

Short-term Changes in Ambient Particulate Matter and Risk of Stroke: A Systematic Review and Meta-analysis

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Background—Stroke is a leading cause of death and long-term disability in the United States. There is a well-documented association between ambient particulate matter air pollution (PM) and cardiovascular disease morbidity and mortality. Given the pathophysiologic mechanisms of these effects, short-term elevations in PM may also increase the risk of ischemic and/or hemorrhagic stroke morbidity and mortality, but the evidence has not been systematically reviewed.

Methods and Results—We provide a comprehensive review of all observational human studies (January 1966 to January 2014) on the association between short-term changes in ambient PM levels and cerebrovascular events. We also performed meta-analyses to evaluate the evidence for an association between each PM size fraction (PM_{2.5}, PM₁₀, PM_{2.5-10}) and each outcome (total cerebrovascular disease, ischemic stroke/transient ischemic attack, hemorrhagic stroke) separately for mortality and hospital admission. We used a random-effects model to estimate the summary percent change in relative risk of the outcome per 10- $\mu\text{g}/\text{m}^3$ increase in PM.

Conclusions—We found that PM_{2.5} and PM₁₀ are associated with a 1.4% (95% CI 0.9% to 1.9%) and 0.5% (95% CI 0.3% to 0.7%) higher total cerebrovascular disease mortality, respectively, with evidence of inconsistent, nonsignificant associations for hospital admission for total cerebrovascular disease or ischemic or hemorrhagic stroke. Current limited evidence does not suggest an association between PM_{2.5-10} and cerebrovascular mortality or morbidity. We discuss the potential sources of variability in results across studies, highlight some observations, and identify gaps in literature and make recommendations for future studies. (*J Am Heart Assoc.* 2014;3:e000983 doi: 10.1161/JAHA.114.000983)

Key Words: air pollution • cerebrovascular disease • meta-analysis • particulate matter • stroke

Stroke is a leading cause of death and long-term disability in the United States.¹ An estimated 795 000 Americans experience a new or recurrent stroke, resulting in >135 000 deaths and >829 000 hospital admissions per year.² Direct and indirect costs for stroke in 2008 are estimated at >\$65 billion in the United States.³ Because of the large proportion of stroke survivors with long-term disability, the true cost due to diminished productivity and reduced quality of life among disabled survivors of stroke and their caregivers is likely even

greater. Therefore, identifying modifiable risk factors for stroke is of significant public health interest.

A large body of literature shows that short-term increases (ie, over hours to days) in ambient particulate matter (PM) are associated with higher risk of cardiovascular morbidity and mortality⁴⁻¹⁰ and triggering of myocardial infarction,^{11,12} arrhythmias,¹³⁻¹⁵ and heart failure exacerbations.¹⁶⁻¹⁸ The effects of short-term exposure are thought to be mediated through a combination of autonomic, hemostatic, inflammatory, and vascular endothelial disturbances with consequent changes in cardiac and vascular function.¹⁹⁻³⁰

Given the putative pathophysiologic mechanisms thought to underlie these effects, it is plausible that transient elevations in PM could similarly increase the risk of stroke. Specifically, acute PM-related changes in blood pressure, vascular function, atherosclerotic plaque stability, and hemostatic balance could increase the risk of atherothrombotic strokes; acute elevations in blood pressure or vascular endothelial activation could trigger small vessel (lacunar) strokes; episodes of atrial fibrillation could lead to increased risk of cardioembolic stroke; and transient elevations in arterial blood pressure could increase the risk of cerebral

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hemorrhage.³¹ However, relatively fewer studies have evaluated this hypothesis and the results have been inconsistent, with some,^{32–35} but not other,^{36–40} studies finding evidence of a positive association.

The evidence linking short-term changes in ambient PM to the risk of stroke morbidity or mortality has not been systematically reviewed. Accordingly, our aim is to provide a comprehensive review and meta-analysis of the association between short-term changes in ambient PM levels and risk of stroke morbidity and mortality.

Methods

Search Strategy and Data Abstraction

We searched PubMed, Web of Knowledge, and Embase databases to identify all observational human studies, published in English from January 1966 to January 2014, evaluating the relationship between short-term changes in ambient PM levels and hospital admissions, emergency department visits, or deaths for stroke or cerebrovascular disease, using the terms “particulate matter” or “particle” in combination with “stroke” or “cerebrovascular disease.” We also retrieved additional studies from the references of these articles to identify studies not captured by the initial search.

The initial study selection was based on the examination of the titles and/or abstracts among all the identified articles. The full texts of all potentially relevant articles were further reviewed. Studies were included in the meta-analysis if they examined the association of fine PM (PM_{2.5}, PM with aerodynamic diameter <2.5 μm), respirable PM (PM₁₀, PM with aerodynamic diameter <10 μm), or coarse PM (PM_{2.5–10},

PM with aerodynamic diameter between 10 and 2.5 μm) 0 to 4 days before the event with total cerebrovascular disease, ischemic stroke, transient ischemic attack, or hemorrhagic stroke. We excluded from review any studies that did not report point estimates or 95% CIs, and those where the outcome reflected a composite end point of stroke and other diseases (eg, *International Classification of Diseases, Ninth Revision* [ICD-9]: 430 to 448 or diagnosis related group [DRG] 14 to 17, 22).

Two reviewers independently abstracted data from each article, including study population (geographic location, age, sex), study design, outcome definition, outcome assessment (death certificate, administrative data, medical records), PM size fractions and average exposure levels, available lags considered, and measures of association. For each study we abstracted results for all outcomes, PM size fractions, and/or lagged exposures reported. All discrepancies regarding study eligibility or details were resolved by consensus between the reviewers.

Statistical Analyses

We separately evaluated the evidence for or against an association between each PM size fraction (PM_{2.5}, PM₁₀, PM_{2.5–10}), each outcome (total cerebrovascular disease, ischemic stroke/transient ischemic attack, hemorrhagic stroke), and separately for mortality and hospital admission, yielding a total of 3×3×2=18 potential separate analyses. For each analysis, we used a DerSimonian and Laird random-effects model to estimate the summary percent change in relative risk of the outcome per 10-μg/m³ increase in PM. When results from both single- and multi-pollutant models were available, we included only results from single-pollutant

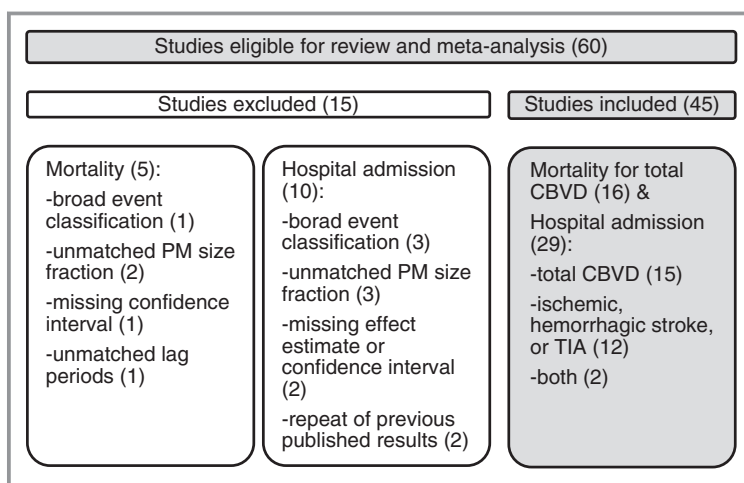


Figure 1. Search strategy and rationale for excluding 15 studies. CBVD indicates cerebrovascular disease; PM, particulate matter; TIA, transient ischemic attack.

