

## Impact of Air Pollution and Seasonal Haze on Neurological Conditions

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### Abstract

**Introduction:** Air pollution is a global problem and seasonal haze from forest clearing and peat land burning in Indonesia is an annual phenomenon in Southeast Asia. As neurological disorders comprise 6.3% of the burden of disease globally, we reviewed evidence of the association between common neurological conditions and air pollution exposure, and summarised existing data on the impact of the haze phenomenon in Southeast Asia. **Materials and Methods:** A PubMed search for relevant studies on air pollution, Alzheimer's disease (AD), dementia, epilepsy, haze, headache, migraine, stroke, Parkinson's disease (PD) and neuromuscular conditions was performed. There were 52 articles which were relevant and were reviewed. **Results:** There were associations between short-term air pollution exposure with AD, epilepsy, ischaemic stroke and migraine. Long-term air pollution exposure was associated with AD, amyotrophic lateral sclerosis, dementia and ischaemic stroke. Evidence on the link between air pollution and PD was inconsistent. Currently, there is no specific data on the effects haze has on neurological conditions in Southeast Asia. **Conclusion:** Air pollution is associated with increased risk of certain common neurological disorders. More specific studies are needed to investigate the impact of seasonal haze on neurological conditions in Southeast Asia.

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**Key words:** Alzheimer's disease, Epilepsy, Migraine, Parkinson's disease, Stroke

### Introduction

Worldwide, air pollution is a serious problem and it has harmful effects on human health. It is reported that >3 million deaths are attributed to air pollution every year.<sup>1</sup> An aggregate of gases—such as carbon monoxide (CO), nitrogen dioxide (NO<sub>2</sub>), nitrogen oxides (NO<sub>x</sub>), ozone (O<sub>3</sub>) and sulfur dioxide (SO<sub>2</sub>)—particulate matter (PM), metals and organic compounds are commonly discharged through industrial and vehicle combustions, especially in developed and rapidly developing countries.<sup>2</sup>

Air pollution is strongly linked to increased morbidity and mortality from cardiopulmonary diseases. Short-term exposure to increased ambient air pollutants leads to

higher rates of acute hospitalisations for cardiovascular and respiratory diseases such as arrhythmias, asthma, heart failure, ischaemic heart disease and lung cancer.<sup>3</sup> Long-term exposure to elevated levels of gases and PM—such as PM <2.5 micrometres (PM<sub>2.5</sub>), PM <10 micrometres (PM<sub>10</sub>) and PM 2.5–10 micrometres (PM<sub>10–2.5</sub>)—has also been implicated in reduction of overall life expectancy among populations at risk.<sup>3,4</sup> At first, these deleterious effects were mainly reported in studies in Western populations, but growing evidence in major Asian cities suggests that air pollution is also a significant public health burden and some effect estimates resembled those reported in North America and Western Europe.<sup>5</sup>

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Environmental sources of air pollution—such as forest fires—are also cause for concern, particularly in Southeast Asia. Seasonal haze from peat land burning and forest clearing for agricultural use in Indonesia has affected her neighbouring countries for >40 years.<sup>6–8</sup> Acrid smoke, dust and PM<sub>2.5</sub> form haze which is transported by inter-monsoon winds towards Brunei, Malaysia, Singapore, southern Thailand and as far away as northern Laos and the southern regions of the Philippines.<sup>9,10</sup> Haze crises—such as those in 1997, 2006, 2013 and 2015—have damaging effects on food and water quality, tourism, transport, urban and rural livelihoods and overall human productivity.<sup>6,11</sup>

Haze episodes have a negative impact on human health. In 1997, there was a 30% increase in outpatient visits in Singapore for haze-related conditions such as asthma, rhinitis and upper respiratory tract illnesses.<sup>12</sup> Hazy days were also associated with an increase of 31% in hospital admissions, and adverse health outcomes were attributed to increased particle deposition in the respiratory system.<sup>13,14</sup> Exposure to haze from wildfires in the United States has caused increased emergency department (ED) visits for asthma, bronchitis, chronic obstructive pulmonary disease, heart failure and pneumonia.<sup>15</sup>

Neurological disorders account for 6.3% of the burden of disease and 12% of all deaths globally.<sup>16</sup> Among non-communicable neurological disorders, the World Health Organization lists cerebrovascular disease (55%) as the top cause of disease burden followed by Alzheimer's disease (AD) and other dementias (12%), epilepsy (7.9%), migraine (8.3%) and Parkinson's disease (PD, 1.8%).<sup>16</sup> Today, prevalence estimates for stroke from around the world range from 500–1000 per 100,000 population and approximately 24.3 million people have dementia.<sup>16</sup> Global migraine prevalence is 11.6%.<sup>17</sup> For epilepsy, the overall prevalence ranges from 2.7–41 per 1000 population.<sup>16</sup> The crude prevalence of PD ranges from 100–200 per 100,000 individuals.<sup>18</sup> The global incidence of neuromuscular diseases is varied and ranges from 0.05–9 per 100,000 person years.<sup>19</sup>

Although there is a preponderance of research into the effects of air pollution on cardiovascular and respiratory health, the literature on the effects of air pollution on neurological disorders is far more limited and has only accelerated in the last 15 years. It is postulated that long-term air pollution exposure may have a role in the inflammation cascade that eventually leads to brain degeneration. Pathologic findings such as brain inflammation and accumulation of amyloid beta-42 peptides—similar to that seen in degenerative diseases—have been observed in the frontal cortex, hippocampus and olfactory bulb of urban residents who were exposed to severe air pollution.<sup>20</sup>

Although a recent review<sup>21</sup> of the clinical effects of air pollution on the central nervous system examined carotid

artery disease, cognitive dysfunction, stroke and white matter injury, it did not discuss common neurological conditions such as epilepsy and migraine. To the best of our knowledge, there is no published review of data on the effect haze has on neurological disorders in Southeast Asia.

In this review, we examined evidence on the association between air pollution exposure and common neurological conditions, namely dementia, epilepsy, headache, migraine, PD, stroke and neuromuscular disorders. Additionally, we explored and summarised existing data on the impact of haze on neurological diseases in Southeast Asia.

