportation can lead to not only improved air quality but also increased physical activity. Even as the scientific database continues to evolve and our understanding of the mechanisms of air pollutant effects grows, the evidence supports policies to reduce air pollutant exposures as a path to reducing risk of cerebrovascular disease.

ARTICLE INFORMATION

Affiliations

Department of Epidemiology and Biostatistics, Temple University College of Public Health, Philadelphia, PA (E.R.K.). Department of Medicine, University of Washington, Seattle (J.D.K., C.S.). Department of Environmental and Occupational Health Sciences, University of Washington, Seattle (J.D.K., C.S.). Department of Epidemiology, University of Washington, Seattle (J.D.K.).

Acknowledgments

All authors contributed to writing the original draft, review, editing, and resources. All Authors approved the final version of the article to be published.

Sources of Funding

This work was supported by grants from the US National Institute of Environmental Health Sciences P30ES007033 (Drs Kaufman and Sack) and K23 ES030725 (Dr Sack).

Disclosures

Dr Kaufman has received support from the US National Institutes of Health and the US Environmental Protection Agency.

REFERENCES

1. Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, Abbasifard M, Abbasi-Kangevari M, Abd-Allah F, Abedi V, 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;20:1–26. doi: 10.1016/S1474-4422(21)00252-0
2. GBD2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392:1923–1994. doi: 10.1016/S0140-6736(18)32225-6
3. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah GA, Norrving B, Shiue I, Ng M, et al. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol.* 2016;15:913–924. doi: 10.1016/S1474-4422(16)30073-4
4. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet.* 2016;388:761–775. doi: 10.1016/S0140-6736(16)30506-2
5. World Health Organization. Ambient (outdoor) air pollution. Accessed September 29, 2021. https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health.
6. Dickey JH. Selected topics related to occupational exposures Part VII. Air pollution: overview of sources and health effects. *Dis Mon.* 2000;46:566–589. doi: 10.1016/S0011-5029(00)90024-5
7. United States Environmental Protection Agency. Our Nation's Air 2021 [Internet]. Research Triangle Park, NC: 2021. Accessed April 5, 2021. https://gispub.epa.gov/air/trendsreport/2021/#welcome.
8. Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, Cox C. Translocation of inhaled ultrafine particles to the brain. *Inhal Toxicol.* 2004;16:437–445. doi: 10.1080/08958370490439597
9. Utell MJ, Frampton MW. Acute health effects of ambient air pollution: the ultrafine particle hypothesis. *J Aerosol Med.* 2009;13:355–359. doi: 10.1089/jam.2000.13.355
10. US Environmental Protection Agency. Our nation's air status and trends through 2010. Research Triangle Park, NC: 2012.
11. Ljungman PL, Mittleman MA. Ambient air pollution and stroke. *Stroke.* 2014;45:3734–3741. doi: 10.1161/STROKEAHA.114.003130
12. Maheswaran R. Air pollution and stroke – an overview of the evidence base. *Spat Spatiotemporal Epidemiol.* 2016;18:74–81. doi: 10.1016/j.sste.2016.04.004