Table 1. Description of 29 Studies of Associations Between Short-term Exposure to PM and Hospital Admission for CBVD or Ischemic or Hemorrhagic Stroke

Source	Location	Design	Outcome/Number of Daily Events	Outcome Source	N	Age (y)	Mean Exposure Level (µg/m ³)	Lag (d)	% Change in Observed Effect (95% CI) *
PM_{2.5}									
Dominici et al ³³	204 urban counties, US	T	CBVD (ICD-9: 430 to 438)/5.4	A	11.5 million	75+, 65 to 74, 65+	13.4	0	0.8% (0.3% to 1.3%) to 2.1% (0.6% to 3.6%)
Lisabeth et al ³⁴	Nueces County, TX	T	Ischemic stroke and TIA/2	M	3508	45+	7	0, 1	6.0% (-1.7% to 14.2%)
Delfino et al ³⁵	Southern CA, US	T	CBVD (ICD-9: 430 to 438)/NA	A	10 438	45+	NA	NA	1.9% (0.3% to 3.5%)
Peng et al ³⁶	108 urban counties, US	T	CBVD (ICD-9: 430 to 438)/NA	A	NA	75+, 65 to 74, 65+	13.5	0, 1, 2	NA
O'Donnell et al ⁴⁰	Ontario, Canada	C	Ischemic stroke and TIA (TOAST)/NA	M	9202	All ages	6.9	0-1	-0.7% (-6.2% to 5.1%)
Wellenius et al ⁵⁹	Boston, MA	C	Ischemic stroke/NA	M	1705	21+	NA	0	17.7% (4.2% to 33.0%)
PM₁₀									
Wong et al ⁴⁶	Hong Kong	T	CBVD (ICD-9: 430 to 438)/NA	A	NA	All ages	44.99	2	0.3% (-0.4% to 1.0%)
Wordley et al ⁴⁷	Bringingham, England	T	CBVD (ICD-9: 430 to 436)/6.6	A	NA	All ages	25.6	0	2.1% (0.1% to 4.1%)
Le Tertre et al ⁴⁵	Eight cities, Europe	T	CBVD (ICD-9: 430 to 438)/NA	A	NA	65+	NA	0-1	0% (-0.3% to 0.3%)
Tsai et al ⁴²	Kaohsiung, Taiwan	C	Ischemic stroke (ICD-9: 433 to 435)/8.73	A	12 758	All ages	78.82	0-2	-0.5% (-6.2% to 5.7%), 5.9% (4.3% to 7.4%)
Wellenius et al ⁶³	9 cities, US	C	Ischemic stroke/NA	A	155 503	65+	28.36	0	0.4% (0% to 0.9%)
Henrotin et al ⁵⁸	Dijon, France	C	Hemorrhage/NA	M	19 314	65+	28.36	0	-0.3% (-2.4% to 2.0%)
			Ischemic stroke (TOAST)/NA		762	40+	21.1	0, 1, 2, 3	-4.0% (-11.0% to 3.6%) to 1.1% (-6.6% to 9.4%)
			Hemorrhage (TOAST)/NA		99	40+	21.1	0, 1, 2, 3	-9.9% (-26.9% to 11.1%) to 10% (-9.6% to 33.9%)
Larrieu et al ⁶	Eight cities, France	T	Stroke (ICD-10: 60 to 64, G45 to 46)/34.4	A	11 105 389	All ages	21.0 to 28.9	0-1	0.2% (-1.5% to 1.9%)
			Stroke (ICD-10: 60 to 64, G45 to 46)/24.9		11 105 389	65+	21.0 to 28.9	0-1	0.8% (-0.9% to 2.5%)
Vidale et al ⁶⁰	Como, Italy	T	Ischemic stroke/0.73	M	759	All	NA	0, 1, 2, 3, 4, 5	NA
Andersen et al ⁵⁷	Copenhagen, Denmark	C	Ischemic stroke (SSS)/NA	M	6798	All ages	27.1	0, 1, 2, 3, 4, 0-4	-3.9% (-11.5% to 6.5%) to 8.7% (-0.9% to 19.3%)
			Hemorrhage (SSS)/NA		585	All ages	27.1	0, 1, 2, 3, 4, 0-4	-3.9% (-11.6% to 6.5%) to 13.3% (2.3% to 25.5%)

Continued

Table 1. Continued

Source	Location	Design	Outcome/Number of Daily Events	Outcome Source	N	Age (y)	Mean Exposure Level (µg/m ³)	Lag (d)	% Change in Observed Effect (95% CI) *
Bedata et al ⁶²	Manchester and Liverpool, England	C	Minor stroke+TIA/NA	M	709	All	22.6/20.6	0, 1, 2, 3	-8.8% (-15.6% to 1.3%) to 12.9% (-1.3% to 29.2%)
Corea et al ⁵⁴	Mantua, Italy	C	CBVD/NA	M	781	All	NA	0	NA
			Ischemic stroke/NA		567	All	NA	0	NA
			Hemorrhage/NA		106	All	NA	0	NA
			TIA/NA		108	All	NA	0	NA
Nascimento et al ⁵¹	Sao Jose dos Campos, Brazil	T	Stroke (ICD-10: 60 to 64)/0.8	A	407	All	24.4	0, 1, 2	0.5% (-0.4% to 1.4%) to 1.4% (0.5% to 2.3%)
Oudin et al ⁵⁵	Scania, Sweden	C	Ischemic stroke/6	M	11 267	All	16.3	0-1	NA
Zheng et al ⁵³	Lanzhou, China	T	CBVD (ICD-9: 430 to 438)/6	A	28 243	All	187.07	0, 1, 2, 3, 0-1, 0-2, 0-3	-0.1% (-0.3% to 0.1%)
PM _{2.5-10} +PM _{2.5}									
Halonen et al ³⁹	Heisinki, Finland	T	Stroke (ICD-10: I60 to 61, I63 to 64)/4	A	10 383	65+	9.5	0, 1, 2, 3, 0-4	-2.2% (-5.0% to 0.6%) to 0% (-2.8% to 3.0%)
PM ₁₀ +PM _{2.5}									
Chan et al ³²	Taipei, Taiwan	T	CBVD (ICD-9: 430 to 437)/1.0	A	7341	50+	PM ₁₀ (50.2)	0, 1, 2, 3	0% (-1.2% to 1.3%) to 1.2% (0.4% to 1.9%)
			Stroke (ICD-9: 430 to 434)/3.5		2184	50+	PM _{2.5} (31.5)		-3.6% (-8.9% to 2.1%) to 1.1% (0.3% to 1.9%)
			Ischemic stroke (ICD-9: 433 to 434)/0.7		1494	50+	PM ₁₀ (50.2)		-1.4% (-4.5% to 1.9%) to 0.1% (-3.0% to 3.2%)
							PM _{2.5} (31.5)		-6.8% (-3.6% to 0.5%) to -4.1% (-8.6% to 0.5%)
			Hemorrhage (ICD-9: 430 to 432)/0.3		690	50+	PM ₁₀ (50.2)		-0.6% (-2.6% to 1.4%) to 1.6% (-0.6% to 3.9%)
							PM _{2.5} (31.5)		-2.1% (-5.7% to 1.8%) to 3.0% (-0.6% to 6.6%)
Jalaludin et al ⁴⁹	Sydney, Australia	T	CBVD (ICD-9: 430 to 438)/11.3	A	NA	65+	PM ₁₀ (16.8)	0, 1, 2, 3, 0-1	-2.6% (-4.9% to -0.3%) to -1.6% (-4.0% to 0.8%)
								PM _{2.5} (9.5)	