## Materials and Methods

A PubMed search for relevant articles published to September 2017 was performed using these search terms: AD, air pollution, dementia, epilepsy, haze, headache, migraine, myopathy, neuromuscular disorders, neuropathy, PD, Southeast Asia and stroke.

Additionally, we searched bibliographies of included articles to identify pertinent studies. The search yielded 699 articles. Animal studies were excluded. As stroke was the most extensively investigated neurological condition, we included only meta-analyses, reviews and studies on stroke in relation to air pollution published since 2015. A limitation of this review was the lack of hand searching and review of databases.

After screening the abstracts, titles and article texts, 52 relevant articles were identified for this review. A summary of studies that investigated the association between air pollution exposure and common neurological conditions—including hazard ratio (HR), odds ratio (OR), relative risk (RR), percentage increase in risk and 95% confidence interval (CI)—is shown in Table 1.

## Stroke

The impact of air pollution exposure on stroke was studied extensively. Evidence for increased risk of ischaemic stroke after short- and long-term exposure to higher levels of combustion-related pollution was consistent, and the association with haemorrhagic stroke was moderately consistent.<sup>22</sup>

Evidence for short-term impact of air pollution on stroke risk is substantive. A meta-analysis of 34 studies found positive associations of CO (2.96%; 95% CI, 0.70–5.27), NO<sub>2</sub> (2.24%; 95% CI, 1.16–3.33), O<sub>3</sub> (2.45%; 95% CI, 0.35–4.60), PM<sub>2.5</sub> (1.20%; 95% CI, 0.22–2.18), PM<sub>10</sub> (0.58%; 95% CI, 0.31–0.86) and SO<sub>2</sub> (1.53%; 95% CI, 0.66–2.41) with stroke admissions and stroke mortality that were more significant on the day of exposure; the results were also stronger for ischaemic stroke than haemorrhagic stroke.<sup>23</sup>

Table 1. Summary of Studies on Air Pollution Exposure and Neurological Conditions

Condition/Study	Locale	Study Design	Outcome	Exposure	% Increase in Risk, HR, OR or RR (95% CI)
<b>Stroke</b>					
Shah et al <sup>*</sup>	–	Meta-analysis	Stroke incidence and mortality	Short-term	Per 1 ppm increase in CO: RR, 1.015 (1.004 – 1.026)
					Per 10 ppb increase in SO <sub>2</sub> : RR, 1.019 (1.011 – 1.027)
					Per 10 ppb increase in NO <sub>2</sub> : RR, 1.014 (1.009 – 1.019)
					Per 10 µg/m <sup>3</sup> increase in PM <sub>2.5</sub> : RR, 1.011 (1.011 – 1.012)
					Per 10 µg/m <sup>3</sup> increase in PM <sub>10</sub> : RR, 1.003 (1.002 – 1.004)
Yang et al <sup>†</sup>	–	Meta-analysis	Stroke admissions and mortality	Short-term	Per 10 µg/m <sup>3</sup> increase in PM <sub>2.5</sub> : 1.20% (0.22 – 2.18%)
					Per 10 µg/m <sup>3</sup> increase in PM <sub>10</sub> : 0.58% (0.31 – 0.86%)
					Per 10 ppb increase in SO <sub>2</sub> : 1.53% (0.66 – 2.41%)
					Per 10 ppb increase in NO <sub>2</sub> : 2.24% (1.16 – 3.33%)
					Per 10 ppb increase in O <sub>3</sub> : 2.45% (0.35 – 4.60%)
					Per 1 ppm increase in CO: 2.96% (0.70 – 5.27%)
Matsuo et al <sup>‡</sup>	Japan	Case-crossover	Ischaemic stroke	Short-term	Per 10 µg/m <sup>3</sup> increase in PM <sub>2.5</sub> : OR, 1.03 (1.00 – 1.06)
Liu et al <sup>§</sup>	26 cities in Mainland China	Case-crossover	Ischaemic stroke	Short-term	Per IQR increase (47.5 µg/m <sup>3</sup> ) in PM <sub>2.5</sub> : 1.0% (0.7 – 1.4%)
					Per IQR increase (76.9 µg/m <sup>3</sup> ) in PM <sub>10</sub> : 0.8% (0.3 – 1.3%)
					Haemorrhagic stroke
Cited by Ljungman et al <sup>l</sup>				Long-term	
Atkinson et al	England	Cohort	Any stroke admission		Per 3.0 µg/m <sup>3</sup> increase in PM <sub>10</sub> : RR, 0.98 (0.95 – 1.01)
Johnson et al	Edmonton, Canada	Ecological	Any stroke admission		Highest (16.7 – 20.3 ppb) to lowest (10.1 – 14.0 ppb) NO <sub>2</sub> quintile: RR, 1.29 (1.16 – 1.43)
Ueda et al	Japan	Cohort	Any stroke mortality		Per 10 µg/m <sup>3</sup> annual mean in PM <sub>10</sub> : RR, 0.86 (0.74 – 1.01)
Miller et al	36 cities in USA	Cohort	Any stroke mortality		Per 10 µg/m <sup>3</sup> annual mean in PM <sub>10</sub> : RR, 1.83 (1.11 – 3.00)

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; CI: Confidence interval; CO: Carbon monoxide; ED: Emergency department; HR: Hazard ratio; IQR: Interquartile range; NO<sub>2</sub>: Nitrogen dioxide; NO<sub>x</sub>: Nitrogen oxides; O<sub>3</sub>: Ozone; OR: Odds ratio; PD: Parkinson's disease; PM<sub>2.5</sub>: Particulate matter ≤2.5 micrometres; PM<sub>10</sub>: Particulate matter ≤10 micrometres; PM<sub>10-2.5</sub>: Particulate matter 2.5–10 micrometres; RR: Relative risk; SO<sub>2</sub>: Sulfur dioxide; USA: United States of America

<sup>\*</sup>Shah ASV, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ* 2015;350:h1295. Erratum in: *BMJ* 2016;354:i4851.

