Topical Review

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Ambient Air Pollution and Stroke

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Stroke is a leading cause of death in the United States[1] and worldwide (http://www.who.int) and may lead to considerable neurological sequelae including aphasia, paraplegia, and dementia. The estimated healthcare costs of stroke in the United States exceed $36 billion per year.[1] A large body of evidence supports the association between ambient air pollution exposure and increased cardiovascular mortality and morbidity,[2] but only recently have several studies specifically demonstrated an association with increased stroke risk.

Background

Major sources of air pollution include traffic, power plants and in developing countries, biomass combustion. Both particles and gases are emitted through combustion. Particulate matter with aerodynamic diameter <10 μm (PM_{10}) include ultrafine particles ($PM_{1.0}$), fine particles ($PM_{2.5}$), and coarse particles ($PM_{10–2.5}$). Ultrafine particles are emitted in fresh exhaust and coalesce into $PM_{2.5}$ within a short time frame. $PM_{2.5}$ includes both local sources from traffic emissions and domestic heating and regional sources from power plants, biogenic emissions, and traffic, whereas coarse particles are a heterogeneous mixture that include road dust, endotoxins, and suspended crustal matter. CO, NO_2, NO_x, SO_2, and ground-level ozone (O_3) are gaseous pollutants emitted as a result of combustion processes. CO is mainly attributed to mobile sources in urban environments, and NO_2 and NO_x are rapidly formed in emissions from combustion sources such as traffic and power plants. The main source of SO_2 is from fossil fuel power plants. Ground-level O_3 is formed as a result of atmospheric reactions of NO_2 with hydrocarbons in the presence of sunlight and is a major constituent of photochemical smog. Several of the mentioned pollutants are regulated based on evidence of adverse health effects.[3] Possible mechanistic pathways including induction of oxidative stress, inflammation, atherosclerosis, and autonomic dysregulation have been outlined in detail[2–4] and are beyond the scope of the current review.

This review aims to assess the current evidence on the association of air pollution exposure with incidence of ischemic and hemorrhagic stroke considering long-term and short-term exposure to ambient pollutants.

Long-Term Air Pollution Exposure

Most studies of long-term exposure to air pollution and stroke outcomes have used estimates of exposure at residential address in months to years as a proxy for long-term accumulated individual exposure. Exposure has then been assessed using residential distance to major roadways, measurements from closest available fixed monitor, or advanced modeling of pollutants combining fixed monitoring measurements with land-use data, emissions databases, traffic density counts, and meteorology incorporated into geographical information systems. These geographical information system models can also include population-based data such as average income level and average smoking prevalence.

Long-Term Air Pollution Exposure and Stroke Mortality

Studies considering long-term exposure to air pollution and stroke mortality have reported that living in areas with higher ambient pollution is associated with higher risk of stroke mortality (Table 1). Studies from the United Kingdom[5,6] and Northwest Florida[7] contain large administrative databases with cause of death, residence, sex, and area-based data such as socioeconomic status, urbanization, smoking prevalence, and greenness. Living near a main road,[5] traffic sources,[7] point sources of emissions,[7] or higher modeled exposure to PM_{10}, CO, and NO_x[6] were all associated with stroke mortality. Several cohort studies have also studied the association between long-term exposure to air pollution and stroke mortality.[8–13] These studies have more detailed individual-level data that improve the ability to adjust for potential confounders that may influence the place of residence and the risk of stroke mortality. Strongest associations were reported in the prospective Womens' Health Initiative cohort[11] that included well-validated outcome assessment. In the Californian residents of the American Cancer Society cohort study,[9] associations were reported for NO_2 and any stroke mortality and borderline significant associations for $PM_{2.5}$. In the California Teachers Study,[10] however, higher long-term PM_{10} and $PM_{2.5}$ exposure were not associated with cerebrovascular mortality. In 232 rural districts of Japan,[12] including 250 stroke

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Table 1. Studies of Long-Term Air Pollution Exposure and Stroke Mortality