Continued

Table 1. Continued

Source	Location	Design	Outcome/Number of Daily Events	Outcome Source	N	Age (y)	Mean Exposure Level (µg/m ³)	Lag (d)	% Change in Observed Effect (95% CI) *
Villeneuve et al ³⁷	Edmonton, Canada	C	Ischemic stroke (ICD-9: 434, 436)/NA	A	4850	65+	PM ₁₀ (24.2)	0, 1, 0-2	-1.3% (-4.3% to 1.9%) to 0% (-3.0% to 3.1%)
							PM _{2.5} (8.5)		0% (-7.5 to 8.1%) to 0% (-6.0% to 6.4%)
							PM ₁₀ (24.2)		0.6% (-5.7% to 7.3%) to 1.9% (-4.9% to 9.1%)
			Hemorrhage (ICD-9: 430, 432)/NA		2329	65+	PM _{2.5} (8.5)		-1.6% (-14.3% to 13.0%) to 11.3% (-2.1% to 26.6%)
							PM ₁₀ (24.2)		-3.8% (-8.0% to 0.6%) to -0.6% (-4.2% to 3.1%)
							PM ₁₀ (49.1)	0, 1, 2, 3, 0-3	-0.7% (-1.6% to 0.1%) to 0.9% (0.1% to 1.8%)
Bell et al ⁴⁸	Taipei, Taiwan	T	CBVD (ICD-9: 430 to 437)/3.9	A	11 466	All ages	PM _{2.5} (31.6)		-0.7% (-2.8% to 1.4%) to 0.6% (-0.7% to 1.9%)
							PM _{2.5} (8.5)		-6.3% (-16.2% to 4.8%) to -1.6% (-9.0% to 6.4%)
							PM ₁₀ (31.6)	0-1, 0-2, 0-3, 0-4	-3.9% (-13.0% to 6.3%) to -2.9% (-15.6% to 11.5%)
PM₁₀+PM_{2.5-10}+PM_{2.5}									
Lippmann et al ⁵⁰	Detroit, US	T	Stroke (ICD-9: 431 to 437)/13	A	NA	65+	PM ₁₀ (31)	0, 1	0.9% (-1.1% to 3.0%)
							PM _{2.5} (18)		0.7% (-2.2% to 3.7%)
							PM _{2.5-10} (13)		1.9% (-1.9% to 5.9%)
Anderson et al ³⁶	Midland area, England	T	CBVD (ICD-9: 430 to 438)/NA	M	NA	65+	PM ₁₀ (23.3)	0-1	-1.4% (-3.3% to 0.6%), -0.9% (-3.7% to 2.0%), 6.0% (-1.7% to 14.2%)
							PM _{2.5} (14.5)		
							PM _{2.5-10} (14.6)		
Alessandrini et al ⁵²	Rome, Italy	T	CBVD (ICD-9: 430 to 438)/NA	A	26 557	35+	PM ₁₀ (37)	0	0.5% (-1.2% to 2.1%)
							PM _{2.5} (23.4)		1.1% (-1.8% to 4.2%)
							PM _{2.5-10} (14.6)		-2.2% (-4.4% to 0%)

A indicates administrative records; C, case-crossover; CBVD, cerebrovascular disease; M, medical record review; PM, particulate matter; T, time-series. *Per 10 µg/m³ increase in pollutant levels.

Table 2. Description of 16 Studies of Associations Between Short-term Exposure to PM and Mortality for CBVD Mortality Based on Death Certificate

Source	Location	Design	Outcome	Daily Number of Events	N	Age (y)	Mean Exposure Level (µg/m ³)	Lag (d)	% Change in Observed Effect (95% CI) *
PM_{2.5}									
Franklin et al ⁷¹	27 communities, US	C	CBVD (ICD-9: 430 to 438)	NA	95 687	All ages	15.7	0, 1, 0-1	1.0% (0% to 2.0%)
Yorifuji et al ⁷²	Tokyo, Japan	T	CBVD (ICD-10: 60 to 61, 63, 69.0 to 69.3)	19.7	41 440	All ages	21.6	0, 1, 2, 0-1, 0-2	-0.2% (-1.2% to 0.8%) to 1.3% (0.2% to 2.4%)
			Subarachnoid hemorrhage (ICD-10: 60, 69.3)	2.4					0.9% (-1.9% to 3.8%) to 4.3% (0.4% to 8.4%)
			Intracerebral hemorrhage (ICD-10: 61, 69.1)	5.6					-1.4% (-3.4% to 0.6%) to 1.2% (-0.9% to 3.3%)
			Ischemic stroke (ICD-10: 63, 69.3)	11.7					-0.3% (-1.7% to 1.1%) to 1.4% (0% to 2.8%)
PM₁₀									
Hong et al ⁶⁴	Seoul, Korea	T	CBVD (ICD-10: 60 to 69)	15.3	NA	All ages, 65+, 65-	71.1	0	0% (-1.7% to 1.6%) to 1.0% (-0.3% to 2.2%)
Wong et al ⁶⁹	Hong Kong, China	T	CBVD (ICD-9: 430 to 438)	NA	NA	All ages	9	2	0.7% (-0.2% to 1.6%)
Kan et al ⁶⁵	Shanghai, China	T	CBVD (ICD-9: 430 to 438)	3.3	2426	All ages	97	1	0.8% (0% to 1.6%)
Kim et al ⁶⁶	Seoul, Korea	T	CBVD (ICD-10: 60 to 69)	15	NA	All ages	69.2	0, 1, 2	0.6% (0.1% to 1.0%) to 0.7% (0.2% to 1.2%)
Qian et al ⁶⁷	Wuhan, China	T	CBVD (ICD-9: 430 to 438)	14	20 409	65+	141.8	0, 1, 0-1, 0-4	0.3% (-0.2% to 0.8%) to 0.6% (0.3% to 0.9%)
Kettunen et al ⁴¹	Helsinki, Finland	T	CBVD (ICD-10: 60 to 61, 63 to 64)	NA	3265	65+	16.3	1	-5.9% (-11.9% to 0.5%) to 13.3% (2.3% to 25.5%)
Revich and Shaposhnikov ⁶⁸	Moscow, Russia	T	CBVD (ICD-10: 60 to 69)	68.8	NA	All ages	34	0	0.5% (0% to 0.9%) to 0.7% (0.1% to 1.3%)
Li et al ⁴³	Tianjin, China	T	CBVD (ICD-10: 60 to 69)	41	NA	75+	34	0	
Romieu et al ⁷⁶	Multicities, Latin America	T	CBVD (ICD-9: 60 to 69)	21.5	111 087	65+	95	0-1	-0.6% (-2.0% to 0.8%) to 1.0% (0.3% to 1.7%)
Diaz et al ⁷⁴	Madrid, Spain	C	CBVD (ICD-10: 60 to 69)	4.3	NA	All	29.6 to 78.4	0-3	0.2% (-1.6% to 2.1%) to 2.6% (0.8% to 4.5%)
PM_{2.5-10}									
Perez et al ⁷³	Barcelona, Spain	C	CBVD (ICD-10: 60 to 69)	3	3269	All ages	14	1, 2, 0-1	-0.1% (-1.2% to 1.0%) to 8.7% (1.8% to 16.1%)
Perez et al ⁷⁵	Barcelona, Spain	C	CBVD (ICD-10: 60 to 69)	3.2	1375	All	13.5	1, 2	3.5% (-0.6% to 7.9%)

Continued

Table 2. Continued

Source	Location	Design	Outcome	Daily Number of Events	N	Age (y)	Mean Exposure Level ($\mu\text{g}/\text{m}^3$)	Lag (d)	% Change in Observed Effect (95% CI) *
$\text{PM}_{2.5}+\text{PM}_{10}$									
Faustini et al ⁷⁷	Rome, Italy	C	CBVD (ICD-9: 430 to 438)	3.6, 14.5	15 884, 8 552 785	All	PM_{10} (36.4), $\text{PM}_{2.5}$ (20.2)	0, 1, 2, 3, 4, 5, 0-1, 2-5, 0-5	0.6% (-0.7% to 1.9%) to 1.4% (-0.1% to 2.8%)
$\text{PM}_{2.5}+\text{PM}_{2.5-10}$									
Zanobetti and Schwartz ⁷⁰	112 cities, US	T	CBVD (ICD-10: 60 to 69)	11.7	330 613	All	NA	0-1 0-2	1.0% (0% to 2.0%) 1.8% (0.9% to 2.6%)

C indicates case-crossover; CBVD, cerebrovascular disease; PM, particulate matter; T, time-series.