<sup>†</sup>Yang WS, Wang X, Deng Q, Fan WY, Wang WY. An evidence-based appraisal of global association between air pollution and risk of stroke. *Int J Cardiol* 2014;175:307–13.

<sup>‡</sup>Matsuo R, Michikawa T, Ueda K, Ago T, Nitta H, Kitazono T, et al. Short-term exposure to fine particulate matter and risk of ischemic stroke. *Stroke* 2016;47:3032–4.

<sup>§</sup>Liu H, Tian Y, Xu Y, Zhang J. Ambient particulate matter concentrations and hospitalization for stroke in 26 Chinese cities: a case-crossover study. *Stroke* 2017;48:2052–9.

<sup>l</sup>Ljungman PL, Mittleman MA. Ambient air pollution and stroke. *Stroke* 2014;45:3734–41.

Table 1. Summary of Studies on Air Pollution Exposure and Neurological Conditions (Cont'd)

Condition/Study	Locale	Study Design	Outcome	Exposure	% Increase in Risk, HR, OR or RR (95% CI)
Maheswaran et al <sup>†</sup>	South London	Case-crossover	Large artery atherosclerosis	Short-term	Per IQR increase in PM <sub>10</sub> concentration: OR, 1.28 (1.07 – 1.53)
					Per IQR increase in NO <sub>2</sub> concentration: OR, 1.35 (1.02 – 1.80)
			Small vessel disease		Per IQR increase in PM <sub>10</sub> concentration: OR, 1.21 (1.07 – 1.36)
					Per IQR increase in NO <sub>2</sub> concentration: OR, 1.51 (1.12 – 2.02)
Cardioembolic stroke	Per IQR increase in SO <sub>2</sub> concentration: OR, 1.30 (1.12 – 1.51)				
	Per IQR increase in O <sub>3</sub> concentration: OR, 1.36 (1.13 – 1.63)				
Chung et al <sup>‡</sup>	South Korea	Cohort	Cardioembolic stroke	Short-term	Per 10 µg/m <sup>3</sup> increase in PM <sub>10</sub> : OR, 1.06 (1.01 – 1.10)
					Per 10 ppb increase in SO <sub>2</sub> : OR, 1.63 (1.11 – 2.40)
					Per 10 ppb increase in NO <sub>2</sub> : OR, 1.12 (1.06 – 1.18)
Headache and migraine					
Szyszkowicz et al <sup>**</sup>	Edmonton, Canada	Time series (women)	ED visit (migraine)	Short-term	Per IQR increase in PM <sub>2.5</sub> levels in cold season: 3.3% (0.6 – 6.0%)
					Per IQR increase in SO <sub>2</sub> levels in warm season: 2.5% (0.3 – 4.6%)
Szyszkowicz et al <sup>††</sup>	Canada	Time series (women)	ED visit (migraine)	Short-term	Per mean change of 4.6 ppb in SO <sub>2</sub> level in warm season: 4.0% (0.8 – 7.3%)
					Per mean change of 8.3 µg/m <sup>3</sup> in PM <sub>2.5</sub> level in cold season: 4.6% (1.2 – 8.1%)
Chang et al <sup>**</sup>	Taiwan	Case-crossover	Clinic visit (headache)	Short-term	Per IQR increase in PM <sub>2.5</sub> levels on warm days: 12% (10 – 14%)
Chen et al <sup>§§</sup>	Taiwan	Case-crossover	Clinic visit (migraine)	Short-term	Per IQR increase in PM <sub>2.5</sub> levels on warm days: 13% (8 – 19%)
Chiu et al <sup>  </sup>	Taiwan	Case-crossover	Clinic visit (migraine)	Short-term	Positive associations with CO, NO <sub>2</sub> , O <sub>3</sub> , PM <sub>10</sub> and SO <sub>2</sub> on warm days
					Positive associations with NO <sub>2</sub> , O <sub>3</sub> and PM <sub>10</sub> on cool days

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; CI: Confidence interval; CO: Carbon monoxide; ED: Emergency department; HR: Hazard ratio; IQR: Interquartile range; NO<sub>2</sub>: Nitrogen dioxide; NO<sub>x</sub>: Nitrogen oxides; O<sub>3</sub>: Ozone; OR: Odds ratio; PD: Parkinson's disease; PM<sub>2.5</sub>: Particulate matter ≤2.5 micrometres; PM<sub>10</sub>: Particulate matter ≤10 micrometres; PM<sub>10-2.5</sub>: Particulate matter 2.5–10 micrometres; RR: Relative risk; SO<sub>2</sub>: Sulfur dioxide; USA: United States of America

<sup>†</sup>Maheswaran R, Pearson T, Beevers SD, Campbell MJ, Wolfe CD. Air pollution and subtypes, severity and vulnerability to ischemic stroke—a population based case-crossover study. *PLoS One* 2016;11:e0158556.

<sup>‡</sup>Chung JW, Bang OY, Ahn K, Park SS, Park TH, Kim JG, et al. Air pollution is associated with ischemic stroke via cardiogenic embolism. *Stroke* 2017;48:17–23.

<sup>\*\*</sup>Szyszkowicz M, Stieb DM, Rowe BH. Air pollution and daily ED visits for migraine and headache in Edmonton, Canada. *Am J Emerg Med* 2009;27:391–6.

<sup>††</sup>Szyszkowicz M, Kaplan GG, Grafstein E, Rowe BH. Emergency department visits for migraine and headache: a multi-city study. *Int J Occup Med Environ Health* 2009;22:235–42.

<sup>\*\*</sup>Chang CC, Chiu HF, Yang CY. Fine particulate air pollution and outpatient department visits for headache in Taipei, Taiwan. *J Toxicol Environ Health A* 2015;78:506–15.

<sup>§§</sup>Chen CC, Tsai SS, Yang CY. Association between fine particulate air pollution and daily clinic visits for migraine in a subtropical city: Taipei, Taiwan. *Int J Environ Res Public Health* 2015;12:4697–708.

<sup>||</sup>Chiu HF, Yang CY. Air pollution and daily clinic visits for migraine in a subtropical city: Taipei, Taiwan. *J Toxicol Environ Health A* 2015;78:549–58.