Study	Location	Study Design	Stroke Outcome	Relative Risk (95% Confidence Intervals)	Exposure
Maheswaran and Elliott[5]	England and Wales	Ecological	Any stroke	1.05 (1.04–1.07)	Living within 200 m of main road compared with ≥1000 m
Maheswaran et al[6]	Sheffield, UK	Ecological	Any stroke	1.37 (1.19–1.57) PM_{10}	Highest to lowest quintile of modeled pollutant
				1.26 (1.10–1.46) CO	
				1.33 (1.14–1.56) NO_x	
Hu et al[7]	Florida, USA	Ecological	Any stroke	1.09 (1.03–1.15)*	Per 10 000 vehicles/d within census tract
Andersen et al[8]	Denmark	Cohort	Any stroke	1.22 (1.00–1.50)	Per interquartile range increase (43%) in mean modeled NO_2 since 1971
			Ischemic	1.46 (0.90–2.39)	
			Hemorrhagic	1.00 (0.76–1.31)	
Jerrett et al[9]	California, USA	Cohort	Any stroke	1.07 (0.99–1.15) $PM_{2.5}$	Per 5.3 μg/m³ $PM_{2.5}$
				1.08 (1.02–1.15) NO_2	Per 4.12 ppb NO_2
				1.01 (0.92–1.11) O_3	Per 24.2 ppb O_3
Lipsett et al[10]	California, USA	Cohort	Any stroke	0.99 (0.89–1.09) PM_{10}	Per 10 μg/m³ mean PM_{10} 1996–2005 or mean $PM_{2.5}$ 1999–2005
				1.16 (0.92–1.46) $PM_{2.5}$	
Miller et al[11]	36 US cities	Cohort	Any stroke	1.83 (1.11–3.00) $PM_{2.5}$	Annual mean in 2000 at closest monitor per 10 μg/m³
Ueda et al[12]	Japan	Cohort	Any stroke	0.86 (0.74–1.01) PM_{10}	Per 10 μg/m³ annual mean at closest monitor
Yorifuji et al[13]	Shizuoka, Japan	Cohort	Any stroke	1.19 (1.06–1.34)	Per 10 μg/m³ annual mean NO_2
			Ischemic	1.20 (1.04–1.39)	
			Hemorrhagic	1.28 (1.05–1.57)	

PM_{10} indicates particles with aerodynamic diameter ≤10 μm; $PM_{2.5}$, fine particles with aerodynamic diameter ≤2.5 μm; and ppb, parts per billion.
*95% credible interval from a Bayesian analysis.

deaths, higher long-term PM_{10} exposure was not associated with stroke mortality. Specific characterization of stroke into types and subtypes was available in 2 studies: in Shizuoka, Japan[13] and in Denmark.[8] Yorifuji et al[13] reported associations between NO_2 and mortality from ischemic stroke and intracerebral hemorrhage but not subarachnoid hemorrhage. Andersen et al[8] reported borderline significant associations between long-term NO_2 exposure and ischemic stroke but not for hemorrhagic strokes and did not further subtype hemorrhagic strokes.

Long-Term Air Pollution Exposure and Hospitalization for Stroke

In studies of long-term exposure to air pollution and hospitalization for stroke, higher exposure at home addresses was also associated with higher risk of admission for stroke in some studies, but results were less consistent than for stroke mortality (Table 2). Most commonly reported pollutants included long-term exposure to PM_{10},[6,10,14,15] $PM_{2.5}$,[10,11,16] and NO_x[6,17,18] or NO_2.[8,14,15,19,20] Many of the cohort studies reported positive associations,[8,10,11,14,21] whereas ecological studies[6,15,19] and case–control studies[17,18,21] showed mixed results. In a random-effects meta-analysis of 11 European cohorts,[16] long-term $PM_{2.5}$ was associated more strongly with stroke in subjects >60 years old, never-smokers, and among subjects with exposure levels <25 μg/m³ (current annual mean air quality standard in Europe). Studies that compared long-term air pollution exposure and hospital admissions according to specific stroke type reported positive associations for NO_2, CO, and traffic density and admissions for both ischemic and hemorrhagic stroke[19] in Edmonton, Canada, whereas NO_2[8,20] in Denmark or NO_x[15] in London, UK, demonstrated associations consistent with ischemic stroke but not hemorrhagic stroke. Two studies from Scania, Sweden[17,18] only including hospital admissions for ischemic stroke observed associations between higher long-term exposure to NO_x and higher risk of hospital admission for ischemic stroke in participants with diabetes mellitus but found no association in the overall population, in smokers, or in participants with hypertension or atrial fibrillation. A recent population-based cohort study in Denmark studying long-term NO_2 and traffic noise exposure and stroke incidence reported positive associations for ischemic stroke in separate analyses for both noise and NO_2 but in combined analyses NO_2 was only associated with fatal ischemic strokes.[20]

Short-Term Air Pollution Exposure

Day-to-day differences in air pollution exposure in the days preceding stroke are used to study possible triggering effects of air pollution on stroke. In time-series analyses, daily counts of stroke deaths or admissions are compared with air pollution levels on the same day or preceding days in a study region. In case-crossover analyses, exposure levels preceding stroke mortality or hospitalization in an individual are contrasted with control periods within the same calendar month within each individual controlling for season and day of week and perfectly matching time-invariant patient characteristics by design.