*Per $10\text{-}\mu\text{g}/\text{m}^3$ increase in pollutant levels.

models. If effect estimates were reported for several different lag periods, we selected the available lag emphasized by the study authors or the lag most commonly evaluated among studies in that category. In addition, when effect estimates were reported for multiple cities, seasons (warm/cold) or temperatures (high/low), we selected an overall effect estimate derived from all cities, seasons, or temperatures. If no overall effect estimate was reported for individual seasons⁴¹ or nonoverlapping temperature ranges,^{42,43} we included effect estimates for each season or temperature range. When effect estimates were reported for multiple age groups (eg, 65+, 45+, or all ages), we selected the age group with the most events.

We assessed publication bias by performing Egger regression test for funnel asymmetry in addition to visual inspection of the funnel plots. If there was evidence of publication bias, we additionally applied trim and fill methods to adjust for publication bias.⁴⁴ We assessed the heterogeneity across studies by computing a *P* value based on the Cochran's Q statistic, although this statistic has low power when the sample size is small. We also calculated the I^2 statistic, the percentage of variation across studies explained by heterogeneity rather than chance. Unlike the Q statistics, the I^2 statistics is not inherently dependent on sample size and is more intuitive.

Sensitivity Analyses

We performed sensitivity analyses pooling effect estimates of the same lag group reported in individual studies or by geographic locations (Europe, East Asia, Latin America, North America, and Australia). We also performed sensitivity analyses excluding studies that defined cerebrovascular disease using a subset of ICD codes (eg, ICD-10: 60 to 61, 63 to 64), as opposed to the broader definition of ICD-10: 60 to 69 in other studies for the same category or excluding studies using administrative records in case ascertainment, as opposed to medical review performed in stroke registry.

All analyses were performed using “metafor” package in R statistical software (R v2.13). A 2-sided *P* value of <0.05 was considered statistically significant.

Results

In our initial literature search, we identified 480 human observational studies potentially eligible for inclusion. After reviewing the titles, abstracts, and full texts, there were 60 studies that were potentially eligible for review and meta-analysis (Figure 1). We excluded 15 of these studies because they did not report point estimates or confidence

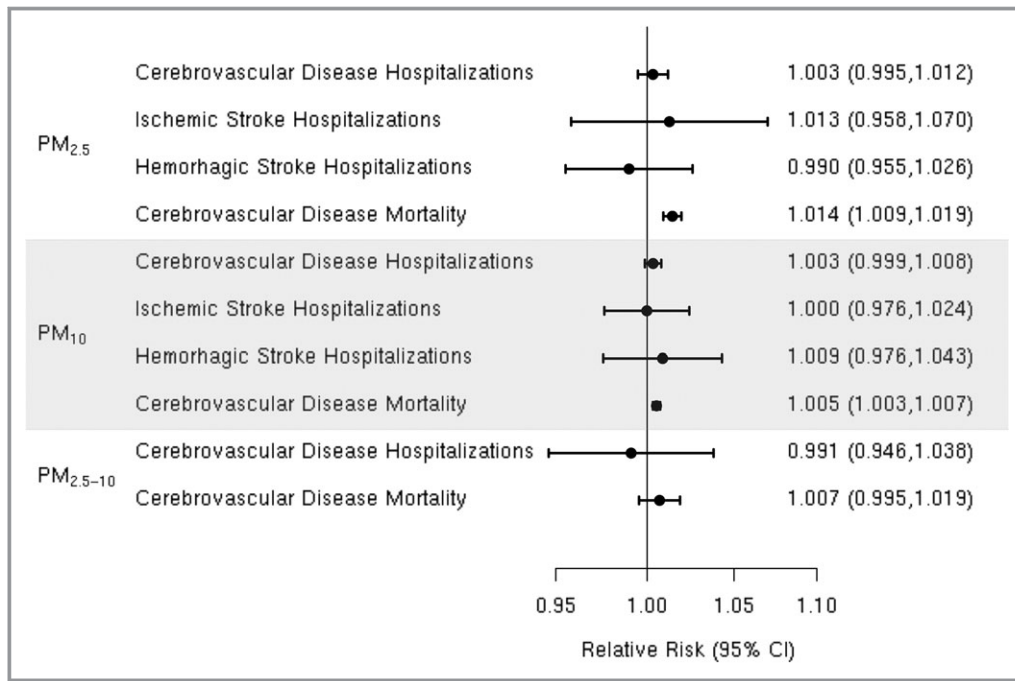


Figure 2. Summary relative risk (95% CI) for the associations between short-term exposure to particulate matter PM_{2.5}, PM₁₀, and PM_{2.5-10} mortality and hospitalization for cerebrovascular disease (CBVD) and hospitalization for ischemic or hemorrhagic stroke.

intervals, defined the outcome very broadly, and or reported results for a PM size fraction other than PM_{2.5}, PM₁₀, or PM_{2.5-10}.

Thus, this review and meta-analysis consisted of 45 studies reporting point estimates and 95% CIs for the association between short-term exposures to PM_{2.5}, PM₁₀, or PM_{2.5-10} and

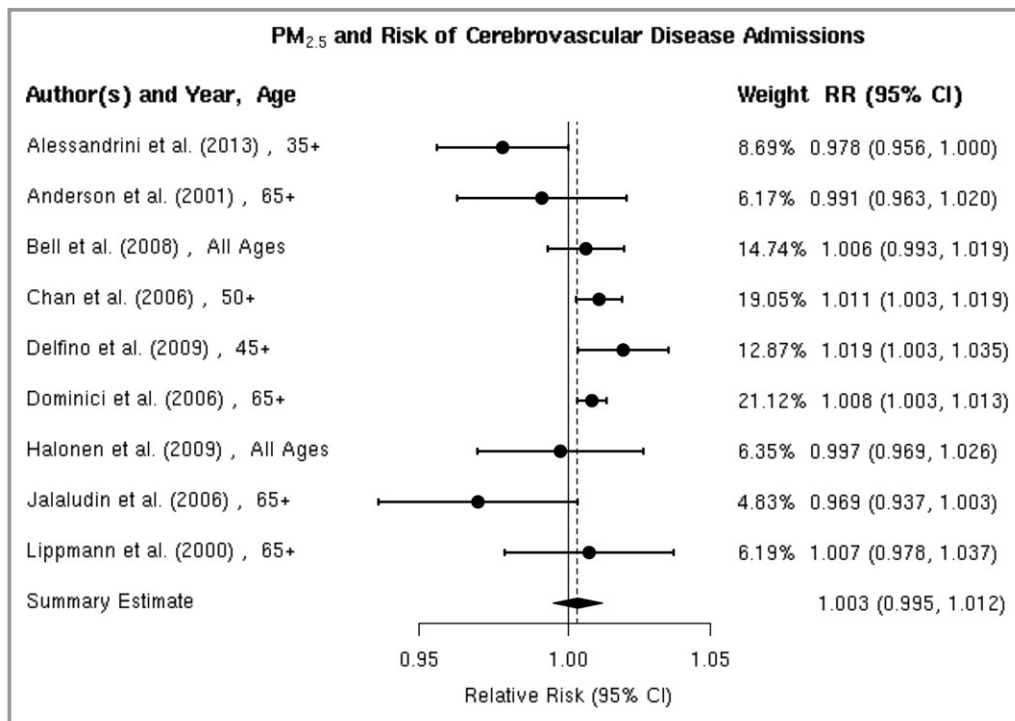


Figure 3. Individual study relative risk (95% CI) for the association between particulate matter PM_{2.5} and hospital admissions for cerebrovascular disease (CBVD).^{32,33,35,36,39,48–50,52}

