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INVITED REVIEW

Outdoor air pollution as a possible modifiable risk factor to reduce mortality in post-stroke population

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Abstract
Outdoor air pollution is a known risk factor for mortality and morbidity. The type of air pollutant most reliably associated with disease is particulate matter (PM), especially finer particulate matter that can reach deeper into the lungs like $PM_{2.5}$ (particulate matter diameter < 2.5 μm). Some subpopulations may be particularly vulnerable to PM pollution. This review focuses on one subgroup, long-term stroke survivors, and the emerging evidence suggesting that survivors of a stroke may be at a higher risk from the deleterious effects of PM pollution. While the mechanisms for mortality are still under debate, long-term stroke survivors may be vulnerable to similar mechanisms that underlie the well-established association between PM pollution and cardiovascular disease. The fact that long-term stroke survivors of ischemic, but not hemorrhagic, strokes appear to be more vulnerable to the risk of death from higher PM pollution may also bolster the connection to ischemic heart disease. Survivors of an ischemic stroke may be more vulnerable to dying from higher concentrations of PM pollution than the general population. The clinical implications of this association suggest that reduced exposure to PM pollution may result in fewer deaths amongst stroke survivors.

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Introduction
The deleterious effects of particulate matter (PM) outdoor air pollution on the general population have been well documented. It is estimated by the World Health Organization that $PM_{2.5}$ pollution (PM with a diameter < 2.5 μm) contributes to the pre-mature deaths of approximately 800,000 people per year, making it the 13th leading cause of mortality worldwide (Anderson et al., 2012). However, there is evidence to suggest that the associated risk of death with higher PM concentrations may be spread unevenly throughout the population; certain subpopulations appear to exhibit an enhanced response to PM that may make them more prone to mortality and morbidity (Bateson and Schwartz, 2004).

The benefits of identifying the populations susceptible to dying when exposed to higher PM concentration levels are multi-fold. Individuals that are known to be part of such subpopulations can take concentrated steps to decrease their risk of death. Health practitioners and public health advisors could target these individuals for educational campaigns on the risks associated with living in areas with higher PM pollution levels. One other potential benefit is that it may direct investigators toward more specific biologic mechanisms for the observed effects of PM pollution on human health (Bateson and Schwartz, 2004). If certain human subpopulations are more highly affected by chronic PM pollution, it is possible that certain shared aspects of these groups may better illustrate the mechanisms of action that causes the chronic exposure to PM pollution to have a toxic effect in the human body.

Groups that may be more susceptible to the effects of PM pollution and are at a higher risk of mortality have begun to be characterized. Morbidity and mortality related to cardiovascular disease have been well documented during short-term PM spikes and long-term chronic PM exposure in a variety of cities across North America, Europe and Asia (Anderson et al., 2012). Evidence is now emerging that people with a history of myocardial infarction or congestive heart failure appear to have higher PM-associated mortality risks than the general population (Bateson and Schwartz, 2004). An increased risk of death with associated higher concentrations of PM has also been documented in people previously diagnosed with diabetes (Bateson and Schwartz, 2004) and respiratory diseases (Anderson et al., 2012).

There is now evidence to suggest that survivors of a stroke may also be vulnerable to the effects of PM pollution (Maheswaran et al., 2010; Wilker et al., 2013; Desikan et al., 2016). Air pollution therefore may represent

a potentially modifiable risk factor that could be targeted to reduce deaths in the stroke survivor population over the long-term. Considering that survival after stroke is particularly poor, even years after stroke (Hardie et al., 2003), and that stroke survivors are well represented in the population at about 500 per every 100,000 people (Donnan et al., 2008), even a small or modest decrease in deaths due to reduced exposure to PM pollution could result in a relatively large number of people spared from a pre-mature death. In this review, I will look at people with a history of a previous stroke and how living in areas with high PM exposure may be contributing to pre-mature death in this population.

Long-term Stroke Survival

Survival after stroke remains particularly poor. About a quarter of stroke patients are dead within a month, about a third by 6 months, and a half by 1 year (Donnan et al., 2008). While the highest risk of dying occurs within the first 30 days of stroke onset, even long-term survivors of stroke continue to exhibit a heightened risk of mortality. The cumulative risk of death 10 years after an initial stroke is 79%, a 2-fold excess risk of mortality as compared to the general population for the same age and sex (Hardie et al., 2003).

The cause of death of long-term stroke survivors appears to differ depending on when it occurred post-stroke. Hardie et al. (2003) found that, of the patients who died within the first 30 days of stroke onset, 80% was due to the direct neurological effects of the stroke. Patients who survived the first 30 days after stroke were at a higher likelihood of dying from a cardiovascular disease; 33% of deaths in patients 1–5 years after stroke were due to a cardiovascular event. This indicates that different strategies may be required to reduce mortality in long-term stroke survivors, particularly strategies that reduce the incidence of cardiovascular disease in this population.