Table 1. Summary of Studies on Air Pollution Exposure and Neurological Conditions (Cont'd)

Condition/Study	Locale	Study Design	Outcome	Exposure	% Increase in Risk, HR, OR or RR (95% CI)
Dales et al <sup>¶¶</sup>	Chile	Time series	Admission (migraine)	Short-term	Per IQR increase in O <sub>3</sub> levels: RR, 1.17 (1.08 – 1.26)
			Admission (headache of specified cause)		Per IQR increase in NO <sub>2</sub> levels: RR, 1.13 (0.982 – 1.29)
Vodanos et al <sup>##</sup>	Israel	Retrospective cohort	Headache	Short-term	Per 10-unit increase in NO <sub>2</sub> levels: RR, 1.11 (1.057 – 1.167)
Mukamal et al <sup>***</sup>	Boston, USA	Case-crossover	Headache	Short-term	Per IQR increase in PM <sub>2.5</sub> concentration: OR, 1.005 (0.967 – 1.045)
					Per IQR increase in black carbon concentration: OR, 0.995 (0.955 – 1.036)
					Per IQR increase in NO <sub>2</sub> concentration: OR, 0.983 (0.936 – 1.032)
					Per IQR increase in SO <sub>2</sub> concentration: OR, 0.975 (0.933 – 1.018)
<b>Epilepsy</b>					
Cakmak et al <sup>†††</sup>	Chile	Time series	Hospitalisation		Per IQR increase in CO concentration: RR, 1.098 (1.045 – 1.155)
					Per IQR increase in O <sub>3</sub> concentration: RR, 1.100 (1.025 – 1.181)
					Per IQR increase in SO <sub>2</sub> concentration: RR, 1.085 (1.03 – 1.144)
					Per IQR increase in NO <sub>2</sub> concentration: RR, 1.108 (1.021 – 1.204)
					Per IQR increase in PM <sub>10</sub> concentration: RR, 1.083 (1.038 – 1.13)
					Per IQR increase in PM <sub>2.5</sub> concentration: RR, 1.065 (1.002 – 1.132)
Xu et al <sup>†††</sup>	China	Time series	Outpatient consultation	Short-term	Per 10 µg/m <sup>3</sup> increase in NO <sub>2</sub> concentration: 3.17% (1.41 – 4.93%)
					Per 10 µg/m <sup>3</sup> increase in SO <sub>2</sub> concentration: 3.55% (1.93 – 5.18%)
<b>AD/dementia</b>					
Chang et al <sup>§§§</sup>	Taiwan	Retrospective cohort	Dementia	Long-term	Annual mean NO <sub>2</sub> concentration: HR, 1.54 (1.34 – 1.77)
					Annual mean CO concentration: HR, 1.61 (1.39 – 1.85)

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; CI: Confidence interval; CO: Carbon monoxide; ED: Emergency department; HR: Hazard ratio; IQR: Interquartile range; NO<sub>2</sub>: Nitrogen dioxide; NO<sub>x</sub>: Nitrogen oxides; O<sub>3</sub>: Ozone; OR: Odds ratio; PD: Parkinson's disease; PM<sub>2.5</sub>: Particulate matter ≤2.5 micrometres; PM<sub>10</sub>: Particulate matter ≤10 micrometres; PM<sub>10-2.5</sub>: Particulate matter 2.5–10 micrometres; RR: Relative risk; SO<sub>2</sub>: Sulfur dioxide; USA: United States of America

<sup>¶¶</sup>Dales RE, Cakmak S, Vidal CB. Air pollution and hospitalization for headache in Chile. *Am J Epidemiol* 2009;170:1057–66.

<sup>##</sup>Vodanos A, Novack V, Zlotnik Y, Ifergane G. Ambient air pollution, weather and daily emergency department visits for headache. *Cephalalgia* 2015;35:1085–91.

<sup>\*\*\*</sup>Mukamal KJ, Wellenius GA, Suh HH, Mittleman MA. Weather and air pollution as triggers of severe headaches. *Neurology* 2009;72:922–7.

<sup>†††</sup>Cakmak S, Dales RE, Vidal CB. Air pollution and hospitalization for epilepsy in Chile. *Environ Int* 2010;36:501–5.

<sup>†††</sup>Xu C, Fan YN, Kan HD, Chen RJ, Liu JH, Li YF, et al. The novel relationship between urban air pollution and epilepsy: a time series study. *PLoS One* 2016;11:e0161992.

<sup>§§§</sup>Chang KH, Chang MY, Muo CH, Wu TN, Chen CY, Kao CH. Increased risk of dementia in patients exposed to nitrogen dioxide and carbon monoxide: a population-based retrospective cohort study. *PLoS One* 2014;9:e103078.

Table 1. Summary of Studies on Air Pollution Exposure and Neurological Conditions (Cont'd)