Table 3. Sensitivity Analyses of Summary Relative Risk (95% CI) for the Associations of Particulate Matter (PM) With Cerebrovascular Disease (CBVD), Ischemic Stroke (IS), or Hemorrhagic Stroke (HS)

Analysis	PM _{2.5}		PM ₁₀	
	Studies Included	Effect Estimate (95% CI)	Studies Included	Effect Estimate (95% CI)
Studies by individual lag subgroups				
Hospital admission (CBVD)				
Lag 0	32,33,39,48–50	1.000 (0.988 to 1.013)	32,47,49,51	1.001 (0.989 to 1.013)
Lag 1	32,48,49	0.997 (0.989 to 1.006)	32,48–51,53	0.999 (0.997 to 1.001)
Lag 2	32,48,49	1.001 (0.990 to 1.011)	32,46,48,49,51,53	1.000 (0.999 to 1.007)
Lag 3	32,48,49	1.002 (0.984 to 1.020)	32,48,49,53	1.002 (0.994 to 1.010)
Lag 0–1	35,36,49	0.999 (0.973 to 1.025)	8,36,45,49,53	0.996 (0.996 to 1.002)
Hospital admission (IS)				
Lag 0	32,34,37,59	1.066 (0.929 to 1.223)	32,37,57,58,62,63	0.994 (0.980 to 1.008)
Lag 1	32,34,37	1.016 (0.890 to 1.160)	32,37,57,58,62	1.007 (0.992 to 1.022)
Lag 2	—	—	32,57,58,62	1.000 (0.973 to 1.027)
Lag 3	—	—	32,57,58,62	1.001 (0.984 to 1.017)
Hospital admission (HS)				
Lag 0	32,37	0.990 (0.955 to 1.026)	32,37,58	0.995 (0.981 to 1.010)
Lag 1	32,37	1.035 (0.934 to 1.147)	32,37,58	0.999 (0.980 to 1.019)
Lag 2	—	—	32,58	0.997 (0.977 to 1.017)
Lag 3	—	—	32,58	1.016 (0.994 to 1.039)
Mortality (CBVD)				
Lag 0	41,71,72	1.011 (1.002 to 1.019)	41,64,66–68	1.006 (1.004 to 1.009)
Lag 1	41,71,72	1.006 (0.995 to 1.017)	41,65–67	1.007 (1.003 to 1.011)
Lag 2	—	—	41,66,69,72	1.004 (1.000 to 1.008)
Lag 0–1	70–72	1.012 (1.004 to 1.019)	—	—
Excluding studies using a subset of ICD-10 codes to define CBVD				
Hospital admission	32,36,45–50	1.002 (0.995 to 1.009)	32,33,35,36,48–50	1.006 (0.994 to 1.017)
Mortality	43,64–69	1.004 (1.000 to 1.008)	71,72	1.015 (1.007 to 1.022)
Excluding studies using administrative data for case ascertainment				
Hospital admission (IS)	57,58	0.994 (0.967 to 1.022)	34,40,59,62	0.972 (0.927 to 1.018)
Studies by geographic locations				
Hospital admission (CBVD)				
Europe	39,52,57	0.987 (0.972 to 1.002)	8,45,47,52,57	1.003 (0.995 to 1.011)
East Asia	32,48	1.009 (1.003 to 1.016)	32,46,48,53	1.002 (0.996 to 1.009)
Latin America	—	—	51	1.014 (1.005 to 1.023)
North America	33,35,50	1.010 (1.003 to 1.017)	50	1.009 (0.989 to 1.008)
Australia	49	0.969 (0.937 to 1.003)	49	0.984 (0.960 to 1.008)
Hospital admission (IS)				
Europe	61	0.971 (0.846 to 1.115)	52,57,58,62	0.977 (0.931 to 1.025)
East Asia	32	0.932 (0.864 to 1.005)	32,42	1.017 (0.969 to 1.067)
Latin America	—	—	—	—
North America	34,37,40,59	1.039 (0.977 to 1.104)	37,63	1.003 (0.994 to 1.012)
Australia	—	—	—	—

Continued

Table 3. Continued

Analysis	PM _{2.5}		PM ₁₀	
	Studies Included	Effect Estimate (95% CI)	Studies Included	Effect Estimate (95% CI)
Hospital admission (HS)				
Europe	—	—	58	0.901 (0.731 to 1.111)
East Asia	32	0.990 (0.954 to 1.028)	32,42	1.016 (0.960 to 1.075)
Latin America	—	—	—	—
North America	37	0.984 (0.857 to 1.130)	37,63	0.998 (0.978 to 1.019)
Australia	—	—	—	—
Mortality (CBVD)				
Europe	41,77	1.014 (1.000 to 1.028)	41,68,74,77	1.005 (1.001 to 1.009)
East Asia	72	1.013 (1.002 to 1.024)	43,64–67,69	1.005 (1.003 to 1.008)
Latin America	—	—	76	1.004 (1.003 to 1.005)
North America	70,71	1.015 (1.007 to 1.022)	—	—
Australia	—	—	—	—

hospitalization or mortality for total cerebrovascular diseases, ischemic stroke, or hemorrhagic stroke (Figure 1). Of these studies, 17 studies (Table 1) reported on hospital admissions

for total cerebrovascular disease,^{8,32,33,35,36,39,45–56} 14 studies (Table 1) reported on hospital admissions for ischemic or hemorrhagic stroke,^{32,34,37,40,42,54,57–63} and 16 studies (Table 2) reported on mortality for total cerebrovascular disease.^{41,43,64–77}

Studies were conducted in Europe (n=20), East Asia (n=12), North America (n=11), Australia (n=1), and Latin America (n=1), using either time-series (n=29) or case-crossover (n=16) study designs. Mean PM levels reported in the studies varied widely for PM_{2.5} (range 5.0 to 31.6 μg/m³), PM₁₀ (6.9 to 187.1 μg/m³), and PM_{2.5-10} (7.5 to 14.6 μg/m³). In mortality studies, mortality was ascertained based on death certificates from local, regional, and national public health agencies. Hospital admission events were ascertained based on administrative/billing data, emergency department logs, or review of medical records or from existing stroke registries. The lag periods considered included single-day lags (lag 0, 1, 2, 3, 4) and cumulative lags up to 4 days (ie, 1- to 4-day moving average) before the event.

