Current trend in air pollution exposure and stroke

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REVIEW

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Stephan Gabet[a] *and Laurent Puy*[b]

Purpose of review
Stroke is the second leading cause of death worldwide, and exposure to particulate air pollution is now recognized as one of the major modifiable risk factors. However, air pollution can vary in terms of physicochemical composition and exposition specificities. Therefore, its relationships with stroke outcomes remain under intense investigation.

Recent findings
This review highlights, alongside particles, that short-term and long-term exposure to nitrogen dioxide (NO_2) and ozone is likely to be also linked to stroke-related morbidity and mortality. Moreover, air pollution may increase the risk of transitioning from a healthy status to incident stroke and morbimortality after stroke. Additionally, relationships may vary depending on the air pollution mixture (e.g., particle-related components, pollutant interactions), pollutant sources (e.g., traffic-related or not), stroke etiology (ischemic or hemorrhagic), or exposed individual's characteristics (e.g., age, sex, genetic predisposition, weight status). Nonlinear dose-response functions and short-term effect lags have been reported, but these features need further refinement.

Summary
The relationship between stroke and air pollution is now well established. Nonetheless, future research should further consider the physicochemical properties of air pollutants, multiple exposures, and individual vulnerabilities. Moreover, advanced statistical methods should be more commonly used to better describe the relationship shapes.

Keywords
air pollution, modifying effects, review, stroke

INTRODUCTION

Stroke stands as the second foremost cause of death worldwide, with approximately 6.6 million deaths each year; it also ranks third among leading cause of mortality and disability combined, contributing to 5.7% of total disability-adjusted life years (DALYs) [1]. The burden of stroke has increased sharply worldwide over the past century to an annual incidence of 12.2 million cases, with an annual cost of approximately US$720 billion (0.66% of the global GDP) [1].

The main modifiable risk factors for stroke include high blood pressure, diabetes, dyslipidemia, malnutrition, smoking, and lack of physical activity. In addition, the global burden of air pollution on cardiovascular health is a compelling concern. Especially, short-term (hour to days) and long-term (weeks to years) exposure to particulate air pollution emerged as a recognized modifiable risk factor for stroke morbidity and mortality [2–4]. In 2019, air pollution was the fourth leading risk factor contributing to stroke death and disability combined [5].

This review summarizes the most recent advances in our understanding of stroke, due to short- and long-term exposure to air pollution. We address the impact of air pollution on stroke incidence and outcome, and discuss recent data which have deepened the understanding of the above relationships by considering exposure specificities or potential modifying and mitigating effects.

HOW TO DEFINE AIR POLLUTION?

Air pollution, which represents less than 0.1% of the total composition of the air, is a ubiquitous and complex mixture of solid and liquid particles and

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KEY POINTS

- Exposure to air pollution emerged as a major modifiable risk factor for stroke.
- The pathophysiology is complex but is mostly mediated by an exacerbated systemic inflammation, which is deleterious for the cardiovascular system (endothelium dysfunction, accelerated atherosclerosis, immunothrombosis, and dysautonomia).
- Short-term and long-term exposures increase the risk of new incident stroke and worsen stroke-related morbimortality.
- Beyond particles, many pollutants are now being studied, such as ozone, which is a major concern in the context of climate change.
- Some evidence for modifying factors, such as older age, overweight, or cardiometabolic comorbidities, has been suggested but requires further investigation.

gases, both indoors and outdoors. Prominent components of atmospheric pollution include airborne particulate matter, nitrogen oxides (NO_X) such as nitrogen dioxide (NO_2), ground-level ozone (O_3), and to a lesser extent, sulfur dioxide (SO_2) and carbon monoxide (CO). In indoor air, we primarily find combustion products (e.g., particulate matter, NO_2), volatile organic compounds (VOCs), and bioaerosols (allergens and bacterial and fungal compounds; of biological nature, they are not covered in this review focusing on chemical air pollution).

Particulate matter is commonly characterized by size, distinguished by aerodynamic diameter: particles less than 10 μm (PM_{10}), which are small enough to be inhaled, particles less than 2.5 μm ($PM_{2.5}$, also called fine particles), which can reach the pulmonary alveoli, and particles less than 1 μm (PM_1), which are small enough to enter the bloodstream; particles less than 0.1 μm ($PM_{0.1}$), part of the PM_1 fraction, are called ultrafine particles (UFP). Particulate matter can be further characterized by its components such as black carbon, elemental carbon, organic carbon, and ions (e.g., nitrate, sulfate, ammonium).

Main anthropogenic sources of particles include heating and cooking equipment, road traffic, and industry. There are also nonanthropogenic particles such as pollen, sea spray, and volcanic ash. Regarding gases, major outdoor and indoor sources of NO_X include, respectively, fossil fuel combustion (e.g., combustion engine vehicles, stationary power generation) and gas and coal heating and cooking equipment. Tobacco smoke is an additional indoor air pollution. Ozone is not emitted but formed by the conversion of NO_2 and VOCs present in the atmosphere under the influence of ultraviolet rays. Ozone is therefore a secondary pollutant of particular concern in the context of climate change, which is leading to increase heat and sunshine.