Condition/Study	Locale	Study Design	Outcome	Exposure	% Increase in Risk, HR, OR or RR (95% CI)
Wu et al <sup>III</sup>	Taiwan	Case-control	AD	Long-term	Estimated annual mean exposure to O <sub>3</sub> (in tertiles): OR, 2.00 (1.14 – 3.5)
					Estimated annual mean exposure to PM <sub>10</sub> (in tertiles): OR, 4.17 (2.31 – 7.54)
					Vascular dementia
					Estimated annual mean exposure to O <sub>3</sub> (in tertiles): OR, 2.09 (1.01 – 4.33)
					Estimated annual mean exposure to PM <sub>10</sub> (in tertiles): OR, 3.61 (1.67 – 7.81)
Jung et al <sup>IV</sup>	Taiwan	Cohort	AD	Long-term	Per 4.34 µg/m <sup>3</sup> increase in PM <sub>2.5</sub> levels: 138% (2.21 – 2.56)
					Per 10.91 ppb increase in O <sub>3</sub> levels: 211% (2.92 – 3.33)
Oudin et al <sup>III</sup>	Sweden	Longitudinal study	Dementia	Long-term	Per 10 µg/m <sup>3</sup> increase in NO <sub>x</sub> concentration: HR, 1.43 (0.998 – 2.05)
			AD		Per 10 µg/m <sup>3</sup> increase in NO <sub>x</sub> concentration: HR, 1.38 (0.87 – 2.19)
			Vascular dementia		Per 10 µg/m <sup>3</sup> increase in NO <sub>x</sub> concentration: HR, 1.47 (0.83 – 2.61)
Culqui et al <sup>****</sup>	Madrid, Spain	Ecological time series	ED admissions (AD)	Short-term	Mean daily concentration of NO <sub>2</sub> , O <sub>3</sub> and PM <sub>2.5</sub> : RR, 1.38 (1.15 – 1.65)
PD					
Finkelstein et al <sup>****</sup>	Canada	Cohort	PD	Long-term	Per 10 ng/m <sup>3</sup> increase in ambient manganese: OR, 1.034 (1.00 – 1.07)
Ritz et al <sup>****</sup>	Denmark	Case-control	PD	Long-term	Per IQR increase in modelled NO <sub>2</sub> : 9% (3 – 16.0%); OR, 1.09 (1.03 – 1.16)
Lee et al <sup>§§§§</sup>	Taiwan	Case-control	PD	Long-term	Mean ambient pollutant exposure to NO <sub>x</sub> from 1998 to PD onset: OR, 1.37 (1.23 – 1.52)
					Mean ambient pollutant exposure to CO from 1998 to PD onset: OR, 1.17 (1.07 – 1.27)
Liu et al <sup>III</sup>	USA	Case-control	PD	Long-term	Estimated mean ambient PM <sub>10</sub> concentration in women: OR, 1.65 (1.11 – 2.45)
					Estimated mean ambient PM <sub>2.5</sub> concentration in non-smokers: OR, 1.29 (0.94 – 1.76)

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; CI: Confidence interval; CO: Carbon monoxide; ED: Emergency department; HR: Hazard ratio; IQR: Interquartile range; NO<sub>2</sub>: Nitrogen dioxide; NO<sub>x</sub>: Nitrogen oxides; O<sub>3</sub>: Ozone; OR: Odds ratio; PD: Parkinson's disease; PM<sub>2.5</sub>: Particulate matter ≤2.5 micrometres; PM<sub>10</sub>: Particulate matter ≤10 micrometres; PM<sub>10-2.5</sub>: Particulate matter 2.5–10 micrometres; RR: Relative risk; SO<sub>2</sub>: Sulfur dioxide; USA: United States of America

<sup>III</sup>Wu YC, Lin YC, Yu HL, Chen JH, Chen TF, Sun Y, et al. Association between air pollutants and dementia risk in the elderly. *Alzheimers Dement (Amst)* 2015;1:220–8.

<sup>IV</sup>Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. *J Alzheimers Dis* 2015;44:573–84.

<sup>III</sup>Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. Traffic-related air pollution and dementia incidence in Northern Sweden: a longitudinal study. *Environ Health Perspect* 2016;124:306–12.

<sup>\*\*\*\*</sup>Culqui DR, Linares C, Ortiz C, Carmona R, Díaz J. Association between environmental factors and emergency hospital admissions due to Alzheimer's disease in Madrid. *Sci Total Environ* 2017;592:451–7.

<sup>\*\*\*\*</sup>Finkelstein MM, Jerrett M. A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. *Environ Res* 2007;104:420–32.

<sup>\*\*\*\*</sup>Ritz B, Lee PC, Hansen J, Lassen CF, Ketznel M, Sørensen M, et al. Traffic-related air pollution and Parkinson's disease in Denmark: a case-control study. *Environ Health Perspect* 2016;124:351–6.

<sup>§§§§</sup>Lee PC, Liu LL, Sun Y, Chen YA, Liu CC, Li CY, et al. Traffic-related air pollution increased the risk of Parkinson's disease in Taiwan: a nationwide study. *Environ Int* 2016;96:75–81.

<sup>III</sup>Liu R, Young MT, Chen JC, Kaufman JD, Chen H. Ambient air pollution exposures and risk of Parkinson's disease. *Environ Health Perspect* 2016;124:1759–65.

Table 1. Summary of Studies on Air Pollution Exposure and Neurological Conditions (Cont'd)

Condition/Study	Locale	Study Design	Outcome	Exposure	% Increase in Risk, HR, OR or RR (95% CI)
Palacios et al <sup>****</sup>	USA	Cohort	PD	Long-term	Cumulative mean exposure to PM <sub>10</sub> : RR, 1.03 (0.78 – 1.37)
					Cumulative mean exposure to PM <sub>2.5</sub> : RR, 1.10 (0.83 – 1.45)
					Cumulative mean exposure to PM <sub>10-2.5</sub> : RR, 0.93 (0.69 – 1.26)
Kirrane et al <sup>####</sup>	USA	Cohort	PD	Long-term	Per IQR increase in O <sub>3</sub> concentration: OR, 1.39 (0.98 – 1.98)
					Per IQR increase in PM <sub>2.5</sub> concentration: OR, 1.34 (0.93 – 1.93)
ALS					
Seelen et al <sup>****</sup>	The Netherlands	Case-control	ALS	Long-term	Upper exposure quartile of annual mean PM <sub>2.5</sub> concentration: OR, 1.67 (1.27 – 2.18)
					Upper exposure quartile of annual mean NO <sub>2</sub> concentration: OR, 1.74 (1.32 – 2.30)
					Upper exposure quartile of annual mean NO <sub>x</sub> concentration: OR, 1.38 (1.07 – 1.77)
Malek et al <sup>****</sup>	USA	Case-control	ALS	Long-term	Residential exposure to aromatic solvents in 1999: OR, 4.27 (1.09 – 16.79)
					Residential exposure to aromatic solvents in 2002: OR, 5.03 (1.29 – 19.53)
Myung et al <sup>****</sup>	South Korea	Case-crossover	ALS	Short-term	Upper exposure quartile of hourly mean PM <sub>2.5</sub> concentration: OR, 1.21 (1.08 – 1.35)
					Upper exposure quartile of hourly mean PM <sub>10</sub> concentration: OR, 1.13 (1.02 – 1.25)
					Upper exposure quartile of hourly mean SO <sub>2</sub> concentration: OR, 1.19 (1.01 – 1.41)
					Upper exposure quartile of hourly mean CO concentration: OR, 1.19 (1.03 – 1.36)