Table 2. Studies of Long-Term Air Pollution Exposure and Hospitalization for Stroke

Study	Location	Study Design	Stroke Outcome	Relative Risk (95% Confidence Intervals)	Exposure
Maheswaran et al[6]	Sheffield, UK	Ecological	Any stroke	1.13 (0.99–1.29) PM_{10}	Highest to lowest quintile of modeled pollutant
				1.11 (0.99–1.25) CO	
				1.13 (1.04–1.27) NO_x	
Andersen et al[8]	Denmark	Cohort	Any stroke	1.05 (0.99–1.11)	Per interquartile range increase (43%) in mean modeled NO_2 since 1971
			Ischemic	1.05 (0.95–1.17	
			Hemorrhagic	0.93 (0.81–1.07)	
Lipsett et al[10]	California	Cohort	Any stroke	1.06 (1.00–1.13) PM_{10}	Per 10 $\mu g/m^3$ annual mean pollutant at closest monitor
				1.14 (0.99–1.32) $PM_{2.5}$	
Miller et al[11]	36 US cities	Cohort	Any stroke	1.28 (1.01–1.61) $PM_{2.5}$	Per 10 $\mu g/m^3$ mean of closest monitor during 2000
Maheswaran et al[15]	London, UK	Ecological	Ischemic	1.22 (0.77–1.93) PM_{10}	Per 10 $\mu g/m^3$ of modeled pollutant exposure
				1.11 (0.93–1.32) NO_2	
			Hemorrhagic	0.52 (0.20–1.37) PM_{10}	
				0.86 (0.60–1.24) NO_2	
Atkinson et al[14]	England	Cohort	Any stroke	0.98 (0.95–1.01) PM_{10}	Per 3.0 $\mu g/m^3$ PM_{10}
				0.99 (0.95–1.03) NO_2	Per 10.7 $\mu g/m^3$ NO_2
				1.02 (1.00–1.05) SO_2	Per 2.2 $\mu g/m^3$ SO_2
				1.00 (0.97–1.04) O_3	Per 3.0 $\mu g/m^3$ O_3 modeled annual mean
Stafoggia et al[16]	11 cohorts, Europe	Cohort	Any stroke	1.19 (0.88–1.62)	Per 5 $\mu g/m^3$ annual mean
Oudin et al[17]	Scania, Sweden	Case–control	Ischemic	0.95 (0.86–1.06)	Annual mean modeled NO_x of 20–30 vs <10 $\mu g/m^3$
Oudin et al[18]	Scania, Sweden	Case–control	Ischemic	In diabetics:	Modeled annual NO_x:
				2.0 (1.2–3.4) high NO_x	High NO_x ≥25 $\mu g/m^3$
				1.3 (1.1–1.6) low NO_x	Low NO_x <15 $\mu g/m^3$
					Reference: nondiabetics with low NO_x
Johnson et al[19]	Edmonton, Canada	Ecological	Any stroke	1.29 (1.16–1.43)	Highest (16.7–20.3 ppb) to lowest quintile (10.1–14.0 ppb) of NO_2 exposure
			Nonhemorrhagic	1.36 (1.19–1.56)	
			Hemorrhagic	1.46 (1.19–1.80)	
Sørensen et al[20]	Denmark	Cohort	Any stroke	1.08 (1.01–1.16)	Per 10 $\mu g/m^3$ annual mean NO_2
			Ischemic	1.11 (1.03–1.20)	
			Hemorrhagic	1.00 (0.80–1.24)	
Johnson et al[21]	Edmonton, Canada	Case–control	Any stroke	1.01 (0.94–1.08)	Per 5 ppb NO_2
			Ischemic	1.03 (0.94–1.13)	
			TIA	0.95 (0.86–1.05)	
			Hemorrhagic	1.07 (0.92–1.24)	

PM_{10} indicates particles with aerodynamic diameter ≤10 μm; $PM_{2.5}$, fine particles with aerodynamic diameter ≤2.5 μm; ppb, parts per billion; and TIA, transient ischemic attack.