13. Shah AV, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, Langrish JP, Newby DE, Mills NL. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ.* 2015;350:h1295. doi: 10.1136/bmj.h1295
14. Wang Y, Eliot MN, Wellenius GA. Short-term changes in ambient particulate matter and risk of stroke: A systematic review and meta-analysis. *J Am Heart Assoc.* 2014;3:e000983. doi: 10.1161/JAHA.114.000983
15. 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
16. Chen C, Liu X, Wang X, Qu W, Li W, Dong L. Effect of air pollution on hospitalization for acute exacerbation of chronic obstructive pulmonary disease, stroke, and myocardial infarction. *Environ Sci Pollut Res.* 2020;27:3384–3400. doi: 10.1007/s11356-019-07236-x
17. Guo Y, Xie X, Lei L, Zhou H, Deng S, Xu Y, Liu Z, Bao J, Peng J, Huang C, et al. Short-term associations between ambient air pollution and stroke hospitalisations: time-series study in Shenzhen, China. *BMJ Open.* 2020;10:32974. doi: 10.1136/bmjopen-2019-032974
18. Hayes RB, Lim C, Zhang Y, Cromar K, Shao Y, Reynolds HR, Silverman DT, Jones RR, Park Y, Jerrett M, et al. PM2.5 air pollution and cause-specific cardiovascular disease mortality. *Int J Epidemiol.* 2020;49:25. doi: 10.1093/ije/dyz114
19. Zhang Y, Ma R, Ban J, Lu F, Guo M, Zhong Y, Jiang N, Chen C, Li T, Shi X. Risk of cardiovascular hospital admission after exposure to fine particulate pollution. *J Am Coll Cardiol.* 2021;78:1015–1024. doi: 10.1016/j.jacc.2021.06.043
20. Zanobetti A, Schwartz J. The effect of fine and coarse particulate air pollution on mortality: a national analysis. *Environ Health Perspect.* 2009;117:898–903. doi: 10.1289/ehp.0800108
21. Filigrana P, Milando C, Batterman S, Levy JI, Mukherjee B, Pedde M, Szpiro AA, Adar SD. Exposures to primary air pollutants generated by highway traffic and the risk of daily mortality in near road communities: a case-crossover study. *Am J Epidemiol.* 2022;191:63–74. doi: 10.1093/aje/kwab215
22. Nhung NTT, Schindler C, Chau NQ, Hanh PT, Hoang LT, Dien TM, Thanh NTN, Künzli N. Exposure to air pollution and risk of hospitalization for cardiovascular diseases amongst Vietnamese adults: case-crossover study. *Sci Total Environ.* 2020;703:134637. doi: 10.1016/j.scitotenv.2019.134637
23. Zhang R, Liu G, Jiang Y, Li G, Pan Y, Wang Y, Wei Z, Wang J, Wang Y. Acute Effects of Particulate Air Pollution on Ischemic Stroke and Hemorrhagic Stroke Mortality. *Front Neurol.* 2018;9:827. doi: 10.3389/fneur.2018.00827
24. Wellenius GA, Schwartz J, Mittleman MA. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke.* 2005;36:2549–2553. doi: 10.1161/01.STR.0000189687.78760.47
25. Kloog I, Coull BA, Zanobetti A, Koutrakis P, Schwartz JD. Acute and chronic effects of particles on hospital admissions in New-England. *PLoS One.* 2012;7:e34664. doi: 10.1371/journal.pone.0034664
26. O'Donnell MJ, Fang J, Mittleman MA, Kapral MK, Wellenius GA; Investigators of the Registry of Canadian Stroke Network. Fine particulate air pollution (PM2.5) and the risk of acute ischemic stroke. *Epidemiology.* 2011;22:422–431. doi: 10.1097/EDE.0b013e3182126580
27. Wang Z, Peng J, Liu P, Duan Y, Huang S, Wen Y, Liao Y, Li H, Yan S, Cheng J, et al. Association between short-term exposure to air pollution and ischemic stroke onset: a time-stratified case-crossover analysis using a distributed lag nonlinear model in Shenzhen, China. *Environ Heal.* 2020;19:1. doi: 10.1186/s12940-019-0557-4
28. Song J, Lim Y, Ko I, Kim J-Y, Kim D-K. Association between Air pollutants and initial hospital admission for ischemic Stroke in Korea from 2002 to 2013. *J Stroke Cerebrovasc Dis.* 2021;30:106080. doi: 10.1016/j.jstrokecerebrovasdis.2021
29. Chen L, Zhang Y, Zhang W, Chen G, Lu P, Guo Y, Li S. Short-term effect of PM1 on hospital admission for ischemic stroke: a multi-city case-crossover study in China. *Environ Pollut.* 2020;260:113776. doi: 10.1016/j.envpol.2019.113776
30. Fisher JA, Puett RC, Laden F, Wellenius GA, Sapkota A, Liao D, Yanosky JD, Carter-Pokras O, He X, Hart JE. Case-crossover analysis of short-term particulate matter exposures and stroke in the health professionals follow-up study. *Environ Int.* 2019;124:153–160. doi: 10.1016/j.envint.2018.12.044
31. Verhoeven JI, Allach Y, Vaartjes ICH, Klijn CJM, de Leeuw F-E. Ambient air pollution and the risk of ischaemic and haemorrhagic stroke. *Lancet Planet Heal.* 2021;5:e542–e552. doi: 10.1016/S2542-5196(21)00145-5
