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Air pollution and stroke

A new modifiable risk factor is in the air

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Abstract

Evidence from epidemiological studies has demonstrated that outdoor air pollution is now a well-known major problem of public health, mainly in low and middle income countries. Contrasting with myocardial infarction, there are few data on the association of air pollution and stroke.

Methods : We propose a narrative literature review of the effects and the underlying biological mechanisms of short- and long-term exposure to air pollutants on stroke risk and mortality, using the following key-words : stroke, cerebrovascular events, ischemic and haemorrhagic stroke, transient ischaemic attack, mortality, air pollution and air pollutants.

Results : Twenty one papers were selected. Air pollution, of which whose small particulate matter are the most toxic, contributes to about one-third of the global burden of stroke. We can identify vulnerable patients with classical neuro-vascular risk factors or a prior history of stroke or transient ischemic attack or persons living in low - income countries. Biological mechanisms of this new morbid association are discussed.

Conclusion : Air pollution should be recognized as a silent killer inducing stroke whose mortality rates remain elevated by its role as a new modifiable neuro-vascular risk factor, needing public health policies.

Key-words : Stroke, ischaemic and hemorrhagic stroke, , mortality, air pollution and air pollutants

Introduction

Exposure to air pollution is now well recognized by scientists, media and the population as a major public health issue [1-6].

It ranks within the top five risk factors for mortality in emerging countries [1-6]. Forty per cent of all deaths could be induced by outdoor air pollution [4,5] and 89 % of death attributed to ambient air pollution are observed in low and medium income countries as a result of rapid industrialization [7]. Robust data confirm the high risk of morbidity and mortality due to particulate matter measuring less than 2.5 μm (PM_{2.5}) for myocardial infarction and congestive heart failure [4,6,8], lung disease and cancer [1,4,9], diabetes [1] and Nitrogen dioxide (NO₂) for fetal growth in multiple pregnancy [10]. However, the association between air pollution and stroke overall and by subtype, is less clear [6,11-14].

The recent works of the Global Burden of Disease study [15] which evaluated data from 1990 to 2013 in 188 developed and developing countries, demonstrated for the first time that air pollution contributed 30 % to the burden of stroke. This new vascular risk factor can be considered as a potentially modifiable risk factor for stroke that is a major public health problem being the first cause of motor handicap and the second cause of cognitive disorder and death worldwide [5,6,16].

The aim of this review is to clarify biological and clinical features of the association between air pollution and risk and mortality of stroke.

Gaseous pollution is in the air

Air pollution is a complex association of several components produced by different sources [6]. Air pollution includes small particulate matter (PM) and gaseous pollution consisting of ozone (O₃), sulfur dioxide (SO₂), nitrogen dioxide (NO₂) and carbon monoxide (CO). PM_{2.5} represent 70 % of PM measuring less than 10 μm (PM₁₀) [14] and they are able to penetrate into the alveoli of the lungs [14] and the brain cells [17].

Combustion of fossil energies, including motorized road traffic, power plants, industrial and home heating using coal, oil or wood [6], storms and volcanic eruptions, produces PM and SO₂. Vehicle engine exhaust (mainly diesel engines) presents high levels of nanoparticles able to have a greater reactive area for a given mass [6].

NO₂ and CO are produced by fuel combustion and O₃ and is produced by photochemical reactions [18]. Air pollutant levels have spatial and temporal variations related to climate conditions (wind, temperature, sunlights, and rain) and geographic sources.

Air pollution and stroke : epidemiological results

Methods

Several resources were evaluated (PubMed, Web of Sciences, Embase) for publications in all languages available from 1960 through August 2018, using classical keywords : stroke, ischemic and hemorrhagic stroke, cerebrovascular disease, transient ischemic attack, incidence, mortality air pollution, air pollutants (PM_{2.5}, PM₁₀, O₃, NO₂, CO, SO₂). We included all types of study design, evaluating short-term and long-term exposures to air pollutants, acute and chronic effects.

To be eligible for the analysis of cause-effect association and its strength, studies should provide clear definitions of stroke [19] and air pollution [5]. Two investigators (MGr, MGi) evaluated all the eligible publications and the results were shared with all the authors.

Results

Cohort studies, ecological studies, case-crossover studies, daily time-series, observational studies, and big data evaluated effects of acute exposure to air pollutants. Cohorts and case-control studies evaluated chronic exposure [5,11,14] (Table 1).

