Air Pollution and Intracranial Hemorrhage

Mervyn Lim Jun Rui1, Jaclyn Tan1, Benjamin Yong-Qiang Tan2,3, Tseng Tsai Yeo1, Vijay K. Sharma1,3

1Department of Surgery, Division of Neurosurgery, National University Hospital, Singapore, 2Department of Medicine, Division of Neurology, National University Health System, Singapore, 3Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Abstract

Air pollution is a significant contributor to cardiovascular and cerebrovascular diseases, including intracranial hemorrhage (ICH). However, associations between air pollution, various pollutants, and ICH are complex and remain poorly understood. Limited data are available on the relationship between ICH and individual air pollutants. In this review, we present an overview of the current literature about ambient air pollutants that are believed to contribute towards ICH as well as possible underlying mechanisms.

Keywords: Air pollution, cerebrovascular diseases, intracranial hemorrhage, pollutants

INTRODUCTION

Intracranial hemorrhage (ICH) refers to bleeding within the intracranial vault, including intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage.1,2 Primary ICH occurs when there is a spontaneous rupture of small vessels within the brain tissue and is usually associated with hypertension or cerebral amyloid angiopathy, while secondary ICH may occur as a result of vascular malformations or tumours.3 ICH had an absolute number of incident cases of 3,366,175 (95% uncertainty interval 3,199,978 – 3,543,213) people globally in 2013.4 Moreover, it is a leading cause of mortality and morbidity, with a mortality rate of 52.8 per 100,000 people, and has contributed to 1,015.6 disability-adjusted life years (DALYs) per 100,000 people globally in 2013.4 Thus, it is important to identify modifiable risk factors of ICH that may be targeted using public health interventions to reduce the incidence of ICH.5

Air pollution is caused by the presence of harmful substances in the air, which arises due to the interaction between natural and anthropogenic environmental conditions.6 Components of air pollution include the particulate matter of aerodynamic diameter of ≤2.5 µm (PM2.5) and 10 µm (PM10), ozone (O3), nitrogen dioxide (NO2), sulphur dioxide (SO2), and carbon-monoxide (CO).7,8 Having contributed to approximately 6.5 million cases of mortality and 167.3 million DALY in 2015, air pollution is a significant public health problem.9 Existing reports in the international literature suggest that air pollution may be associated with ICH.10-12 However, the evidence remains conflicting, and the association between individual air pollutants and ICH, as well as the mechanisms through which they are linked required further clarification.13 In this review, we present the current understanding of the associations between air pollution and ICH, as well as possible mechanisms underlying this relationship.

Association between air pollution and intracranial hemorrhage

Existing evidence supports the association between ambient air pollutants and the incidence of ICH, as well as outcomes associated with ICH, with the strongest associations reported for PM2.5, PM10, and NO2.10-12,14,15 Evidence from cross-sectional studies highlighted the associations between individual ambient air pollutants and ICH, such as Chien et al.’s15 study (2017) in Taiwan which showed a correlation between NO2 levels and the occurrence of spontaneous intracerebral hemorrhage across all age groups. However, these studies were unable to show the direction of the association, or account for seasonal and temporal trends associated with air pollution.16

The use of population-based time-stratified case-crossover designs to investigate the association of individual air pollutants and risk for ICH allowed for control over individual confounders, as well as to control for seasonal variation and time trends in air pollutant levels.14,17-20 Tsai et al.’s11 (2003) reported a positive association between PM10 and NO2 and intracerebral hemorrhage on warm days, while Yamazaki et al.’s21 (2007) found that the hourly time-lagged concentration of PM with a diameter of less than 7 µm (PM7) was positively associated with mortality due to ICH in patients aged 65 years

Address for correspondence: Dr. Vijay K. Sharma, Yong Loo Lin School of Medicine, National University of Singapore, Level 10, NUHS Tower Block, 1E Kent Ridge Road, 119228, Singapore. E-mail: mdcvks@nus.edu.sg

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and above at the time of death. In addition, Liu et al.\[20\] reported a significant association between NO\textsubscript{2} levels on the current day and hospital admissions for ICH, while Villeneuve et al.\[19\] reported that CO exposure in Edmonton, Canada, was associated with an increased risk of ICH.\[14\] These reports provided strong evidence for the short-term risks of individual ambient air pollutants and the risk of ICH internationally.