The impact of air pollution on health is huge. An estimated 4.1 million (95% confidence interval: 3.5–4.8) and 2.3 million (1.6–3.1) people die each year worldwide from outdoor and indoor fine particles, respectively. About one-fifth of them die from stroke, making air pollution the leading environmental risk factor for stroke, with an attributable fraction estimated at about 15–20% [1,6,7].

AIR POLLUTION AND STROKE: UNDERLYING PATHOPHYSIOLOGY

Multiple pathophysiological mechanisms have been implicated in the relationship between air pollution and stroke (Fig. 1). Air pollutants inhaled into the lungs trigger a local then systemic pro-inflammatory status. The release of pro-inflammatory and pro-oxidant mediators (increase of circulating levels of leukocytes and various inflammatory cytokines) is deleterious for the cardiovascular system, especially for endothelium integrity [8]. The smallest particles (PM_1) can also directly affect the vasculature and circulating blood cells. They act by activating a proinflammatory response in endothelial cells, upregulating the expression of adhesion molecules, and generating reactive oxygen species, which are key mediators of accelerated atherosclerosis [9].

Exposition to PM can also induce a prothrombotic state by enhancing platelet activation and von Willebrand function, and also trigger an immunothrombosis reaction mediated by neutrophils extracellular traps (NETs) [10]. Data also suggest that particles may translocate to central regions at the level of the nasal passage, particularly the olfactory bulb where high doses of particles are deposited through the first airflow passage, raising the hypothesis of a direct neurotoxicity [11]. In addition, exposure to air pollution may induce cardiorespiratory dysautonomia and can also contribute to the development of common risk factors for cerebrovascular disease, including diabetes, hypertension, atrial fibrillation, and atherosclerosis, inducing a vicious cycle [12].

Finally, some recent epidemiological research sought to better discern underlying pathways, hence causal links [13,14]. Notably, Liang *et al.* [13], by retrieving genome-wide association study (GWAS) statistics for $PM_{2.5}$ and CVDs, showed that exposure to fine particles may increase the risk of stroke diagnosis *via* several single nucleotide polymorphisms (SNPs).