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; CI: Confidence interval; CO: Carbon monoxide; ED: Emergency department; HR: Hazard ratio; IQR: Interquartile range; NO<sub>2</sub>: Nitrogen dioxide; NO<sub>x</sub>: Nitrogen oxides; O<sub>3</sub>: Ozone; OR: Odds ratio; PD: Parkinson's disease; PM<sub>2.5</sub>: Particulate matter ≤2.5 micrometres; PM<sub>10</sub>: Particulate matter ≤10 micrometres; PM<sub>10-2.5</sub>: Particulate matter 2.5–10 micrometres; RR: Relative risk; SO<sub>2</sub>: Sulfur dioxide; USA: United States of America

<sup>\*\*\*\*</sup>Palacios N, Fitzgerald KC, Hart JE, Weisskopf MG, Schwarzschild MA, Ascherio A, et al. Particulate matter and risk of Parkinson's disease in a large prospective study of women. *Environ Health* 2014;13:80.

<sup>####</sup>Kirrane EF, Bowman C, Davis JA, Hoppin JA, Blair A, Chen H, et al. Associations of ozone and PM<sub>2.5</sub> concentrations with Parkinson's disease among participants in the Agricultural Health Study. *J Occup Environ Med* 2015;57:509–17.

<sup>\*\*\*\*</sup>Seelen M, Toro Campos RA, Veldink JH, Visser AE, Hoek G, Brunekreef B, et al. Long-term air pollution exposure and amyotrophic lateral sclerosis in Netherlands: a population-based case-control study. *Environ Health Perspect* 2017;125:097023.

<sup>\*\*\*\*</sup>Malek AM, Barchowsky A, Bowser R, Heiman-Patterson T, Lacomis D, Rana S, et al. Exposure to hazardous air pollutants and risk of amyotrophic lateral sclerosis. *Environ Pollut* 2015;197:181–6.

<sup>\*\*\*\*</sup>Myung W, Lee H, Kim H. Short-term air pollution exposure and emergency department visits for amyotrophic lateral sclerosis: a time-stratified case-crossover analysis. *Environ Int* 2019;123:467–75.

Similarly, another meta-analysis of 94 studies showed clear temporal associations of increases in pollutant concentrations with stroke incidence and mortality for CO (RR, 1.015; 95% CI, 1.004–1.026), NO<sub>2</sub> (RR, 1.014; 95% CI, 1.009–1.019), PM<sub>2.5</sub> (RR, 1.011; 95% CI, 1.011–1.012), PM<sub>10</sub> (RR, 1.003; 95% CI, 1.002–1.004) and SO<sub>2</sub> (RR, 1.019; 95% CI, 1.011–1.027); the strongest associations were observed in low- to middle-income countries.<sup>1</sup> The

findings of this meta-analysis were further supported by 2 recent studies that used case-crossover analyses. In Japan, ischaemic stroke was associated with short-term exposure to PM<sub>2.5</sub> (adjusted OR, 1.03; 95% CI, 1.00–1.06) within a day before stroke onset.<sup>24</sup> In China, a multi-city study showed that short-term elevations of PM<sub>2.5</sub> and PM<sub>10</sub> were significantly associated with a 1.0% (95% CI, 0.7–1.4) and 0.8% (95% CI, 0.3–1.3) rise in admissions for ischaemic

stroke, respectively.<sup>25</sup> Stronger associations were observed in northern China compared to the southern region of the country, a finding similar to that of effect modification by region observed in previous studies.<sup>25</sup> The finding of a geographical difference between the regions was attributed to higher levels of PM pollution in northern China, higher incidence of stroke in northern China and differences in weather patterns and population susceptibility between the regions.<sup>25</sup>

Associations of long-term air pollution exposure with increased stroke hospitalisations were more apparent in cohort studies and less consistently reported in case-control and ecological studies. Relative risks for stroke hospitalisation ranged from 0.98–1.29, most commonly from exposure to PM<sub>2.5</sub>, PM<sub>10</sub> and NO<sub>x</sub> or NO<sub>2</sub>.<sup>21</sup> Relative risks for stroke mortality ranged from 0.86–1.83 and were associated with point sources of emissions, traffic sources, proximity to a main road and higher exposure to CO, NO<sub>x</sub> and PM<sub>10</sub>.<sup>22</sup>

Data on aetiologies of ischaemic stroke was limited. Findings from a time-stratified case-crossover analysis in South London showed positive associations of NO<sub>2</sub> (OR, 1.35; 95% CI, 1.02–1.80) and PM<sub>10</sub> (OR, 1.28; 95% CI, 1.07–1.53) with large artery atherosclerosis; NO<sub>2</sub> (OR, 1.51; 95% CI, 1.12–2.02), PM<sub>10</sub> (OR, 1.21; 95% CI, 1.07–1.36) and SO<sub>2</sub> (OR, 1.30; 95% CI, 1.12–1.51) with small vessel disease; and O<sub>3</sub> (OR, 1.36; 95% CI, 1.13–1.63) with cardioembolic strokes.<sup>26</sup> Overall, however, no consistent pattern was found between pollutant exposure and risk of ischaemic stroke subtypes or severity.<sup>26</sup> In South Korea, a time series study<sup>27</sup> on the impact of short-term air pollution exposure on cardioembolic stroke found a significant association between the condition and exposure to PM<sub>10</sub> (adjusted OR, 1.06; 95% CI, 1.01–1.10) and SO<sub>2</sub> (OR, 1.63; 95% CI, 1.11–2.40); however, NO<sub>2</sub> was associated with the crude model only (OR, 1.12; 95% CI, 1.06–1.18) and no association was found with CO and O<sub>3</sub>.<sup>27</sup>