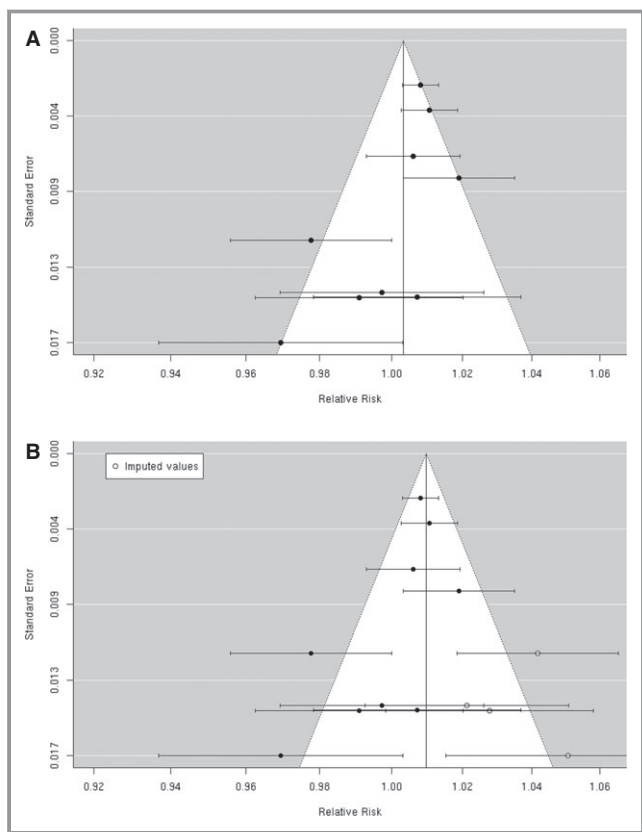


Figure 4. A, Funnel plot of individual study relative risk (95% CI) for the association between particulate matter PM_{2.5} and hospital admissions for cerebrovascular disease (CBVD); (B) after applying trim and fill methods to adjust for publication bias.

PM_{2.5} and Hospital Admission

Total cerebrovascular disease

A random-effects summary estimate of the association between PM_{2.5} and hospital admission for total cerebrovascular disease suggests a nonsignificant 0.3% (95% CI –0.5% to 1.2%) higher risk of hospitalization for total cerebrovascular disease per 10-μg/m³ increase in PM_{2.5} (Figure 2). These studies were significantly heterogeneous (I²=64.16%, P=0.04). The largest study was Dominici et al,³³ which evaluated this association among 11.5 million Medicare beneficiaries aged ≥65 years residing in 204 US urban

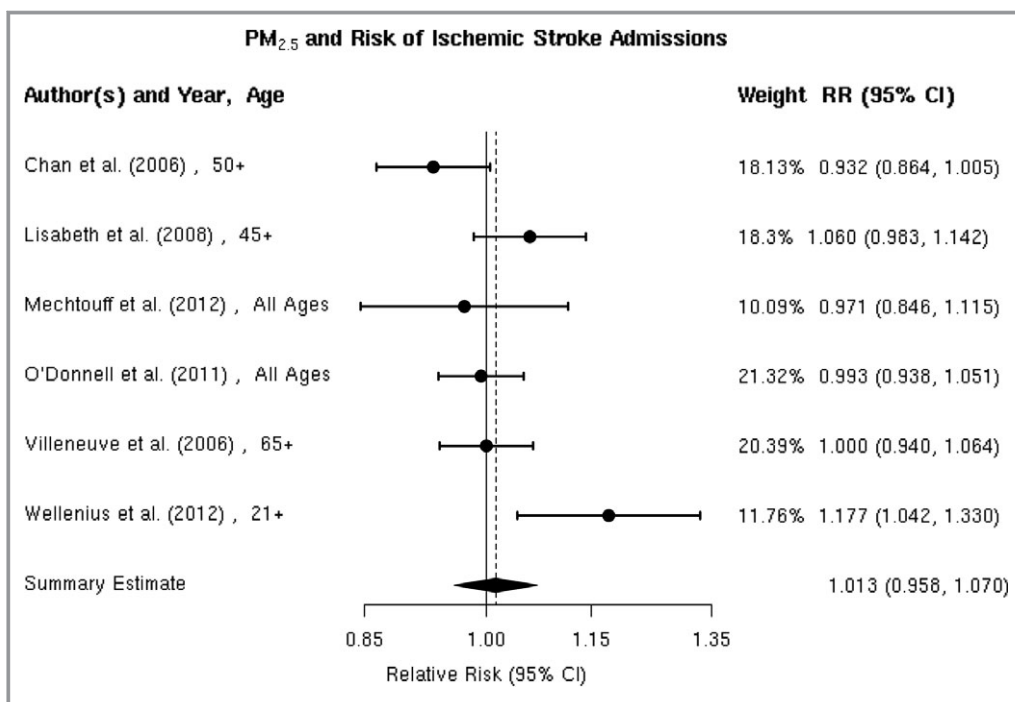


Figure 5. Individual study relative risk (95% CI) for the association between particulate matter PM_{2.5} and hospital admissions for ischemic stroke.^{32,34,37,40,59,61}

counties. The authors found a statistically significant 0.8% (95% CI 0.3% to 1.3%) higher risk of hospital admission for total cerebrovascular disease per 10-μg/m³ increase in PM_{2.5}. An additional 8 studies evaluated this association in diverse populations, with 4 reporting a positive association and 4 reporting a negative association between PM_{2.5} and risk of hospitalization for total cerebrovascular disease (Figure 3). We found that the association between PM_{2.5} and hospital admission for total cerebrovascular disease varied by geographic locations, with East Asia and North America showing

statistically significant positive associations (Table 3). Sensitivity analyses pooling point estimates by individual lag subgroups (lag 0, lag 1, lag 2, lag 3 and lag 0 to lag 1) did not materially change the results (Table 3). The results did not materially change when excluding studies that defined hospital admissions using ICD-10: 60 to 61, 63 to 64³⁹ as opposed to ICD-10: 60 to 69 as used in all other studies (Table 3). We observed evidence suggestive of publication bias (Egger regression test, *P*=0.02; Figure 4A). When we applied trim and fill methods (estimated 4 studies missing) to adjust for publication bias, such evidence disappeared (Egger regression test, *P*=0.95; Figure 4B), but these studies remained heterogeneous (*I*²=79.55%, *P*=0.001).

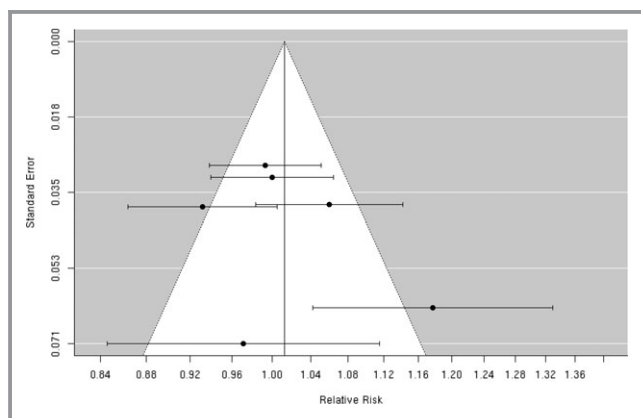


Figure 6. Funnel plot of individual study relative risk (95% CI) for the association between particulate matter PM_{2.5} and hospital admissions for ischemic stroke.