Several studies have investigated associations between short-term exposure to air pollutants including PM_{10}, $PM_{2.5}$, CO, NO_2, SO_2, and O_3 and stroke mortality or hospitalizations for stroke in many cities in North America, Europe, and East Asia. Mean levels of pollutants varied considerably between study locations from low-polluted cities such as Dijon, France (daily mean PM_{10} 20 $\mu g/m^3$) to highly polluted cities such as Wuhan, China (daily mean PM_{10} 119 $\mu g/m^3$).

Short-Term Air Pollution Exposure and Stroke Mortality

A majority of studies investigating short-term exposure to air pollution and stroke mortality have been time-series studies,[22–36] the remainder used case-crossover design.[37–41] A qualitative summary of the studies is provided in Table 3 (for detailed estimates, see Table I in the online-only Data Supplement). Most studies do not differentiate between ischemic and hemorrhagic stroke mortality. Several studies reported associations between short-term exposure to particle matter, including several size fractions, or gases and any stroke mortality. Only a few studies further characterized stroke into ischemic and hemorrhagic stroke mortality.[24,33–35,38] Short-term exposure to particulate matter and gases was associated with both ischemic stroke and hemorrhagic stroke. In Tokyo,[34] the risk increase for subarachnoid hemorrhage mortality per 10 $\mu g/m^3$ $PM_{2.5}$ or NO_2 was roughly double the risk increase for ischemic or intracerebral

Table 3. Studies of Short-Term Air Pollution Exposure and Stroke Mortality

Study	Location	Study Design	Stroke Outcome	Positive Associations*	Null Associations†
Chen et al[22]	8 Chinese cities	Time series	Any stroke	PM_{10}, NO_2, and SO_2	...
Hoek et al[23]	Netherlands	Time series	Any stroke	Black smoke, CO, SO_2, and O_3.	PM_{10} and NO_2
Hong et al[24]	Seoul, Korea	Time series	Ischemic	TSP, CO, NO_2, SO_2, and O_3	...
			Hemorrhagic	TSP	CO, NO_2, SO_2, and O_3
Hong et al[25]	Seoul, Korea	Time series	Any stroke	PM_{10}, CO, NO_2, SO_2, and O_3	...
Kan et al[26]	Shanghai, China	Time series	Any stroke	PM_{10} and NO_2	SO_2
Kettunen et al[27]	Helsinki, Finland	Time series	Any stroke	$PM_{2.5}$ and CO in warm season	PM_{10}, coarse PM, $PM_{0.1}$, NO_2, and O_3 in warm season. No associations in cold season
Li et al[28]	Tianjin, Taiwan	Time series	Any stroke	PM_{10} on days with >20°C	PM_{10} on days with ≤20°C
Qian et al[29]	Wuhan, China	Time series	Any stroke	PM_{10}	...
Qian et al[30]	Wuhan, China	Time series	Any stroke	NO_2	SO_2 and O_3
Qian et al[31]	Wuhan, China	Time series	Any stroke	PM_{10} all days and NO_2, SO_2 on normal temperature days	O_3 all days and NO_2, SO_2 on high temperature days
Qian et al[32]	Wuhan, China	Time series	Any stroke	NO_2 in spring. PM_{10}, NO_2, SO_2 in winter	PM_{10} and SO_2 in spring. All pollutants summer or fall
Turin et al[33]	Takashima, Japan	Time series	Any stroke	...	Suspended PM, NO_2, SO_2, and O_3
			Ischemic	NO_2	Suspended PM, SO_2, and O_3
			Hemorrhagic	...	Suspended PM, NO_2, SO_2, and O_3
Yorifuji et al[34]	Tokyo, Japan	Time series	Any stroke	$PM_{2.5}$ and NO_2	...
			Ischemic	...	$PM_{2.5}$ and NO_2
			Hemorrhagic	$PM_{2.5}$ and NO_2	...
Yorifuji and Kashima[35]	47 Japanese cities	Time series	Any stroke	...	PM_{10}
			Ischemic	PM_{10}	...
			Hemorrhagic	...	PM_{10}
Zanobetti and Schwartz[36]	112 US cities	Time series	Any stroke	$PM_{2.5}$ and PM_{coarse}	
Maynard et al[37]	Massachusetts, USA	Case crossover	Any stroke	Black carbon	SO_4
Qian et al[38]	Shanghai, China	Case crossover	Any stroke	PM_{10}, NO_2, and SO_2	...
			Ischemic	PM_{10}, NO_2, and SO_2	...
			Hemorrhagic	NO_2 and SO_2	PM_{10}
Ren et al[39]	Massachusetts, USA	Case crossover	Any stroke	O_3	...
Zeka et al[40]	20 US cities	Case crossover	Any stroke	PM_{10}	...
Zeka et al[41]	20 US cities	Case crossover	Any stroke	PM_{10} if pneumonia or ≥75-y old	PM_{10} if no pneumonia or ≤75-y old