### Headache and Migraine

Weather is cited as one of many triggers of headache, but the link with air pollution is less established.<sup>28,29</sup> Short-term exposure to ambient air pollutants and PM was associated with increased medical visits for migraine. In Canada, studies have demonstrated a positive association between PM<sub>2.5</sub> and increased ED visits for migraine by 3.3% (95% CI, 0.6–6.0) up to 2 days after exposure.<sup>30</sup> In women, daily ED visits for migraine increased by 4.0% (95% CI, 0.8–7.3) for mean change of 4.6 ppb in SO<sub>2</sub> level during warm season and 4.6% (95% CI, 1.2–8.1) for mean change of 8.3 µg/m<sup>3</sup> in PM<sub>2.5</sub> level in cold season.<sup>31</sup>

In contrast, studies in Taiwan showed an increase in ED visits for headache and migraine by 12% (95% CI,

10–14) and 13% (95% CI, 8–19), respectively, that were significantly associated with higher PM<sub>2.5</sub> levels on warm days.<sup>32,33</sup> In Taipei, positive associations were observed between migraine incidence with CO, NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub> and SO<sub>2</sub> on warm days.<sup>34</sup>

In Chile, acute rise in ambient air pollution was associated with increased hospital admissions for headache, a third of which was for migraine.<sup>35</sup> In the study, the largest pooled risk was O<sub>3</sub> (RR, 1.17; 95% CI, 1.08–1.26) with migraine followed by NO<sub>2</sub> (RR, 1.13; 95% CI, 0.982–1.29) with headache of specified cause. Although there was a high correlation among gaseous pollutants in the study, NO<sub>2</sub> was shown to have an independent effect on migraine.<sup>35</sup> In Israel, a 10-unit increase in NO<sub>2</sub> levels was associated with headache (RR, 1.11; 95% CI, 1.057–1.167), especially in older patients.<sup>36</sup>

On the other hand, a preliminary study in Boston showed interquartile range (IQR) increases in levels of black carbon (OR, 0.995; 95% CI, 0.955–1.036), NO<sub>2</sub> (OR, 0.983; 95% CI, 0.936–1.032), PM<sub>2.5</sub> (OR, 1.005; 95% CI, 0.967–1.045) and SO<sub>2</sub> (OR, 0.975; 95% CI, 0.933–1.018) did not influence acute risk of headache on day of exposure, and the findings were similar between migraine and non-migraine cases.<sup>37</sup>

### Epilepsy

Two studies investigated the link between epilepsy and short-term air pollution exposure. In Chile, a study of 7 urban centres revealed an association between air pollution and daily hospitalisations for epilepsy.<sup>38</sup> The study found that increases in IQR concentrations were associated with pooled risks of hospitalisation for CO (RR, 1.098; 95% CI, 1.045–1.155), NO<sub>2</sub> (RR, 1.108; 95% CI, 1.021–1.204), O<sub>3</sub> (RR, 1.100; 95% CI: 1.025–1.181), PM<sub>2.5</sub> (RR, 1.065; 95% CI, 1.002–1.132), PM<sub>10</sub> (RR, 1.083; 95% CI, 1.038–1.13) and SO<sub>2</sub> (RR, 1.085; 95% CI, 1.03–1.144).<sup>37</sup>

In the second study, it was found that outpatient visits for epilepsy in China increased by 3.17% (95% CI, 1.41–4.93) and 3.55% (95% CI, 1.93–5.18) for every 10 µg/m<sup>3</sup> rise in NO<sub>2</sub> and SO<sub>2</sub> concentrations, respectively.<sup>39</sup>

### Alzheimer's Disease and Dementia

A systematic review of epidemiologic studies of outcomes such as cognitive decline, cognitive function, dementia or dementia-related neuroimaging features concluded that nearly all of them reported an adverse association between pollutant exposure and at least 1 dementia-related outcome.<sup>40</sup>

In Taiwan, long-term studies revealed that increased risk of dementia was associated with exposure to CO (HR, 1.61; 95% CI, 1.39–1.85) and NO<sub>2</sub> (HR, 1.54; 95% CI, 1.34–1.77).<sup>41</sup> High levels of O<sub>3</sub> (OR, 2.00; 95% CI, 1.14–3.5) and PM<sub>10</sub> (OR, 4.17; 95% CI, 2.31–7.54) were



associated with AD risk and similar findings were observed in vascular dementia.<sup>42</sup> For every increase of 4.34  $\mu\text{g}/\text{m}^3$  in  $\text{PM}_{2.5}$ , AD risk escalated to 138%.<sup>43</sup>

In Sweden, a longitudinal study found that local traffic pollution was associated with dementia incidence (HR, 1.43; 95% CI, 0.998–2.05); comparable estimates for AD (HR, 1.38) and vascular dementia (HR, 1.47) were also found.<sup>44</sup> In the United Kingdom, a systematic review of environmental risk factors for dementia found moderate to strong evidence of association with exposure to all airborne pollutants, particularly  $\text{NO}_x$ ,  $\text{O}_3$  and  $\text{PM}$ .<sup>45</sup>

In Madrid, findings from a study of the association between short-term air pollution exposure and emergency hospital admissions for AD showed a link with exposure to  $\text{PM}_{2.5}$  concentrations after 2 days (RR, 1.38; 95% CI, 1.15–1.65).<sup>46</sup>

### Parkinson's Disease

Evidence on the link between air pollution and PD is scarce. In Canada, a cohort study in 2 cities did not show an association between traffic-generated air pollution markers and PD in Toronto, but some evidence suggested a significant association between exposure to ambient manganese and PD (OR, 1.034; 95% CI, 1.00–1.07) in Hamilton.<sup>47</sup>

In Denmark, findings from a case-control study determined that for every IQR increase in long-term exposure to  $\text{NO}_2$ , an increase of 9% in PD risk was observed and the incidence is similar in men and women (OR, 1.09).<sup>48</sup> In Taiwan, a recent study on multi-pollutant models showed that PD risk was significantly associated with exposure to CO (OR, 1.17; 95% CI, 1.07–1.27) and  $\text{NO}_x$  (OR, 1.37; 95% CI, 1.23–1.52).<sup>49</sup>