Cohort studies

Three studies are the most robust. Ljungman and Mittleman [20] demonstrated a strong association between long-term exposure to air pollutants and stroke mortality, from 6 cohorts studies. NO₂ was associated to stroke mortality in 3 of the 6 studies. NO₂ and PM were associated to hospitalization for stroke induced by long-term exposure to air pollutants.

Scheers et al [21], from 15 cohort studies observed that stroke risk was significantly associated to the rise of PM_{2.5} levels. The urban multiethnic cohort of Kulick et al [22] found evidence that within-city variation in residential proximity to major roadway was associated with higher risk of ischemic stroke among non current smoker.

Ecological studies

Nine studies [11,23-28] confirmed the positive association between air pollution and stroke and the decrease of out-door air pollution levels in developed countries contrasting with the increase of out-door air pollution in developing countries [3 et 11].

The recent work of Zhang et al [24] demonstrated that the rise of PM_{2.5} was associated with the rise of both ischemic and hemorrhagic stroke mortality while the rise of PM₁₀ was associated with only ischemic stroke mortality.

Meta-analyses, time-series and case-crossover studies

Henrotin et al [29,30] provided new data showing that the association of ischemic stroke with air pollution significantly rose with the number of vascular risk factors (tobacco consumption, hypertension, hypercholesterolemia, and diabetes).

Yang et al [31] observed from a meta-analysis of 34 studies found another results with the association of the risk of ischemic strokes with several air pollutants (PM, SO₂, CO and NO₂). The meta-analysis of 94 studies by Shah et al [32] observed an increase of hospital admissions and mortality correlated with the rise of the pollutant levels. The meta-analysis including 45 studies by Wang et al [33] observed a significant association between the PM_{2.5} and PM₁₀ levels and stroke mortality.

Guo et al [16] demonstrated in 2017 a borderline significant association between NO₂, short-term exposure modeled as an averaged lag effect and ischemic stroke risk.

Maheswaran et al [34] demonstrated from the population-based case-crossover study in South London an association between an increased NO₂ exposure with a higher risk of cerebrovascular small vessel disease, within the period 1995-2006.

Contrasting with this positive association, Butland et al [35] did not find any association in 2017. It is a time-stratified case-cross over study, using data from the population-based study of South London from 2005 to 2012. They included 1 311 incident ischemic strokes and 256 haemorrhagic strokes. The authors found no evidence for an association between all strokes or ischemic strokes and same day exposure to PM_{2.5}, PM₁₀, O₃, NO₂. For haemorrhagic strokes, they found a negative association with PM₁₀ suggestive of a 14.6 % fall in risk per 10 µg/m³ increase of pollutant. The change in air pollutants distribution may explain the discrepancy.

The time-series of Dong et al [36] demonstrated that short-term exposure to ambient NO₂ was associated with increased ischemic stroke risk. In addition, SO₂ was associated with increased ischemic stroke onset and death. The role of traffic-related air pollution has been well demonstrated with the cross-over study of Vivanco-Hidalgo et al [37].

Some geographical differences may explain these differences [21] or measurement errors [36]. Time-stratified case-cross-over design may lead to reduced statistical power compared with a Poisson regression time-series approach [35].

Big data

Big data on stroke are now available in stroke disease and they deserve a special place. The Global Burden of Disease 2013 study [15,38] evaluated the population-attributable risk of stroke-related disability-adjusted life-years associated with possible risk factors in 188 developed and developing countries from 1990 through 2013. They observed a significant higher proportion of stroke associated with air pollution, close to 30 %, higher in low-income and middle-income (33.7 %) compared with high-income countries (10.2 %). They observed that only the low income and middle income countries, close to a fifth of stroke risk, was associated with solid fuel combustion in 2013 [15], confirming previous studies [11,38]. They used local available data in low and middle-income countries, and reported that ambient and house-hold air pollution was a new modifiable risk factor for stroke and a new public health problem, leading to new worldwide public health policies.

The mechanisms of action of air pollution

Beside the classical role of air pollution on inflammation, formation and rupture of atheroma plaque [39,40], endothelium dysfunction, cardiac arrhythmia, hypertension, activation of thrombosis [41] and vasoconstriction [5], new fundamental mechanisms may explain the association between air pollution and stroke [6].

Translocation of nanoparticles

The fact that nanoparticles fraction of PM pollution are able to cross the alveolar-capillary barrier towards the systemic circulation, they can directly impact on circulation blood cells [42], from a pro-inflammatory activation on endothelial cells [43]. Combustion-derived nanoparticles may regulate the adhesion of several molecules on the endothelial cells [44,45]. These multiple steps may explain the activation of monocytes and macrophages and increase endothelial cell permeability [46,47].