32. Rich DQ, Zhang W, Lin S, Squizzato S, Thurston SW, van Wijngaarden E, Croft D, Masiol M, Hopke PK. Triggering of cardiovascular hospital admissions by source specific fine particle concentrations in urban centers of New York State. *Environ Int.* 2019;126:387. doi: 10.1016/j.envint.2019.02.018
33. Zhang W, Lin S, Hopke PK, Thurston SW, van Wijngaarden E, Croft D, Squizzato S, Masiol M, Rich D. Triggering of cardiovascular hospital admissions by fine particle concentrations in New York state: before, during, and after implementation of multiple environmental policies and a recession. *Environ Pollut.* 2018;242:1404–1416. doi: 10.1016/j.envpol.2018.08.030
34. Ban J, Wang Q, Ma R, Zhang Y, Shi W, Zhang Y, Chen C, Sun Q, Wang Y, Guo X, et al. Associations between short-term exposure to PM2.5 and stroke incidence and mortality in China: a case-crossover study and estimation of the burden. *Environ Pollut.* 2021;268:115743. doi: 10.1016/j.envpol.2020.115743
35. Vivanco-Hidalgo RM, Wellenius GA, Basagaña X, Cirach M, González AG, Ceballos P de, Zabalza A, Jiménez-Conde J, Soriano-Tarraga C, Giralt-Steinhauer E, et al. Short-term exposure to traffic-related air pollution and ischemic stroke onset in Barcelona, Spain. *Environ Res.* 2018;162:160–165. doi: 10.1016/j.envres.2017.12.024
36. Butland BK, Atkinson RW, Crichton S, Barratt B, Beevers S, Spiridou A, Hoang U, Kelly FJ, Wolfe CD. Air pollution and the incidence of ischaemic and haemorrhagic stroke in the South London stroke register: a case-cross-over analysis. *J Epidemiol Community Health.* 2017;71:707–712. doi: 10.1136/jech-2016-208025
37. Scheers H, Jacobs L, Casas L, Nemery B, Nawrot TS. Long-term exposure to particulate matter air pollution is a risk factor for stroke: meta-analytical evidence. *Stroke.* 2015;46:3058–3066. doi: 10.1161/STROKEAHA.115.009913
38. Alexeeff SE, Liao NS, Liu X, Van Den Eeden SK, Sidney S. Long-term pm2.5 exposure and risks of ischemic heart disease and stroke events: review and meta-analysis. *J Am Heart Assoc.* 2021;10:1–22. doi: 10.1161/JAHA.120.016890
39. Shin S, Burnett RT, Kwong JC, Hystad P, Van Donkelaar A, Brook JR, Goldberg MS, Tu K, Copes R, Martin RV, 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
40. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med.* 2007;356:447–458. doi: 10.1056/NEJMoa054409
41. Danesh Yazdi M, Wang Y, Di Q, Zanobetti A, Schwartz J. Long-term exposure to PM2.5 and ozone and hospital admissions of Medicare participants in the Southeast USA. *Environ Int.* 2019;130:104879. doi: 10.1016/j.envint.2019.05.073
42. Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, Martin RV, van Donkelaar A, Hughes E, Shi Y, et al. Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med.* 2013;188:593–599. doi: 10.1164/rccm.201303-0609OC
43. Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, Smith DF, Garcia C, Chang ET, Bernstein L. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *Am J Respir Crit Care Med.* 2011;184:828–835. doi: 10.1164/rccm.201012-2082OC
44. Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, Caracciolo B, Cyrys J, de Faire U, de Hoogh K, 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;122:919–925. doi: 10.1289/ehp.1307301
45. Amini H, Dehlendorff C, Lim YH, Mehta A, Jørgensen JT, Mortensen LH, Westendorp R, Hoffmann B, Loft S, Cole-Hunter T, et al. Long-term exposure to air pollution and stroke incidence: a Danish nurse cohort study. *Environ Int.* 2020;142:105891. doi: 10.1016/j.envint.2020.105891
46. Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M, Forastiere F. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect.* 2013;121:324–331. doi: 10.1289/ehp.1205862
47. Maheswaran R, Elliott P. Stroke mortality associated with living near main roads in England and Wales: a geographical study. *Stroke* 2003;34:2776–2780. doi: 10.1161/01.STR.0000101750.77547.11
48. Beelen R, Stafoggia M, Raaschou-Nielsen O, Andersen ZJ, Xun WW, Katsouyanni K, Dimakopoulou K, Brunekreef B, Weinmayr G, Hoffmann B, et al. Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts. *Epidemiology.* 2014;25:368–378. doi: 10.1097/EDE.0000000000000076
49. Andersen ZJ, Kristiansen LC, Andersen KK, Olsen TS, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sørensen M, Tjønneland A, et al. Stroke and long-term