Ischemic stroke

We reviewed 6 studies evaluating the association between PM_{2.5} and risk of ischemic stroke hospitalization.^{32,34,37,40,59,61} Chan et al and Villeneuve et al assessed ischemic stroke based on administrative records. Lisabeth et al used population-based stroke surveillance data from the BASIC (Brain Attack Surveillance in Corpus Christi) Project. O'Donnell et al used data from a stroke registry in Ontario, Canada, and Wellenius et al, and Mechtouff et al conducted a detailed medical record review of patients hospitalized with acute ischemic stroke. Lisabeth et al and Wellenius et al reported positive associations between PM_{2.5} and ischemic stroke hospitalization, while the remaining studies found either no

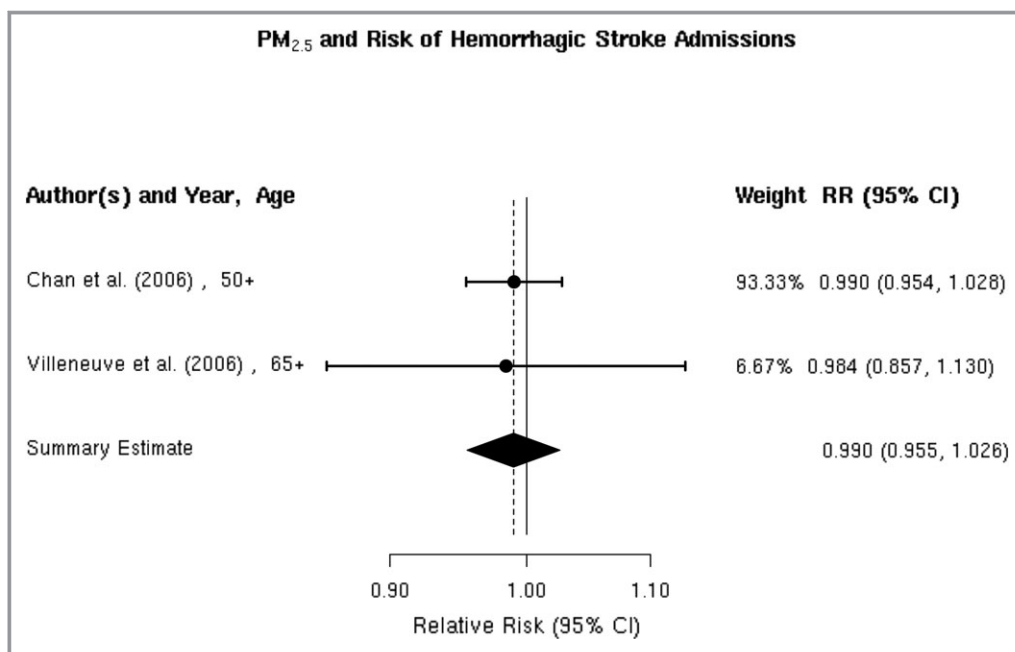


Figure 7. Individual study relative risk (95% CI) for the association between particulate matter PM_{2.5} and hospital admissions for hemorrhagic stroke.^{32,37}

association³⁷ or a negative association^{32,40,61} (Figure 5). A random-effects summary estimate suggests a nonsignificant 1.3% (95% CI –4.2% to 7.0%) higher risk of ischemic stroke hospitalization per 10-μg/m³ increase in PM_{2.5} (Figure 2). These studies were significantly heterogeneous (*I*²=64.41%, *P*=0.03), and there was no evidence of publication bias (Egger regression test, *P*=0.39; Figure 6). Results were qualitatively similar in sensitivity analyses by individual lag subgroups or when excluding studies using administrative records in case ascertainment (Table 3). The associations did not vary by geographic locations (Table 3).

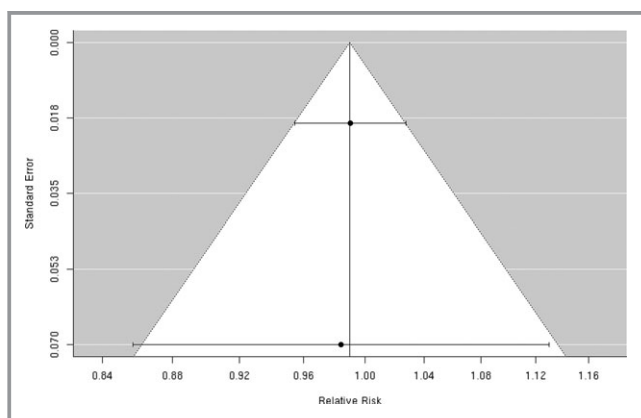


Figure 8. Funnel plot of individual study relative risk (95% CI) for the association between particulate matter PM_{2.5} and hospital admissions for hemorrhagic stroke.

Hemorrhagic stroke

We found only 2 studies that evaluated the association between PM_{2.5} and the risk of hospitalization for hemorrhagic stroke,^{32,37} both of which reported no evidence of an association (Figure 7). The random-effects summary estimate suggests a nonsignificant –1.0% (95% CI –4.5% to 2.6%) lower risk of hospitalization for hemorrhagic stroke per 10-μg/m³ increase in PM_{2.5} (Figure 2). There was no evidence of heterogeneity across studies (*I*²=0, *P*=0.93), and the Egger regression test statistic for funnel plot symmetry could not be computed due to the small sample size (Figure 8). Sensitivity analyses by individual lag subgroups or geographic locations did not materially change the results (Table 3).

PM_{2.5} and Mortality

We reviewed 5 studies^{41,70–72,77} examining the association between PM_{2.5} and cerebrovascular mortality, all of which reported a positive association (Figure 9). The random-effects summary estimate suggests a statistically significant 1.4% (95% CI 0.9% to 1.9%) higher risk of cerebrovascular mortality per 10-μg/m³ increase in PM_{2.5} (Figure 2). These studies were homogeneous (*I*²=6.78%, *P*=0.28), and we found no evidence suggestive of publication bias (Egger regression test *P*=0.43; Figure 10). Results did not materially change in sensitivity analyses pooling point estimates by individual lag subgroups or excluding 2 studies that defined total cerebro-

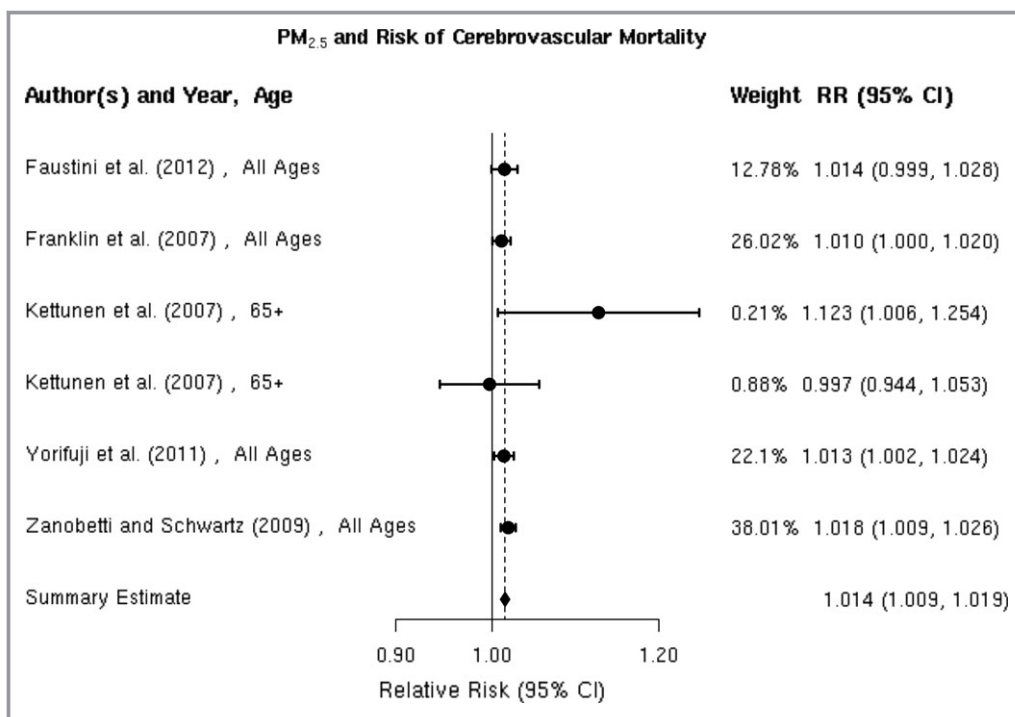


Figure 9. Individual study relative risk (95% CI) for the association between particulate matter PM_{2.5} and mortality for cerebrovascular disease (CBVD).^{41,70–72,77}

vascular disease death by ICD-10: 60 to 61, 63 to 64⁴¹ and ICD-10: 61, 63, and 69⁷², as opposed to ICD-10: 60 to 69 used in other studies (Table 3). The associations did not vary by geographic locations (Table 3).