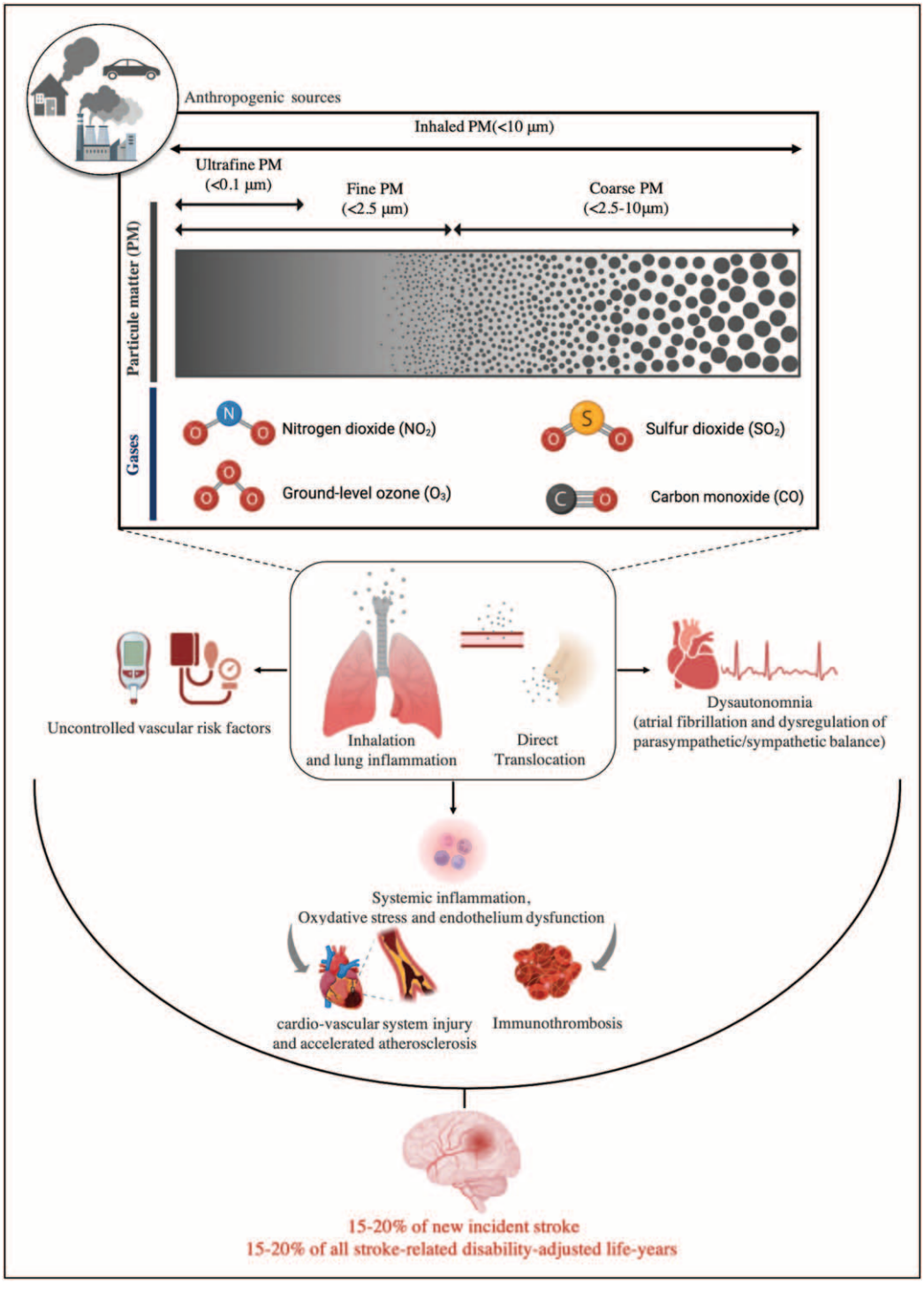

FIGURE 1. Pathophysiologic mechanisms underlying stroke related to air pollution. This figure provides a synthetic overview of the mechanisms at play between air pollution exposure and stroke. Most of these pathways have been demonstrated in ischemic stroke. Statistics are adapted from Feigin *et al.* [5] and Verhoeven *et al.* [7].

EFFECTS OF LONG-TERM EXPOSURE TO AIR POLLUTION

Consequences of long-term exposure on stroke incidence

While published data are consistent and support the link between exposure to air pollution and the risk of new incident stroke, this association may vary according to the subtype of air pollutant. Indeed, Jin *et al.* [15] recently reported significant associations between air pollution and stroke incidence in over 30 million older US fee-for-service Medicare enrollees: adjusted hazard ratio (HRa) 2.79% (95% confidence interval: 2.74–2.84), 0.95% (0.93–0.96), and 0.26% (0.23–0.28) per increase of 1 $\mu g/m^3$ in $PM_{2.5}$, 1 part per billion (ppb) in NO_2, and 1 ppb in warm-season O_3, respectively. As well, Poulsen *et al.* [16▪] reported significant associations with stroke incidence in 2 million individuals aged over 50 years in Denmark: HRa 1.223 (1.175–1.273) per 5 $\mu g/m^3$ increase in $PM_{2.5}$, 1.095 (1.063–1.128) per 10 000 particles/cm^3 increase in UFP, and 1.039 (1.023–1.056) per 5 mg/m^3 increase in NO_2. Consistent results were reported in several Chinese epidemiological studies between incident stroke and exposure to NO_2 [17] or ozone [18–20]. However, null associations were sometimes observed in another Chinese studies with particulate matter, NO_2, O_3, or CO [19,21]. Lastly, the study led by Riggs *et al.* [22] in nearly 27 000 participants of 45 years or above enrolled in the US REasons for Geographic And Racial Differences in Stroke (REGARDS) prospective cohort reported a significant association with PM_{10} only: HRa 1.07 (1.003–1.150) per 5.4 $\mu g/m^3$ increase; no evidence of association was observed for $PM_{2.5}$, O_3, NO_2, SO_2, and CO.

The increased risk of a new stroke can also be observed in the rate of stroke-related hospitalization. Nethery *et al.* [23] showed that stroke-related hospitalizations were positively associated with $PM_{2.5}$ in nearly 2 million US fee-for-service Medicare beneficiaries with acute or chronic cardiovascular conditions: HRa 1.016 (1.013–1.019) per 1 $\mu g/m^3$ increase. Chen *et al.* [24▪▪] investigated the effects of various particulate matter fractions on ischemic stroke-related hospitalizations and showed that the finer the particulate matter fraction the higher the association. Furthermore, the effects on stroke-related hospitalizations seem to affect various age groups, genders, and stroke-subtypes. Thus, Kulick *et al.* [25] reported stronger associations with hospitalization for ischemic than hemorrhagic stroke in about 155 000 postmenopausal women from the US Women's Health Initiative (WHI) prospective cohort: HRa 1.15 (1.12–1.18) versus 1.13 (1.06–1.19) per 3.5 $\mu g/m^3$ increment in $PM_{2.5}$ and 1.05 (1.01–1.09) versus 1.02 (0.93–1.11) per 9.5-ppb increment in NO_2.

Consequences of long-term exposure on the prognosis of stroke

Several Chinese studies reported significant associations of particulate matter exposure with stroke-related mortality [26▪▪,27]. For instance, Cai *et al.* [26▪▪] focused on the effects of $PM_{2.5}$ in a retrospective cohort of over three million hospitalized patients for stroke, and reported significant associations, higher for ischemic than hemorrhagic stroke: adjusted odds-ratio (ORa) 1.158 (1.130–1.188) per 13.9 $\mu g/m^3$ increment and 1.082 (1.047–1.119) per 21.6 $\mu g/m^3$ increment, respectively. Qi *et al.* [28] unusually considered exposure to ambient UFP in an ecological study in the New York State and also showed positive relations.