exposure to outdoor air pollution from nitrogen dioxide: a cohort study. *Stroke.* 2012;43:320–325. doi: 10.1161/STROKEAHA.111.62924
50. Hoffmann B, Weinmayr G, Hennig F, Fuks K, Moebus S, Weimar C, Dragano N, Hermann DM, Kälsch H, Mahabadi AA, 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. doi: 10.3238/arztebl.2015.0195
51. Kim H, Kim J, Kim S, Kang S-H, Kim H-J, Kim H, Heo J, Yi S-M, Kim K, Youn T-J, et al. Cardiovascular effects of long-term exposure to air pollution: a population-based study with 900,845 person-years of follow-up. *J Am Heart Assoc.* 2017;6:e007170. doi: 10.1161/JAHA.117.007170
52. Qiu H, Sun S, Tsang H, Wong C-M, Lee RS-Y, Schooling CM, Tian L. Fine particulate matter exposure and incidence of stroke: a cohort study in Hong Kong. *Neurology.* 2017;88:1709–1717. doi: 10.1212/WNL.0000000000003903
53. Liang F, Liu F, Huang K, Yang X, Li J, Xiao Q, Chen J, Liu X, Cao J, Shen C, et al. Long-term exposure to fine particulate matter and cardiovascular disease in China. *J Am Coll Cardiol.* 2020;75:707–717. doi: 10.1016/j.jacc.2019.12.031
54. Takeuchi A, Nishiwaki Y, Okamura T, Milojevic A, Ueda K, Asakura K, Takebayashi T, Hasegawa S, Sairenchi T, Irie F, et al. Long-Term Exposure to Particulate Matter and Mortality from Cardiovascular Diseases in Japan: The Ibaraki Prefectural Health Study (IPHS). *J Atheroscler Thromb.* 2021;28:230. doi: 10.5551/jat.54148
55. Hystad P, Larkin A, Rangarajan S, AlHabib KF, Avezum A, Calik KBT, Chifamba J, Dans A, Diaz R, du Plessis JL, et al. Associations of outdoor fine particulate air pollution and cardiovascular disease in 157 436 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet Planet Heal.* 2020;4:e235–e245. doi: 10.1016/S2542-5196(20)30103-0
56. Cai Y, Hodgson S, Blangiardo M, Gulliver J, Morley D, Fecht D, Vienneau D, de Hoogh K, Key T, Hveem K, et al. Road traffic noise, air pollution and incident cardiovascular disease: a joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts. *Environ Int.* 2018;114:191–201. doi: 10.1016/j.envint.2018.02.048
57. Puett RC, Hart JE, Suh H, Mittleman M, Laden F. Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study. *Environ Health Perspect.* 2011;119:1130–1135. doi: 10.1289/ehp.1002921
58. Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol.* 2018;72:2054–2070. doi: 10.1016/j.jacc.2018.07.099
59. Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation.* 2010;121:2331–2378. doi: 10.1161/CIR.0b013e3181dbece1
60. Costa LG, Cole TB, Dao K, Chang Y-C, Coburn J, Garrick JM. Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders HHS public access. *Pharmacol Ther.* 2020;210:107523. doi: 10.1016/j.pharmthera.2020.107523
61. Micheu MM, Birsan MV, Szép R, Keresztesi A, Nita IA. From air pollution to cardiovascular diseases: the emerging role of epigenetics. *Mol Biol Rep.* 2020;47:5559–5567. doi: 10.1007/s11033-020-05570-9
62. Cosselman KE, Krishnan RM, Oron AP, Jansen KL, Peretz A, Sullivan JH, Larson TV, Kaufman JD. Blood pressure response to controlled diesel exhaust exposure in human subjects. *Hypertension.* 2012;59:943–948. doi: 10.1161/HYPERTENSIONAHA.111.186593
63. Hudda N, Eliasziw M, Hersey S, Reisner E, Brook RD, Zamore W, Durant J, Brugge D. Effect of reducing ambient traffic-related air pollution on blood pressure: a randomized crossover trial. *Hypertension.* 2021;77:823–832. doi: 10.1161/HYPERTENSIONAHA.120.15580
64. Miller MR, Raftis JB, Langrish JP, McLean SG, Samutrtai P, Connell SP, Wilson S, Vesey AT, Fokkens PHB, Boere AJF, et al. Inhaled nanoparticles accumulate at sites of vascular disease. *ACS Nano.* 2017;11:4542–4552. doi: 10.1021/acsnano.6b08551
65. Calderón-Garcidueñas L, Franco-Lira M, Henríquez-Roldán C, Osnaya N, González-Maciel A, Reynoso-Robles R, Villarreal-Calderon RR, Herritt L, Brooks D, Keefe S, et al. Urban air pollution: influences on olfactory function and pathology in exposed children and young adults. *Exp Toxicol Pathol.* 2010;62:91–102. doi: 10.1016/j.etp.2009.02.117
66. Liu Q, Shkirkova K, Lamorie-Foote K, Connor M, Patel A, Babadjouni R, Huuskonen M, Montagne A, Baertsch H, Zhang H, et al. Air pollution particulate matter exposure and chronic cerebral hypoperfusion and measures of white matter injury in a Murine Model. *Environ Health Perspect.* 2021;129:87006. doi: 10.1289/EHP8792
67. Wellenius GA, Boyle LD, Wilker EH, Sorond FA, Coull BA, Koutrakis P, Mittleman MA, Lipsitz LA. Ambient fine particulate matter alters cerebral hemodynamics in the elderly. *Stroke.* 2013;44:1532–1536. doi: 10.1161/STROKEAHA.111.000395