Potential interventions to increase survival after stroke have focused mostly on providing more effective therapies, improving patient care management, and reducing the risk factors for other health conditions (Donnan et al., 2008). Few studies have focused on outdoor air pollution as a potentially modifiable risk factor on survival rates after suffering a stroke.

PM Pollution

PM pollution is made up of small bits of matter that can come from natural sources, such as dust and pollen, as well as man-made sources like soot, smoke and car exhaust. Researchers traditionally subdivide particles based on the size of the particles and where they are deposited in the human airways: particles with a diameter < 10 and < 2.5 μm (PM_{10} and $PM_{2.5}$, respectively).

PM pollution continues to be to the fraction of air pollution that is most reliably associated with human disease, and a dose-response relationship between PM exposure and adverse health effects has been identified. PM_{10} particles have a relatively small suspension half-life and, though they are largely filtered out by the nose and upper airway, PM_{10} pollution has been associated with adverse health conditions. $PM_{2.5}$ particles are thought to reach deeper into the lungs, thereby leading to greater inflammation and potentially resulting in more deleterious health outcomes (Anderson et al., 2012).

Stroke Survivors and PM Pollution

There are a number of studies that link short term spikes in PM pollution with dying of a stroke (Hong et al., 2002) and link long-term chronic exposure of PM pollution with the onset of stroke (Crichton et al., 2016). However, there is a paucity in the literature of long-term studies examining the associations of mortality in a stroke survivor population and the chronic exposure of PM pollution. In a South London population, the risk of death up to five years after stroke increased by 28% for each interquartile range increase of $PM_{2.5}$ (Desikan et al., 2016). Using the same register, the South London Stroke Register, it was found that a 10-$\mu g/m^3$ increase in PM_{10} was associated with a 52% increase in risk of death for long-term stroke survivors (Maheswaran et al., 2010). Wilker et al. (2013) used proximity to high-traffic roadways as a proxy for air pollution in the greater Boston area. People who had suffered an ischemic stroke and were living < 100 m from high-traffic roadways had a 20% higher mortality rate as compared to post-stroke patients living < 400 m.

One particular trend that has emerged from these studies is that individuals who suffer an ischemic, but not a hemorrhagic, stroke may be linked to a risk of death when exposed to PM pollution. Distinguishing between an ischemic subtype (a stroke due to an insufficient blood flow to the brain) and a hemorrhagic subtype (a stroke due to a bleed in the brain) is considered one of the most important and urgent clinical steps in stroke management (Donnan et al., 2008). Ischemic but not hemorrhagic strokes have been associated with greater PM pollution-associated risks for stroke incidence (Crichton et al., 2016) and acute stroke mortality (Hong et al., 2002). Mortality risks associated with PM pollution for long-term ischemic stroke survivors appear to mirror these results (Wilker et al., 2013; Desikan et al., 2016). In fact, certain long-term survivors of ischemic subtypes may be particularly vulnerable to the deleterious effects of PM

pollution. The ischemic subtypes of lacunar infarcts and total anterior circulation infarctshave been shown to have a 78–200% increased risk of death for every interquartile range increase in $PM_{2.5}$ concentration levels (Desikan et al., 2016).

One possible explanation for the increased mortality risk in ischemic stroke patients living in high PM-polluted areas is that post-stroke patients are more prone to cardiovascular events, which in turn are associated with PM pollution. Like cardiovascular disease, PM pollution is thought to contribute to stroke by the mechanisms of systemic inflammation, direct and indirect coagulation activation, and direct translocation into systemic circulation (Anderson et al., 2012). It is interesting to note that ischemic but not hemorrhagic strokes have been implicated with PM-associated mortality (Desikan et al., 2016), and that ischemic events in stroke and cardiovascular diseases share many risk factors, features, and pathophysiological mechanisms (Anderson et al., 2012). Considering that long-term stroke survivors also have a higher likelihood of dying of cardiovascular disease (Hardie et al., 2003), it is possible that the mechanisms underlying the association of cardiovascular disease and PM pollution may also play a role in the PM-associated mortality risks for long-term survivors of ischemic strokes.

Conclusion

PM air pollution has been well associated with the development of morbidity and mortality in humans across the world. While the increased daily risks from PM exposure are modest for any individual, the costs of the worldwide healthcare burden are staggering when applied to populations. Because the effects of air pollution on illness occur at a population level, many clinicians fail to appreciate the relationship between air pollution and human health (Anderson et al., 2012).

Therefore, it may be important to identify the subpopulations that are particularly vulnerable to the health effects associated with PM exposure. There is now evidence to suggest that long-term survivors of stroke, especially ischemic stroke, may be classified as one of these groups. The mechanisms underlying these vulnerabilities for ischemic stroke survivors are uncertain at present, but they may be related to ischemic cardiovascular events, which in turn are also known to be linked to mortality and morbidity with higher levels of PM exposure. Considering that stroke causes 9% of all deaths and is the second most common cause of death around the world (Donnan et al., 2008), the relationship between PM pollution and long-term stroke mortality may have wide implications.

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