Furthermore, some research has regarded not only stroke morbidity or mortality independently, but also the entire illness trajectory, from health status to incident stroke, poststroke CVDs, hospital readmissions, multimorbidity, and death.

Thus, Tran *et al.* [29] showed long-term exposure to NO_2, $PM_{2.5}$, CO, or SO_2 was significantly associated with 30-day all-cause hospital readmission among nearly 450 000 US fee-for-service Medicare beneficiaries aged 65 years or older and primarily hospitalized for ischemic stroke. Similarly, Cai *et al.* [30] reported, in a cohort of more than one million participants in Sichuan (China), that higher short-term and long-term exposure levels to particulate matter increased the risk of 30-day stroke rehospitalization in stroke patients; higher risks were reported for long-term than short-term exposure.

Moreover, Zou *et al.* (2023) examined the contribution of long-term exposure to $PM_{2.5}$, PM_{10}, NO_2, and NO_X to cardiometabolic diseases (CMDs), including stroke, cardiometabolic multimorbidity (CMM), and subsequent death, in about 370 000 UK Biobank participants [31]. Increased exposure levels, and particularly to $PM_{2.5}$, significantly increased the risks of transition from healthy status to CMD, and then to CMM and death. Moreover, Tian *et al.* [32] showed in the same UK Biobank cohort that increases in particulate matter and NO_X levels were linked to more frequent transitions from healthy status to incident stroke, poststroke CVDs, and subsequent death.

EFFECTS OF SHORT-TERM EXPOSURE TO AIR POLLUTION

Consequences of short-term exposure on stroke incidence

Comparing to long-term exposure, the recent literature dealing with short-term exposure is broadly less extensive. Nonetheless, Toubasi and Al-Sayegh

[33▪▪] conducted an outstanding meta-analysis to examine the acute effects of particulate matter, NO_X, O_3, SO_2, and CO on ischemic stroke incidence. More than 18 million stroke cases were retrieved from 110 observational studies. Ischemic stroke incidence was significantly associated with many air pollutants: meta-analytical relative risk (RR) 1.14 (1.12–1.16), 1.15 (1.13–1.17), and 1.09 (1.06–1.12) per 10 $\mu g/m^3$ increase in PM_{10}, $PM_{2.5}$, and PM_1, respectively; meta-analytical RR 1.30 (1.22–1.37), 1.05 (1.03–1.07), and 1.17 (1.12–1.21) per 10-ppb increase in NO_2, O_3, and SO_2, respectively; and meta-analytical RR 1.26 (1.21–1.32) per 1-part-per-million (ppm) increase in CO. Nonetheless, these results should be interpretated with caution given the high heterogeneity between studies. Moreover, Badida *et al.* [34] performed a meta-analysis focusing on 152 studies led in low and middle-outcome countries (LMICs). Thus, they reported contrasted results: meta-analytical RR 1.0002 (0.9924–1.0080), 1.0044 (1.0007–1.0081), 1.0065 (0.9819–1.0318), and 1.0136 (1.0105–1.0167) per 10 $\mu g/m^3$ increase in PM_{10}, $PM_{2.5}$, NO_2, and SO_2, levels, respectively; here again, heterogeneity between studies was particularly high.

Consequences of short-term exposure on the prognosis of stroke

Regarding mortality, Toubasi and Al-Sayegh [33▪▪] also reported increased risks of ischemic stroke mortality in their meta-analysis: meta-analytical RR 1.02 (1.00–1.04), 1.09 (1.04–1.15), and 1.09 (1.04–1.15) per 10 $\mu g/m^3$ increase in PM_{10}, $PM_{2.5}$, and PM_1, respectively; meta-analytical RR 1.33 (1.07–1.65), 1.26 (0.91–1.72), and 1.60 (1.05–2.44) per 10-ppb increase in NO_2, O_3, and SO_2, respectively; and meta-analytical RR 1.10 (0.81–1.50) per 1-ppm increase in CO. As well, Badida *et al.* [34] reported significant risk associations in LMICs: meta-analytical RR 1.0064 (1.0038–1.0089), 1.0214 (1.0018–1.0413), 1.0219 (1.0048–1.0394), and 1.0173 (1.0074–1.0274) per 10 $\mu g/m^3$ increase in PM_{10}, $PM_{2.5}$, NO_2, and SO_2, levels, respectively. Nonetheless, the heterogeneity between studies was high in the two meta-analyses; accordingly, results should be interpretated with cautious.