68. Wang W, Liu C, Ying Z, Lei X, Wang C, Huo J, Zhao Q, Zhang Y, Duan Y, Chen R, et al. Particulate air pollution and ischemic stroke hospitalization: how the associations vary by constituents in Shanghai, China. *Sci Total Environ.* 2019;695:133780. doi: 10.1016/j.scitotenv.2019.133780
69. Cai L, Yang J, Cosky E, Xin R, Geng X, Ding Y. Enhanced cerebral microbleeds by long-term air pollution exposure in spontaneously hypertensive rats. *Neurol Res.* 2022;44:196–205. doi: 10.1080/01616412.2021.1968705
70. Liang S, Zhang J, Ning R, Du Z, Liu J, Batibawa JW, Duan J, Sun Z. The critical role of endothelial function in fine particulate matter-induced atherosclerosis. *Part Fibre Toxicol.* 2020;17:1–24. doi: 10.1186/s12989-020-00391-x
71. Miller M, McLean S, Duffin R, Lawal A, Araujo J, Shaw CA, Mills NL, Donaldson K, Newby DE, Hadoke PWF. Diesel exhaust particulate increases the size and complexity of lesions in atherosclerotic mice. *Part Fibre Toxicol.* 2013;10:61. doi: 10.1186/1743-8977-10-61
72. Guan L, Geng X, Stone C, Cosky E, Ji Y, Du H, Zhang K, Sun Q, Ding Y. PM 2.5 exposure induces systemic inflammation and oxidative stress in an intracranial atherosclerosis rat model. *Environ Toxicol.* 2019;34:530–538. doi: 10.1002/tox.22707
73. Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, Daviglus ML, Diez Roux AV, Gassett AJ, Jacobs DR, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. *Lancet.* 2016;388:696–704. doi: 10.1016/S0140-6736(16)00378-0
74. Roux AVD, Auchincloss AH, Franklin T, Raghunathan TE, Barr RG, Kaufman JD, Astor B, Keeler J. Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the multi-ethnic study of atherosclerosis. *Am J Epidemiol.* 2008;167:667–675. doi: 10.1093/aje/kwm359
75. Hart JE, Hohensee C, Laden F, Holland I, Whitsel EA, Wellenius GA, Winkelmayer WC, Sarto GE, Martin LW, Manson JE, et al. Long-term exposures to air pollution and the risk of atrial fibrillation in the women's health initiative cohort. *Environ Heal Perspect Perspect.* 2021;129:97007. doi: 10.1289/EHP7683
76. Newman JD, Bhatt DL, Rajagopalan S, Balmes JR, Brauer M, Breysse PN, Brown AGM, Carnethon MR, Cascio WE, Collman GW, et al. Cardiopulmonary impact of particulate air pollution in high-risk populations: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;76:2878–2894. doi: 10.1016/j.jacc.2020.10.020
77. Rajagopalan S, Brauer M, Bhatnagar A, Bhatt DL, Brook JR, Huang W, Münzel T, Newby D, Siegel J, Brook RD, et al. Personal-level protective actions against particulate matter air pollution exposure: a scientific statement from the American Heart Association. *Circulation.* 2020;142:e411–e431. doi: 10.1161/CIR.0000000000000931
78. Bard RL, Ijaz MK, Zhang JJ, Li Y, Bai C, Yang Y, Garcia WD, Creek J, Brook RD. Interventions to reduce personal exposures to air pollution: a primer for health care providers. *Glob Heart.* 2019;14:47–60. doi: 10.1016/j.gheart.2019.02.001
79. Carlsten C, Salvi S, Wong GWK, Chung KF. Personal strategies to minimise effects of air pollution on respiratory health: advice for providers, patients and the public. *Eur Respir J.* 2020;55:1902056. doi: 10.1183/13993003.02056-2019
80. Janjua S, Powell P, Atkinson R, Stovold E, Fortescue R. Individual-level interventions to reduce personal exposure to outdoor air pollution and their effects on long-term respiratory conditions. *Cochrane Database Syst Rev.* 2021;8:CD013441. doi: 10.1002/14651858.CD013441.pub2
81. Kim SR, Choi S, Keum N, Park SM. Combined effects of physical activity and air pollution on cardiovascular disease: a population-based study. *J Am Heart Assoc.* 2020;9:13611. doi: 10.1161/JAHA.119.013611
82. Li H, Cai J, Chen R, Zhao Z, Ying Z, Wang L, Chen J, Hao K, Kinney PL, H C, et al. Particulate matter exposure and stress hormone levels: a randomized, double-blind, crossover trial of air purification. *Circulation.* 2017;136:618–627. doi: 10.1161/CIRCULATIONAHA.116.026796
83. Chen R, Zhao A, Chen H, Zhao Z, Cai J, Wang C, Yang C, Li H, Xu X, Ha S, et al. Cardiopulmonary benefits of reducing indoor particles of outdoor origin: a randomized, double-blind crossover trial of air purifiers. *J Am Coll Cardiol.* 2015;65:2279–2287. doi: 10.1016/j.jacc.2015.03.553
84. Fisk W, Chan W. Health benefits and costs of filtration interventions that reduce indoor exposure to PM2.5 during wildfires. *Indoor Air.* 2017;27:191–204. doi: 10.1111/ina.12285
85. Sack CS, Jansen KL, Cosselman KE, Trenga CA, Stapleton P, Allen JL, Peretz A, Olives C, Kaufman JD. Pretreatment with antioxidants