$PM_{0.1}$ indicates ultrafine particles with <0.1 μm aerodynamic diameter; PM_{10}, particles with aerodynamic diameter ≤10 μm; $PM_{2.5}$, fine particles with aerodynamic diameter ≤2.5 μm; PM_{coarse}, coarse particles with aerodynamic diameter between 2.5 and 10 μm in aerodynamic diameter; and TSP, total suspended particles.

*Positive associations with confidence intervals not including the null.

†Associations with confidence intervals including the null.

Table 4. Studies of Short-Term Exposure to Air Pollution and Hospital Admissions for Stroke

Study	Location	Study Design	Stroke Outcome	Positive Associations*	Null Associations†
Ballester et al[43]	Valencia, Spain	Time series	Any stroke	NO_2	CO, SO_2, and O_3
Burnett et al[44]	Toronto, Canada	Time series	Any stroke	...	PM_{10}, CO, NO_2, and O_3
Chan et al[45]	Taipei, Taiwan	Time series	Any stroke	PM_{10}, $PM_{2.5}$, and O_3	CO, NO_2, and SO_2
			Ischemic	...	PM_{10}, $PM_{2.5}$, CO, NO_2, SO_2, and O_3
			Hemorrhagic	...	PM_{10}, $PM_{2.5}$, CO, NO_2, SO_2, and O_3
Corea et al[46]	Mantua, Italy	Case crossover	Any stroke	PM_{10}	...
			Ischemic	PM_{10} in all ischemic, large vessel, small vessel, and lacunar	PM_{10} in cardioembolic. CO, NO_2, SO_2, and O_3
Jalaludin et al[47]	Sydney, Australia	Time series	Any stroke	...	PM_{10}, $PM_{2.5}$, CO, NO_2, SO_2, and O_3
Larrieu et al[48]	8 French cities	Time series	Any stroke	...	PM_{10}, NO_2, and O_3
Le Tertre et al[49]	8 European cities	Time series	Any stroke	...	PM_{10} and black smoke
Linn et al[50]	Los Angeles, USA	Time series	Any stroke	CO and NO_2 in spring	PM_{10} and O_3
Moolgavkar[51]	Los Angeles, USA	Time series	Any stroke	PM_{10}, CO, NO_2, and SO_2	$PM_{2.5}$
Nascimento et al[52]	Sao Jose Campos, Brazil	Time series	Any stroke	PM_{10} and SO_2	O_3
Poloniecki et al[53]	London, UK	Time series	Any stroke	...	Black smoke, CO, NO_2, SO_2, and O_3
Pönkä and Virtanen[54]	Helsinki, Finland	Time series	Any stroke	NO_2	...
			Ischemic	Total suspended particles	...
Sunyer et al[55]	7 European cities	Time series	Any stroke	...	SO_2
Turin et al[56]	Takashima, Japan	Time series	Any stroke	...	PM_{10},NO_2, SO_2, and O_3
			Ischemic	...	PM_{10},NO_2, SO_2, and O_3
			Hemorrhagic	SO_2	PM_{10},NO_2, and O_3
Villeneuve et al[57]	Edmonton, Canada	Case crossover	Any stroke	...	PM_{10}, $PM_{2.5}$, CO, NO_2, SO_2, and O_3
			Ischemic	$PM_{2.5}$	CO, NO_2, SO_2, and O_3
			TIA	...	PM_{10}, $PM_{2.5}$, CO, NO_2, SO_2, and O_3
			Hemorrhagic	SO_2	PM_{10}, $PM_{2.5}$, CO, NO_2, and O_3
Villeneuve et al[58]	Edmonton, Canada	Case crossover	Any stroke	CO in warm season	$PM_{2.5}$, NO_2, SO_2, O_3, and CO all year
			Ischemic	CO, NO_2,O_3 in warm season	$PM_{2.5}$, SO_2. CO, NO_2, and O_3 all year
			Hemorrhagic	...	$PM_{2.5}$, CO, NO_2, SO_2, and O_3
Wong et al[59]	Hong Kong, China	Time series	Any stroke	...	PM_{10}, NO_2, SO_2, and O_3
Wordley et al[60]	Birmingham, UK	Time series	Any stroke	PM_{10}	...
Xiang et al[61]	Wuhan, China	Case crossover	Any stroke	PM_{10} and NO_2 in cold season	PM_{10}, NO_2, and SO_2 all year and in subtypes. PM_{10} and NO_2 in warm season
Xu et al[62]	Allegheny, USA	Case crossover	Any stroke	O_3	...
			Ischemic	O_3	...
			Hemorrhagic	...	O_3
Yang et al[63]	Taipei, Taiwan	Time series	Any stroke	...	Asian dust
			Ischemic	...	Asian dust
			Hemorrhagic	Asian dust and intracerebral	Asian dust and subarachnoidal
Tsai et al[64]	Kaohsiung, Taiwan	Case crossover	Ischemic	PM_{10}, NO_2, SO_2, O_3 warm days, CO all days	PM_{10}, NO_2, SO_2, and O_3 cool days
			Hemorrhagic	PM_{10}, CO, NO_2, and O_3 warm days	SO2 warm days, all pollutants cool days
Wellenius et al[65]	9 US cities	Case crossover	Ischemic	PM_{10}, CO, NO_2, and SO_2	
			Hemorrhagic	...	PM_{10}, CO, NO_2, and SO_2
Lisabeth et al[66]	Corpus Christi, USA	Time series	Ischemic	$PM_{2.5}$	O_3
O'Donnell et al[67]	8 Canadian cities	Case crossover	Ischemic	$PM_{2.5}$ in diabetics and noncardioembolic	$PM_{2.5}$ in ischemic strokes overall