MODIFYING EFFECTS AND RELATIONSHIP SPECIFICATIONS

Many research works sought to specify the above associations by studying the potential modifying effects of various factors, mainly intrinsic. Thus, older people appeared in many studies to be more vulnerable to particulate matter [25,30,35,36] and ozone [18,20], although this trend was sometimes not reported [21,37]. On the contrary, the potential modifying effect of sex was still unclear, with stronger associations reported sometimes in men [20,36], sometimes in women, particularly for particulate matter [24▪▪,30,35], sometimes in neither, particularly for ozone [17,18,21,37,38]. Stronger associations between air pollution and stroke outcomes were consistently reported in individuals who were genetically predisposed [39,40] or affected [15,35,41] by cardiometabolic comorbidities such as diabetes and high blood pressure, but sometimes not [15,25]. In addition, overweight and obesity were suggested as a vulnerability to air pollution in some studies [17,20], but not all [25]. As well, a high physical activity level has been suggested has a protective modifying factor against particulate matter [24▪▪] or ozone [42] adverse effects. People with low education level [20,24▪▪], low socioeconomic status [41], or living within a deprived neighborhood [41] could be more affected by air pollution, but these interactions need also to be corroborated [20,25]. Finally, no conclusion can be drawn concerning the role of ethnic origin due to very heterogeneous results [15,23,25,28,30,35] while stratified studies on tobacco smoking are too scarce to be conclusive [25,42].

KNOWLEDGE GAPS AND FURTHER CONSIDERATIONS

Recent advances have led to a better understanding of the impact of exposure to air pollution on the incidence and outcomes of stroke, but some issues remain.

According to the literature, the shape of the curve of the relationship between air pollution and stroke is still understudied. Indeed, most studies do not rely on statistical models allowing such analysis, such as those incorporating a spline smoothing exposure term instead of a usual linear term. Thus, nonlinear dose–response functions were sometimes suggested, with steeper curves at lower particulate matter [24▪▪] or ozone [20] concentrations. On the contrary, steeper curves were elsewhere reported at higher particulate matter levels [35,43]; similarly, higher risk estimates were reported when focusing on periods of higher exposure levels, such as the cold season for particles [28,36] or ozone pollution peaks [38]. Moreover, nearly linear curves were also described for exposure to particulate matter [40,44], NO_2 [17,40], or ozone [18,21,38]. The curve patterns also appeared contrasted depending on the chronicity of the exposure [30], the particulate matter fraction [30,44], or particulate matter related components [26▪▪,44,45].

Concerning the latter particulate matter components, their relationships with stroke remain too rarely investigated. Although stroke-related outcomes, such as stroke incidence, ischemic stroke mortality, or poststroke functional disability, may be specifically linked to long-term exposure to particulate matter related EC [16▪], particulate matter related black carbon, organic carbon, and sulfate [26▪▪], or particulate matter related OC and sulfate [45], respectively. Cerebrovascular mortality was elsewhere related to short-term exposure to particulate matter related elemental carbon, organic carbon, and nitrate as well as to traffic-related air pollution (TRAP) [36]. Conversely, stroke risk was sometimes associated with non-TRAP only [16▪]. Haddad *et al.* [46▪▪] specifically meta-analyzed the relationships between long-term TRAP exposure and stroke incidence. They therefore reported some evidence of associations: meta-analytical RR 1.22 (1.03–1.21) per 5 $\mu g/m^3$ increase in traffic-related $PM_{2.5}$ and 1.01 (0.96–1.06) per 10 $\mu g/m^3$ increase in traffic-related NO_2.

Furthermore, concerning specifically short-term effects, the plausible time delay after exposure remains not clearly determined, due in particular to sometimes heterogeneous results but especially to a limited literature. Nevertheless, the adverse effects are likely to occur in the first tens hours following the exposure, and not after a few days according to available data. Indeed, considering day-by-day exposure averages over the 7 days preceding stroke, the effects of NO_2 appeared at their maximum on the day of exposure in a Chinese retrospective cohort [42]. Moreover, some research relied on advanced statistical methods, such as distributed lag nonlinear model (DLNM), to better assess the lag-response relationship specifically. Thus, the time series by Lv *et al.* [43], encompassing hourly exposure levels to $PM_{2.5}$, PM_{10}, NO_2, and SO_2, showed that risk for stroke-related emergency hospital admission was the strongest at lag 0 to 2 h. Another time series, based on $PM_{2.5}$ daily exposure and an incident cerebrovascular disease registry, reported the highest risk estimates around a 4-day lag [47].

Moreover, although a growing body of evidence suggests that exposure to air pollution worsens the prognosis of stroke, the underlying reasons are unclear and are probably multiple. In particular, given the effect of air pollution on hemostasis, it could be argued that exposure could induce clot resistance leading to failure of recanalization procedure (intravenous thrombolysis and/or mechanical thrombectomy), a key predictor of mortality and functional outcome after ischemic stroke [48,49].