Limited evidence exists for the long-term risks of air pollution for ICH. In a nine-year cohort study conducted by Yorifuji et al.,\[21\] which evaluated the relationship between long-term exposure to NO\textsubscript{x} and ICH in Shizuoka, Japan, long-term exposure to NO\textsubscript{2} was associated with increased risk of ICH. More prospective longitudinal studies are needed to further ascertain the causal role air pollution may play in the development of ICH.\[14,9\]

Findings from existing studies also suggest that certain factors may modify the relationship between air pollution and ICH. Subgroup analyses in Chien et al.’s study (2017)\[10\] demonstrated that the association between ICH and air pollutants were different for different age groups: CO was only associated with the incidence of spontaneous ICH in patients over 80 years of age; PM\textsubscript{10} and PM\textsubscript{2.5} were associated with the incidence of spontaneous ICH in patients between 45 and 79 years, while SO\textsubscript{2} was correlated with the incidence of spontaneous ICH in patients aged between 25 and 44 years. Similarly, the association between PM\textsubscript{10} and mortality due to intracranial hemorrhage in Yamazaki et al.’s study\[14\] was also only observed in patients aged at least 65 years at the time of death. In addition, existing studies have shown that the relationship between air pollution and ICH may be modified by factors such as weather and vehicular traffic, which not only affect the concentration of ambient air pollutants but also human behaviour, such as the propensity to spend time outdoors.\[11,19\]

On the contrary, several studies reported no significant associations between air pollution and ICH.\[10,22\] In a longitudinal study that accounted for changes in air pollution levels and weather conditions over time, Hong et al.\[23\] reported no associations between ambient air pollution and ICH mortality in South Korea. Tian et al.\[22\] (2019) also found no significant associations between PM\textsubscript{2.5} and hemorrhagic stroke. Although Tian et al.’s study\[22\] was a time series study that included individual confounders such as age and comorbid conditions in the model, only cities with at least three monitoring stations, health records and PM\textsubscript{2.5} data of more than one year and which used the International Classification of Diseases (ICD) codes were included in the analysis. This may have resulted in misclassification of the exposure and of ICH diagnosis. Overall, the evidence provided by prior time-stratified case crossover and prospective longitudinal studies supported a positive association between air pollution and the risk for ICH, in particular with PM\textsubscript{10}, PM\textsubscript{2.5}, and NO\textsubscript{2}. There is currently little evidence to support associations between ICH and SO\textsubscript{2} or O\textsubscript{3}. In other case-crossover studies, there were no significant associations found between these air pollutants and incidence or hospital admissions for ICH.\[20,24\] Further research may help to clarify whether these individual air pollutants were associated with ICH.

### Possible mechanisms underlying the relationship between air pollution and intracranial hemorrhage

Researchers have proposed several mechanisms that could provide the basis for the relationship between air pollution and ICH: (1) air pollution was associated with hypertension which could lead to remodeling of the intracranial arteries and increasing the risk of ICH, and (2) air pollution may contribute to endothelial injury and vasodilatory effects that could increase the risk of aneurysm rupture. Current systematic reviews and meta-analyses have reported an association between air pollution and hypertension, demonstrating the growing interest in and evidence for this link.\[25-28\] A meta-analysis by Yang et al.\[27\], which included 100 articles, revealed significant associations between short-term exposure to PM\textsubscript{10}, PM\textsubscript{2.5}, SO\textsubscript{2}, and NO\textsubscript{2} and hypertension, as well as long-term exposure to PM\textsubscript{2.5} and hypertension.