(*Continued*)

Table 4. Continued

Study	Location	Study Design	Stroke Outcome	Positive Associations*	Null Associations†
Wellenius et al[68]	Boston, USA	Case crossover	Ischemic	$PM_{2.5}$, black carbon, NO_2, and $PM_{2.5}$ large and small vessel stroke	CO, SO_4, O_3, and $PM_{2.5}$ cardioembolic stroke
Henrotin et al[69]	Dijon, France	Case crossover	Ischemic	O_3 in all ischemic, large vessel, and TIA	PM_{10}, CO, NO_2, and SO_2
			Hemorrhagic		PM_{10}, CO, NO_2, SO_2, and O_3
Henrotin et al[70]	Dijon, France	Case crossover	Ischemic	O_3 in recurrent stroke	O_3 in incident stroke
Yamazaki et al[71]	Japan	Case crossover	Ischemic	...	PM_7, NO_2, and O_3 in 24 h averages
			Hemorrhagic	PM_7 2 h before intracerebral hemorrhage	...
Bedada et al[72]	UK	Case crossover	Minor stroke	NO	CO, NO_2, SO_2, and O_3

$PM_{0.1}$ indicates ultrafine particles with less than 0.1 μm aerodynamic diameter; PM_{10}, particles with aerodynamic diameter ≤10 μm; $PM_{2.5}$, fine particles with aerodynamic diameter ≤2.5 μm; PM_{coarse}, coarse particles with aerodynamic diameter between 2.5 and 10 μm in aerodynamic diameter; and TIA, transient ischemic attack.

*Positive associations with confidence intervals not including the null.

†Associations with confidence intervals including the null.

hemorrhage mortality. It is possible that these hemorrhages may have more precise temporal relationship between air pollution exposure and the timing of stroke onset leading to less exposure misclassification and more precise estimation of the association.[42] Stronger associations between short-term air pollution exposure and stroke mortality were observed in elderly,[25,30] women,[25] and individuals with a history of diabetes mellitus[41] or cardiac disease[38] in some but not all studies.