Finally, understanding of the interactions between environmental exposures has recently been deepened, notably thanks to multiple exposure approaches. Thus, Jiang *et al.* [42] showed that the association between acute NO_2 levels and the risk of stroke was almost doubled in people exposed to higher $PM_{2.5}$ concentrations, while no association was found in those exposed to lower concentrations. Moreover, joint effects of air pollutants on ischemic stroke incidence would be possibly overestimated through single-pollutant models compared with multipollutant models, underscoring the relevancy of multiexposure approaches [37]. In this line, de Bont *et al.* [50] performed a principal component analysis (PCA) to notably summarize the long-term exposure to a mixture of air pollutants ($PM_{2.5}$, NO_2, black carbon, and O_3). They therefore reported significant associations with stroke incidence which were more consistent than single-pollutant model estimates. In another study, exposure to atmospheric pollutants ($PM_{2.5}$, UFP, elemental carbon, and NO_2), ambient noise, and surrounding greenness were all related to stroke in single-exposure analyses, but only $PM_{2.5}$ and noise were independently associated with stroke in the multiexposure analysis [44]. Lastly, several works looked at the interactions between air pollution and other environmental components such as greenness. These studies highlighted a possible mitigation of the adverse effects of air pollution in people having access to green surfaces [51,52,53▪]; however, this phenomenon could depend on stroke etiology (ischemic or hemorrhagic).

The last point emphasizes the importance of embracing the problem of air pollution, not in isolation, but in an increasingly global and holistic manner, taking also into account the whole exposome and other public health contexts. And encouragingly, in light of this literature review, research seems to be clearly moving in this direction. Thus, while epidemiological studies were historically mainly conducted in high-income countries, the issue is now being addressed worldwide, including in LMICs where the health impact of air pollution is dramatic [5]. In addition, while particulate matter was long the focus of research, there is a diversification of the pollutants studied, alone or in mixtures, with an increasingly preponderant place for ozone which is of primary concern in the context of climate change. Moreover, COVID-19 pandemic-related measures such as lockdowns and curfews led to decreases in TRAP, mainly NO_2 but to a lesser extent $PM_{2.5}$ of which the residential and tertiary sectors are the main sources of emissions. Since among the effects of air pollution on stroke, only those linked to $PM_{2.5}$ have been proven so far, the

estimated benefits linked to the improvement of air quality during the pandemic remain limited [54,55]. Linking air pollutants other than $PM_{2.5}$ to stroke and implementing long-term air quality public policies should broaden the range of levers for action and increase health gain estimates.

CONCLUSION

The stroke burden related to air pollution exposure is now well established. This relationship may vary depending on the air pollutant considered as well as the air pollution mixture, the pollutant sources or even individual's characteristics.

Preventive interventions are of utmost importance. The most effective way to reduce the health risks related to air pollution is to implement society-wide policies aiming to reduce emissions, main anthropogenic sources being heating, traffic, and industries [56]. Complementary, exposure can be further reduced through individual preventive measures, such as staying indoors or wearing appropriate air-purifying respirators during acute exposure periods as well as equipping the home with air cleaners at all times [57].