In the United States, several studies showed limited evidence for an association between  $\text{NO}_2$ ,  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  with PD risk, although it was suggested that non-smokers (OR, 1.29; 95% CI, 0.94–1.76) and women (OR, 1.65; 95% CI, 1.11–2.45) had higher risk for PD from exposure to  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$ , respectively.<sup>50</sup> A large prospective female cohort study failed to establish a relationship between PD and exposure to  $\text{PM}_{2.5}$ ,  $\text{PM}_{10}$  and  $\text{PM}_{10-2.5}$ .<sup>51</sup> A third cohort study, however, noted non-significant trends between  $\text{O}_3$  (OR, 1.39; 95% CI, 0.98–1.98) and  $\text{PM}_{2.5}$  (OR, 1.34; 95% CI, 0.93–1.93) levels with PD.<sup>52</sup>

### Neuromuscular Conditions

Although several studies had investigated risk of myopathy or neuropathies from exposure to heavy metals or organic pesticides, for this review only studies of the association between air pollution and amyotrophic lateral sclerosis (ALS) were found. In the Netherlands, a population-based case-control study of the risk of ALS from long-term exposure to air pollution found that it was higher when there was upper quartile exposure to  $\text{NO}_2$  (OR, 1.74;

95% CI, 1.32–2.30),  $\text{NO}_x$  (OR, 1.38; 95% CI, 1.07–1.77) and  $\text{PM}_{2.5}$  (OR, 1.67; 95% CI, 1.27–2.18) concentrations.<sup>53</sup>

In another case-control study, duration of residential ambient air aromatic solvent exposure was associated with higher ALS risk based on findings from 1999 (OR, 4.27; 95% CI: 1.09–16.79) and 2002 (OR, 5.03; 95% CI, 1.29–19.53).<sup>54</sup> A recent study showed that exposure to the fourth quartile of  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  concentrations was significantly associated with increased risk of ED visits for ALS.<sup>55</sup>

### Limitations of Studies and Future Challenges

Several limitations of published studies in the literature should be considered when interpreting their findings. The first limitation is found in the disparities in methodology and statistical models employed by various studies. Case-crossover and time series analyses were the most common study designs that were used to evaluate associations between short-term exposure to outdoor air pollution and adverse health events such as hospital admissions or daily mortality.<sup>56,57</sup>

In time series studies, the association between exposure and outcome was estimated using regression analysis to adjust for confounders such as meteorological variables.<sup>1</sup> However, sensitivity might be influenced by the degree of correlation between air pollutants and weather.<sup>56</sup> In case-crossover studies, the cases served as control subjects and exposure—at time of hospitalisation—was compared against control periods when hospitalisation did not occur.<sup>1,56</sup> As such, any confounding factors that were attributed to the characteristics of subjects could be eliminated and time trends in exposure and outcomes could be controlled for in the analysis.<sup>56</sup> The disadvantage of case-crossover studies is the potential for selection bias in the designation of control periods as time intervals—either too distant or too close—can confound the resulting effect estimates due to seasonal patterns.

Although time series and case-crossover studies could provide reasonable estimates of the effect of short-term air pollution exposure, they were still subjected to inconsistent approximations that resulted from the different methods used to perform the analyses.<sup>56</sup> Studies on association between long-term air pollution exposure and health outcomes are more prone to confounding by risk factors that may exhibit different spatial patterns.<sup>57</sup> Examples of such factors include smoking and comorbid conditions at the individual level and socioeconomic status of a neighbourhood at the area level.<sup>57</sup> Temporal cycles defined by weather, week day and seasonal and long-term trends must also be factored into consideration in the analysis.<sup>57</sup>

Second, there is a propensity for exposure measurement error. Feasibility and cost issues hinder precise measurements

of personal exposure, and most studies in this review used regional or remote monitoring sites to deduce personal air pollution exposure levels at residential addresses.<sup>23,57</sup> Consequently, spatio-temporal variations may be missed when individuals move about over a period of time, leading to underestimation of the reported associations.<sup>57</sup>

Third, outcome assessment may not be accurate in terms of case definitions and temporal course. Hospital admission dates and International Classification of Diseases codes from administrative data are used as surrogates for incidence or disease onset and diagnosis.<sup>22,23</sup> Currently, there is no standard practice to validate diagnoses and outcomes in air pollution studies, and this could lead to a risk of biased results towards the null.<sup>22</sup> Additionally, air pollution often exerts cumulative effects and it is difficult to distinguish between the direct independent effect of every pollutant.<sup>23</sup> In meta-analyses, it is uncertain whether there were partial geographical and temporal overlaps between studies that led to inclusion of patients across multiple studies.<sup>1</sup>

The challenge for future studies on air pollution is to select an appropriate study design that can control for confounding factors as far as possible. More research is needed on how sample designs can be optimised for assessment of exposure to minimise errors.<sup>53</sup> Case definitions, including precise disease onset, must be standardised and validated well. Geographical differences in effect estimates should be subjected to thorough investigation in future studies.

## Conclusion

Findings in the literature have supported an association between air pollution exposure and common neurological conditions. Short-term exposure was associated with increased incidence of epilepsy, ischaemic stroke, migraine and hospital admissions for AD. Long-term exposure was significantly associated with AD, ALS, dementia and ischaemic stroke. Evidence on the link between long-term air pollution exposure and PD is still limited.

Despite the magnitude of the haze problem in Southeast Asia, there are limited specific data and studies that have been published on the effects seasonal haze has on neurological conditions in the region. In Singapore, a cross-sectional survey of the physical and psychological impact of the 2013 haze crisis on 298 residents revealed that headache was one of the most common physical symptoms reported in 50.3% of respondents.<sup>6</sup> A time-stratified case crossover study in Singapore which indirectly investigated the impact of trans-boundary seasonal haze found that moderate (RR, 1.10; 95% CI, 1.06–1.13) or unhealthy (RR, 1.14; 95% CI, 1.03–1.25) Pollutant Standards Index levels were associated with higher incidence of ischaemic stroke.<sup>58</sup> Further research is therefore needed to establish the impact of seasonal haze on various populations in Southeast Asia.

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