The research on this new mechanism is difficult due to the small size and the number of small particles that will translocate, and to the technical difficulties to detect carbon-based nanoparticles in cells. The robust information is that nanoparticles can translocate quickly from lungs towards the blood circulation and areas of vascular inflammation [48].

Autonomic dysfunction

Inhaled small particles may disturb cardiovascular homeostasis via changes in autonomic function induced by activation of neural sensory receptors of the alveolar surface [6]. Some evidence is provided by reduction of heart rate variability after exposure to PM 2.5 [49], leading to atrial fibrillation [50-52] that is a major risk factor for stroke [5].

Epigenetic mechanisms

Epigenetic mechanisms such as post-translational modifications of DNA, RNA-related processes and histones may play an important role in the regulation of many vascular mechanisms [53], including endothelial stem/progenitor cell functions [54]. The clinical consequence is that blood DNA hypomethylation could be considered as a biomarker of atheroma [6] allowing to identify persons at risk of atheroma [55].

The role of DNA methylation on numerous genes contributing to stroke such as endothelial function (54,56,57), the cytokine-mediated inflammatory reactions and coagulation [56,57], are another new way of research. Flavonoids, methyl nutrients, folic acid, vitamin B12, may act on DNA methylation and may have a protective effect on prevention of stroke [58,59].

We can identify several limitations of epidemiological studies, provided from most of developed countries where indoor exposure is not evaluated, individual exposures may be generalized to a larger area and it may be difficult to identify the cause of death that may be multiple. Earlier studies evaluated the combined effects of acute and chronic exposure to air pollutions.

Screening people at risk

Children and elderly people are more vulnerable to air pollution [13,34,60,61], such as Hispanics with diabetes [62], patients with previous vascular risk factors [29,30], people with recurrent stroke [5], patients with neighborhood deprivation living close to roadways or factories [13,14,32], and people living in low-income countries [15,38] .

Finally, greater exposure to air pollution on previous cardiovascular risk factors is associated with a greater risk of stroke [34].

Possible recommendations

Therefore, epidemiology and experimental evidence demonstrate that there is no safe air pollution and that it is necessary to promote public health policy to eradicate both indoor and outdoor air pollution worldwide [6,15], reducing individual and collective combustion of fossil fuels and developing future urban planning including robust monitoring and protection from air pollution [5].

For medical practice, it is necessary to recall that epidemiological studies have shown that people at risk during an acute air pollution exposures are elderly people, as well as people with previous vascular risk as blood hypertension, diabetes, hypercholesterolemia, atrial fibrillation, sleep apnea or tobacco consumption [5].

Conclusion

A new modifiable risk factor for stroke is in the air. Epidemiological studies have demonstrated the significant association between air pollution and stroke. New fundamental mechanisms described suggest urgent effective strategy.

Disclosure of interest

No Financial or personal conflicts or relationship.

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Table 1. Clinical studies on stroke and air pollutions

	Cohort Studies	Ecological studies	Meta-analyses, time-series and case-crossover studies	Big-data
Clinical studies on stroke and air pollutions	<ul style="list-style-type: none"> • Ljungman and Mittleman [20] = 6 cohort studies (UK, USA, Denmark, Japan) • Scheers et al [21] = 20 cohort studies (USA, Europe, Asia) • Kulick et al [22] = 1 population-based cohort in Northern Manhattan (USA) 	<ul style="list-style-type: none"> • Maheswaran et al [11]. South London (UK) • Hu et al [23]. Florida (USA) • Zang et al [24] in Beijing (China) • Maheswaran and Elliot [25]. England and Wates (UK) • Tsai et al [26] in Kaohsiung (Taiwan) • Wellenius et al [27] in 9 US cities • Iribarren et al [28] in San Francisco (USA) 	<ul style="list-style-type: none"> • Guo et al [16] in Guangzhou (China) • Henrotin et al [29,30] = 1 cross-over study in Dijon (France) • Yang et al [31] = 1 meta-analysis from 34 studies • Shah et al [32] = 1 meta-analysis from 94 studies • Wang et al [33] = 1 meta-analysis of 45 studies • Maheswaran R et al [34] in South London (UK) • Butland et al [35] = 1 cross-over study from a community-based study in London (UK) • Dong et al [36] = 1 time-series in Changzhou (China) • Vivanco-Hidalgo et al [37] = 1 cross-over study from a hospital-based study in Barcelone (Spain) 	<ul style="list-style-type: none"> • Feigin et al [15] in worldwide • Brauer et al [38] in worldwide