Future research should address gaps in the literature in understanding the potential influences of exposure specificities and individual vulnerabilities to design more adjusted preventive interventions, hence better supporting stakeholder decision-making and promoting individual-specific measures.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Feigin VL, Brainin M, Norrving B, *et al.* World Stroke Organization (WSO): Global Stroke Fact Sheet. Int J Stroke 2022; 17:18–29.
2. Pope CA, Burnett RT, Thurston GD, *et al.* Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 2004; 109:71–77.
3. Stafoggia M, Cesaroni G, Peters A, *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.
4. Shah ASV, Lee KK, McAllister DA, *et al.* Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ 2015; 350:h1295.
5. Feigin VL, Stark BA, Johnson CO, *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. Lancet Neurol 2021; 20:795–820.
6. Roth GA, Mensah GA, Johnson CO, *et al.* Global burden of cardiovascular diseases and risk factors. J Am Coll Cardiol 2020; 76:2982–3021.
7. Verhoeven JI, Allach Y, Vaartjes ICH, *et al.* Ambient air pollution and the risk of ischaemic and haemorrhagic stroke. Lancet Planet Health 2021; 5: e542–e552.
8. Pope CA, Bhatnagar A, McCracken JP, *et al.* Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation. Circ Res 2016; 119:1204–1214.
9. Miller MR, Shaw CA, Langrish JP. From particles to patients: oxidative stress and the cardiovascular effects of air pollution. Future Cardiol 2012; 8:577–602.
10. Mills NL, Törnqvist H, Robinson SD, *et al.* Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. Circulation 2005; 112:3930–3936.
11. Oberdörster G, Sharp Z, Atudorei V, *et al.* Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. J Toxicol Environ Health A 2002; 65:1531–1543.
12. Pieters N, Plusquin M, Cox B, *et al.* An epidemiological appraisal of the association between heart rate variability and particulate air pollution: a meta-analysis. Heart 2012; 98:1127–1135.
13. Liang X, Liang L, Fan Y. Two-sample mendelian randomization analysis investigates ambient fine particulate matter's impact on cardiovascular disease development. Sci Rep 2023; 13:20129.
14. Cao Y, Feng Y, Xia N, *et al.* Causal associations of particulate matter 2.5 and cardiovascular disease: a two-sample mendelian randomization study. PLoS One 2024; 19:e0301823.
15. Jin T, Di Q, Réquia WJ, *et al.* Associations between long-term air pollution exposure and the incidence of cardiovascular diseases among American older adults. Environ Int 2022; 170:107594.
16. ■ Poulsen AH, Sørensen M, Hvidtfeldt UA, *et al.* 'Source-specific' air pollution and risk of stroke in Denmark. Int J Epidemiol 2023; 52:727–737.
This Danish historical cohort study of 2 million people aged 50 years and older reported clear relationships between long-term exposure to $PM_{2.5}$, UFP, and NO_2 and stroke incidence.
17. Wang K, Yuan Y, Wang Q, *et al.* Incident risk and burden of cardiovascular diseases attributable to long-term NO2 exposure in Chinese adults. Environ Int 2023; 178:108060.
18. Zhu L, Fang J, Yao Y, *et al.* Long-term ambient ozone exposure and incident cardiovascular diseases: national cohort evidence in China. J Hazard Mater 2024; 471:134158.
19. Wright N, Newell K, Chan KH, *et al.* Long-term ambient air pollution exposure and cardio-respiratory disease in China: findings from a prospective cohort study. Environ Health 2023; 22:30.
20. Yang L, Zhu Y, Zhao B, *et al.* Long-term cardiometabolic effects of ambient ozone pollution in a large Chinese population. Ecotoxicol Environ Saf 2023; 261:115115.
21. Liang S, Chen Y, Sun X, *et al.* Long-term exposure to ambient ozone and cardiovascular diseases: evidence from two national cohort studies in China. J Adv Res 2023; 62:165–173.
22. Riggs DW, Baumgartner KB, Baumgartner R, *et al.* Long-term exposure to air pollution and risk of stroke by ecoregions: the REGARDS study. Environ Pollut 2024; 345:123367.
23. Nethery RC, Josey K, Gandhi P, *et al.* Air pollution and cardiovascular and thromboembolic events in older adults with high-risk conditions. Am J Epidemiol 2023; 192:1358–1370.
24. ■■ Chen S, Lin X, Du Z, *et al.* Potential causal links between long-term ambient particulate matter exposure and cerebrovascular mortality: insights from a large cohort in southern China. Environ Pollut 2023; 328:121336.
This Chinese population-based prospective cohort study, including 5 million participants, investigated the associations between long-term exposure to several particulate matter fractions and stroke mortality using spline terms. Thus, it reported nonlinear dose–response functions for $PM_{2.5}$ and PM_{10}.
25. Kulick ER, Eliot MN, Szpiro AA, *et al.* Long-term exposure to ambient particulate matter and stroke etiology: results from the Women's Health Initiative. Environ Res 2023; 224:115519.
26. ■■ Cai M, Lin X, Wang X, *et al.* Long-term exposure to ambient fine particulate matter chemical composition and in-hospital case fatality among patients with stroke in China. Lancet Reg Health West Pac 2023; 32:100679.
This Chinese historical cohort study, including more than 3 million people hospitalized with stroke, reported clear relationships between long-term exposure to $PM_{2.5}$ and stroke mortality. The association was stronger for ischemic stroke than for hemorrhagic stroke.
27. Chen S, Zhang Y, Wang Y, *et al.* Long-term particulate matter exposure and the risk of neurological hospitalization: evidence from causal inference of a large longitudinal cohort in South China. Chemosphere 2023; 345:140397.
28. Qi Q, Yu F, Nair AA, *et al.* Hidden danger: the long-term effect of ultrafine particles on mortality and its sociodemographic disparities in New York State. J Hazard Mater 2024; 471:134317.
29. Tran PM, Warren JL, Leifheit EC, *et al.* Associations between long-term air pollutant exposure and 30-day all-cause hospital readmissions in US patients with stroke. Stroke 2023; 54:e126–e129.

30. Cai M, Lin X, Wang X, *et al.* Ambient particulate matter pollution of different sizes associated with recurrent stroke hospitalization in China: a cohort study of 1.07 million stroke patients. Sci Total Environ 2023; 856:159104.
31. Zou H, Zhang S, Cai M, *et al.* Ambient air pollution associated with incidence and progression trajectory of cardiometabolic diseases: a multistate analysis of a prospective cohort. Sci Total Environ 2023; 862:160803.
32. Tian F, Cai M, Li H, *et al.* Air pollution associated with incident stroke, poststroke cardiovascular events, and death. Neurology 2022; 99:e2474–e2484.
33. ■■ Toubasi A, Al-Sayegh TN. Short-term exposure to air pollution and ischemic stroke. Neurology 2023; 101:e1922–e1932.

This meta-analysis studied the relationships between short-term exposure to various air pollutants and the incidence and mortality of ischemic stroke across a corpus of 110 observational studies, thus collecting more than 18 million cases. Many significant associations were reported, although heterogeneity between studies was high.