Furthermore, experimental evidence in several animal studies supported the hypothesis that increased hypertension mediates the relationship between short-term and long-term exposure to PM\textsubscript{2.5} and ICH.\[29,30\] In an experimental study, Sprague-Dawley rats were exposed either to PM\textsubscript{2.5} or filtered air (FA) for 10 weeks and given an infusion of angiotensin II (AII)—a protein to increase blood pressure after 9 weeks.\[29\] Arterial pressure was significantly higher in the group that was exposed to PM\textsubscript{2.5} compared to the group that was exposed to FA after AII infusion.\[29\] Micro-RNA (mRNA) and protein levels in the aortic tissues suggested that the relative mRNA level of the Rho-associated kinase ROCK1 was significantly higher in the group that was exposed to PM\textsubscript{2.5} compared to the group that was exposed to FA.\[29\] The results of this study suggest that in the short term, PM\textsubscript{2.5} increases blood pressure in rats through O\textsubscript{2}−-mediated upregulation of the Rho-kinase pathway.\[29\] In another experimental study, rats were exposed either to PM\textsubscript{2.5} or FA for 12 weeks, followed by an infusion of AII for a duration of 14 days, together with fasudil—a Rho-kinase antagonist—or placebo treatment.\[30\] Findings suggested that exposure to PM\textsubscript{2.5} increased the risk of AII-induced hypertension.\[30\] Additionally, the fact that this relationship did not exist in the group that received the fasudil treatment is supportive of the ROCK1 pathway as a mediation pathway for this relationship.\[50\] These studies provide strong evidence that air pollutants may increase the risk of hypertension, especially for groups that were already affected by predisposing risk factors. A review on the impact of air pollution on blood pressure observed that pre-existing hypertension made the rats more susceptible to increases in blood pressure when they were exposed to particulate matter.\[31\]

The effects of long-term exposure to PM\textsubscript{2.5} on hypertension have similarly been demonstrated in humans.\[32-34\] Several researchers have further reported that PM\textsubscript{2.5} was associated with the autonomic imbalance and this could result in changes in vascular resistance and reactivity, leading to increased...
blood pressure.\textsuperscript{[35-37]} Chen et al.\textsuperscript{[38]} (2014) conducted a prospective longitudinal study of 35,303 non-hypertensive adults from Ontario, Canada over 7.3 years to examine the relationship between long-term exposure to PM$_{2.5}$ and incident hypertension. Even after taking individual confounders into account, findings suggested that long-term exposure to PM$_{2.5}$ led to an increased risk of incident hypertension.\textsuperscript{[38]} While these studies provide robust evidence that ambient air pollution was associated with hypertension, further studies are required to establish a causal link between ambient air pollution, hypertension, and incident risk of ICH.

Air pollution may also lead to endothelial injury or changes in vasodilation, which may lead to an increased risk of aneurysmal rupture.\textsuperscript{[39,30,39]} Long-term exposure to PM$_{2.5}$ and PM$_{10}$ compared to FA in rats showed that exposure to PM$_{2.5}$ and PM$_{10}$ led to vasodilation via damage to the vascular endothelium.\textsuperscript{[39]} Such changes to the vascular endothelium may contribute to the formation of cerebral aneurysms.\textsuperscript{[40]} In humans, a prospective longitudinal study showed that periods of higher PM$_{2.5}$ levels were associated with increased biomarkers of systemic inflammation and endothelial cell apoptosis.\textsuperscript{[41]} Similarly, endothelial dysfunction was also associated with aneurysm rupture in humans,\textsuperscript{[42]} and may be one potential mechanism through which air pollution leads to increased risk of ICH. Further research is required to investigate the mechanisms by which exposure to ambient air pollution leads to endothelial dysfunction and aneurysmal rupture in humans.

**Conclusion**

Existing research in the international literature provides sufficient evidence on the association between ambient air pollution (in particular PM$_{2.5}$, PM$_{10}$ and NO$_x$) and the risk for ICH. Possible mechanisms to explain this relationship included increased risk for hypertension, as well as endothelial injury leading to increased risk of aneurysm rupture. Population health measures to reduce the effects of air pollution on ICH may be warranted. Further research is required to examine the long-term effects of air pollution on ICH risk, to determine whether there is an association between risk of ICH and SO$_x$, CO, and O$_x$, as well as to further investigate the pathophysiological mechanisms for which air pollution may be associated with increased risk of ICH.

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**Conflicts of interest**

There are no conflicts of interest.

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