augments the acute arterial vasoconstriction caused by diesel exhaust inhalation. *Am J Respir Crit Care Med*. 2016;193:1000–1007. doi: 10.1164/rccm.201506-1247OC

86. Lokken RP, Wellenius GA, Coull BA, Burger MR, Schlaug G, Suh HH, Mittleman MA. Air pollution and risk of stroke: underestimation of effect due to misclassification of time of event onset. *Epidemiology*. 2009;20:137–142. doi: 10.1097/ede.0b013e31818ef34a
87. Brauer M, Casadei B, Harrington RA, Kovacs R, Sliwa K, Brauer M, Davaakhuu N, Hadley M, Kass D, Miller M, et al. Taking a stand against air pollution—the impact on cardiovascular disease. *Circulation*. 2021;143:E800–E804. doi: 10.1161/CIRCULATIONAHA.120.052666
88. Kaufman JD, Elkind MSV, Bhatnagar A, Koehler K, Balmes JR, Sidney S, Burroughs Peña MS, Dockery DW, Hou L, Brook RD, et al. Guidance to reduce the cardiovascular burden of ambient air pollutants a policy statement from the American Heart Association. *Circulation*. 2020;142:E432–E447. doi: 10.1161/CIR.0000000000000930
89. Hoffmann B, Boogaard H, de Nazelle A, Andersen ZJ, Abramson M, Brauer M, Brunekreef B, Forastiere F, Huang W, Kan H, et al. WHO air quality guidelines 2021 – aiming for healthier air for all: a joint statement by medical, public health scientific societies, and patient representative organizations. *Int J Public Health*. 2021;66:23. doi: 10.3389/ijph.2021.1604465