34. Badida P, Krishnamurthy A, Jayaprakash J. Meta analysis of health effects of ambient air pollution exposure in low- and middle-income countries. Environ Res 2023; 216:114604.
35. Gaines B, Kloog I, Zucker I, *et al.* Particulate air pollution exposure and stroke among adults in Israel. Int J Environ Res Public Health 2023; 20:1482.
36. Du P, Du H, Lu K, *et al.* Traffic-related PM2.5 and its specific constituents on circulatory mortality: a nationwide modelling study in China. Environ Int 2022; 170:107652.
37. Liu T, Jiang Y, Hu J, *et al.* Joint associations of short-term exposure to ambient air pollutants with hospital admission of ischemic stroke. Epidemiology 2023; 34:282–292.
38. Jiang Y, Huang J, Li G, *et al.* Ozone pollution and hospital admissions for cardiovascular events. Eur Heart J 2023; 44:1622–1632.
39. Huang K, Jia J, Liang F, *et al.* Fine particulate matter exposure, genetic susceptibility, and the risk of incident stroke: a prospective cohort study. Stroke 2024; 55:92–100.
40. Ma Y, Zhang J, Li D, *et al.* Genetic susceptibility modifies relationships between air pollutants and stroke risk: a large cohort study. Stroke 2024; 55:113–121.
41. Poulsen AH, Sørensen M, Hvidtfeldt UA, *et al.* Air pollution and stroke; effect modification by sociodemographic and environmental factors. A cohort study from Denmark. Int J Hyg Environ Health 2023; 251:114165.
42. Jiang D, Wang L, Han X, *et al.* Short-term effects of ambient oxidation, and its interaction with fine particles on first-ever stroke: a national case-crossover study in China. Sci Total Environ 2024; 907:168017.
43. Lv X, Shi W, Yuan K, *et al.* Hourly air pollution exposure and emergency hospital admissions for stroke: a multicenter case-crossover study. Stroke 2023; 54:3038–3045.
44. Poulsen AH, Sørensen M, Hvidtfeldt UA, *et al.* Concomitant exposure to air pollution, green space, and noise and risk of stroke: a cohort study from Denmark. Lancet Reg Health Eur 2023; 31:100655.
45. Lu H, Wang R, Li J, *et al.* Long-term exposure to the components of fine particulate matters and disability after stroke: findings from the China National Stroke Screening Surveys. J Hazard Mater 2023; 460:132244.
46. ■■ Haddad P, Kutlar Joss M, Weuve J, *et al.* Long-term exposure to traffic-related air pollution and stroke: a systematic review and meta-analysis. Int J Hyg Environ Health 2023; 247:114079.

This meta-analysis, including 19 independent observational studies, studied the relationships between long-term exposure to various chemical components of TRAP and stroke incidence. Thus, it reported low to moderate evidence of an association of TRAP with stroke.

47. Liu J, Wang M, Zhao Y, *et al.* Associations between short-term exposure to ambient PM2.5 and incident cases of cerebrovascular disease in Yantai, China. Environ Sci Pollut Res 2023; 30:21970–21977.
48. Robertson S, Miller MR. Ambient air pollution and thrombosis. Part Fibre Toxicol 2018; 15:1.
49. Lasek-Bal A, Rybicki W, Student S, *et al.* Direct exposure to outdoor air pollution worsens the functional status of stroke patients treated with mechanical thrombectomy. J Clin Med 2024; 13:746.
50. de Bont J, Pickford R, Aström C, *et al.* Mixtures of long-term exposure to ambient air pollution, built environment and temperature and stroke incidence across Europe. Environ Int 2023; 179:108136.
51. Jia X, Zhang B, Yu Y, *et al.* Greenness mitigate cause-specific mortality associated with air pollutants in ischemic and hemorrhagic stroke patients: an ecological health cohort study. Environ Res 2024; 251:118512.
52. Liu C, Yu Y, Liu C, *et al.* Effect of neighbourhood greenness on the association between air pollution and risk of stroke first onset: a case-crossover study in Shandong province, China. Int J Hyg Environ Health 2023; 254:114262.
53. ■ Liu C, Zhang B, Liu C, *et al.* Association of ambient ozone exposure and greenness exposure with hemorrhagic stroke mortality at different times: a cohort study in Shandong Province, China. Ecotoxicol Environ Saf 2024; 278:116356.

This prospective cohort study of about 45 000 hemorrhagic stroke patients showed that greenness exposure could mitigate the adverse effects of warm-season ozone on hemorrhagic stroke mortality.

54. He J, Harkins C, O'Dell K, *et al.* COVID-19 perturbation on US air quality and human health impact assessment. PNAS Nexus 2024; 3:pgad483.
55. Hao X, Li J, Wang H, *et al.* Long-term health impact of PM2.5 under whole-year COVID-19 lockdown in China. Environ Pollut 2021; 290:118118.
56. Bouscasse H, Gabet S, Kerneis G, *et al.* Designing local air pollution policies focusing on mobility and heating to avoid a targeted number of pollution-related deaths: forward and backward approaches combining air pollution modeling, health impact assessment and cost-benefit analysis. Environ Int 2022; 159:107030.
57. Rajagopalan S, Brauer M, Bhatnagar A, *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.