Short-Term Air Pollution Exposure and Hospitalization for Stroke

Studies of short-term air pollution exposure and hospitalization for any stroke have reported mixed results.[43–63] However, in contrast to studies investigating short-term exposure to air pollution and stroke mortality that typically use death certificate data, some studies of associations with hospital admissions for stroke have had more data on stroke type. These studies have reported associations between PM_{10},[45,46,64,65] $PM_{2.5}$,[66–68] black carbon,[68] CO,[51,58,64] NO_2,[43,58,64,68] and O_3[62,69,70] and ischemic stroke (Table 4; for detailed estimates, see Table II in the online-only Data Supplement). A majority did not observe associations between air pollutants and hemorrhagic str oke[45,58,62,65,69] with a few exceptions[56,57,63,64,71] including one study that specifically investigated days in Taiwan polluted by Asian dust storms originating from the Gobi desert.[63] Of the studies with specific data on subtype of ischemic stroke, PM_{10}, $PM_{2.5}$, and O_3 were associated with strokes characterized as large-artery atherosclerotic strokes, small-vessel occlusions, lacunar strokes, or transient ischemic attacks rather than cardioembolic strokes.[46,67–69] Stronger associations were reported for recurrent ischemic strokes or history of stroke,[58,70] in individuals with diabetes mellitus or on diabetes mellitus medication[67,70] and with ≥1 cardiovascular risk factors.[69,70] A few studies reported stronger associations between O_3 and ischemic stroke in men than in women.[62,69,72] Air pollution on warm days was more strongly associated with both hemorrhagic and ischemic stroke in Taiwan.[64] Associations between air pollution and ischemic stroke were stronger in the warm season in Edmonton, Canada[58] and Dijon, France[70] in contrast to Wuhan[61] where associations were stronger in the cold season. Differences may reflect better exposure classification because of time spent outdoors in climates such as Edmonton, Canada but may also be because of seasonal interactions between pollutants.

Summary

The current evidence suggests that exposure to higher levels of air pollutants related to combustion increases the risk of stroke. Studies of both long-term and short-term air pollution exposure suggest consistent evidence of increased risk of ischemic stroke and moderately consistent evidence supporting an association with hemorrhagic stroke. A few studies exploring susceptible subgroups have indicated stronger associations in individuals with several cardiovascular risk factors, diabetes mellitus, previous stroke, and of older age. A recently published meta-analysis focusing on short-term air pollution exposure and stroke incidence or mortality reported significant associations for $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 for stroke with stronger associations for ischemic stroke.[73]

Because much of the existing literature is based on linkage of administrative data, an important limitation of many available studies is limited ability to classify and validate specific stroke outcomes. Ischemic stroke and hemorrhagic stroke and their subtypes have in the majority of studies been analyzed as a combined outcome despite the clear possibility that air pollution may affect underlying pathophysiological pathways differently. Only some have separately analyzed ischemic stroke and hemorrhagic stroke and a handful have considered subtypes of ischemic stroke or hemorrhagic stroke. Similarly, only a handful used thorough chart reviews and adjudicated the diagnosis and onset time of stroke. This highlights the need for high-quality validated diagnostic characterization of stroke outcome in studies of air pollution. In a study of short-term air pollution exposure and stroke specifically investigating the bias introduced through misclassification of time of event of stroke found that incorrect temporal classification caused up to 66% bias toward the null.[42] This may be especially relevant in mortality studies where the date of death from death certificates is used while not accounting for the

time between stroke onset and death. In studies of long-term exposure to air pollution, the ability to investigate associations with stroke is dependent on the validity and resolution of the spatial exposure assessment and the adequate control for confounders related to both air pollution at place of residence and the risk of stroke, in particular socioeconomic factors.

There is growing evidence to suggest that both accumulated exposure to higher air pollution during a period of years and higher mean levels during a period of days increase the risk of stroke. In addition to improving temporal classification of exposure by validating stroke onset time, future research efforts should be directed to careful characterization of stroke subtype because air pollution may variably affect the different pathophysiological pathways. Air pollution exposure and increased risk of stroke may represent a considerable public health problem and regulations have improved air quality in many countries in Europe and the United States, resulting in greater life expectancy.[74] Yet, associations with stroke have been reported at levels in compliance with current standards,[16,68] highlighting the continued importance of effective regulation and monitoring in high-income countries as well as extending efforts to address regulation in low- and middle-income countries where levels of air pollution and prevalence of stroke are on the rise.

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Disclosures

None.

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