PM₁₀ and Hospital Admission

Total cerebrovascular disease

We reviewed 12 studies^{8,32,36,45–53} of the association between PM₁₀ and hospitalization for the composite end

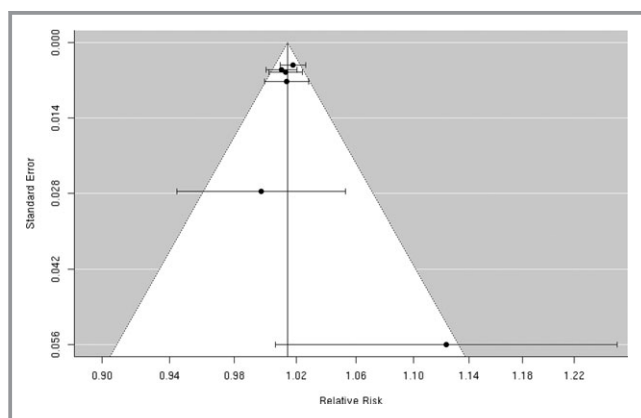


Figure 10. Funnel plot of individual study relative risk (95% CI) for the association between particulate matter PM_{2.5} and mortality for cerebrovascular disease (CBVD).

point of all cerebrovascular disease (Figure 11). Of these, 3 studies including Chan et al, Nascimento et al, and Wordley et al^{32,47,51} reported a positive, statistically significant association between PM₁₀ and cerebrovascular hospitalization. Five additional studies^{8,45,46,50,52} reported positive associations that did not reach statistical significance and the remaining 4 studies^{36,48,49,53} found no evidence of a positive association. The random-effects summary estimate suggests a nonsignificant 0.3% (95% CI –0.1% to 0.8%) higher risk of cerebrovascular hospitalizations per 10-μg/m³ increase in PM₁₀ (Figure 2). These studies were heterogeneous (I²=76.54%, P=0.001) with no evidence of publication bias (Egger regression test, P=0.94; Figure 12). The results did not materially change in sensitivity analyses pooling effect estimates by individual lag subgroups or when excluding hospital admission cases defined by ICD-10: 61 to 64⁸ (Table 3). The associations were largely insensitive to stratification by geographic locations with the exception of Latin America, where we observed a greater increase in risk compared with other locations (Table 3).

Ischemic stroke

We reviewed 8 studies^{32,37,42,57,58,61–63} evaluating the association between PM₁₀ and risk of hospitalization for ischemic stroke (Figure 13). In Taiwan, Tsai et al found a positive, statistically significant association but only on days with a mean temperature ≥20°C. Wellenius et al found a statistically

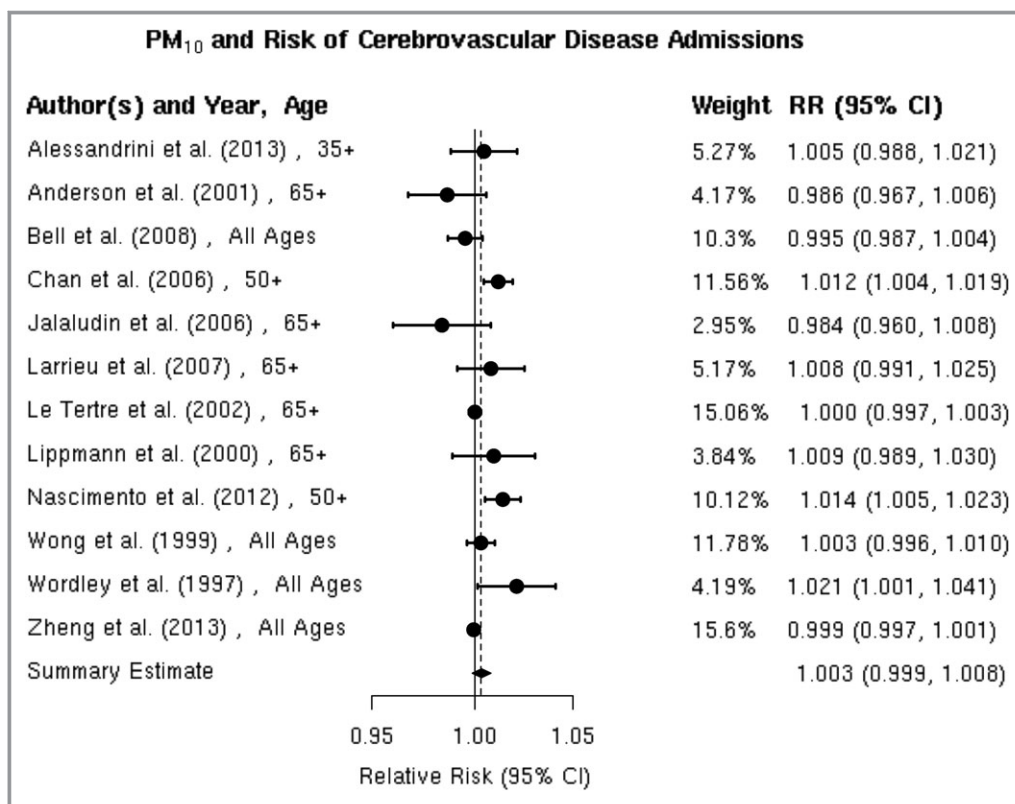


Figure 11. Individual study relative risk (95% CI) for the association between particulate matter PM₁₀ and hospital admissions for cerebrovascular disease (CBVD).^{8,32,36,45–53}

significant, positive association between PM₁₀ and ischemic stroke hospitalization among Medicare beneficiaries aged ≥65 years residing in 6 US cities. The remaining studies failed to find evidence of a statistically significant, positive association between PM₁₀ and ischemic stroke hospitalization. Using data from a Danish national stroke registry, Andersen et al found positive, but not statistically significant, associations, with a somewhat stronger and sometimes statistically signif-

icant association among patients presenting without comorbid atrial fibrillation. Henrotin et al also found a positive, but not statistically significant, association between PM₁₀ levels and ischemic stroke hospitalization in the context of the Dijon Stroke Registry. The random-effects summary estimate is null (0.0% [95% CI –2.4% to 2.4%]) and currently does not support the presence of an overall association between PM₁₀ and ischemic stroke hospitalization (Figure 2). These studies were heterogeneous ($I^2=86.53\%$, $P<0.0001$), and sensitivity analyses pooling estimates by individual lag subgroups did not materially change the results (Table 3). The results were largely insensitive to stratification by geographic locations with the exception of East Asia, where we observed a greater increase in relative risk compared with other locations (Table 3). There is evidence suggestive of publication bias (Egger regression test, $P=0.03$; Figure 14A). When we applied trim and fill methods to adjust for publication bias (estimated 4 missing studies), we no longer observed evidence of publication bias (Egger regression test, $P=0.85$; Figure 14B), but these studies remained heterogeneous ($I^2=86.74\%$, $P<0.0001$).

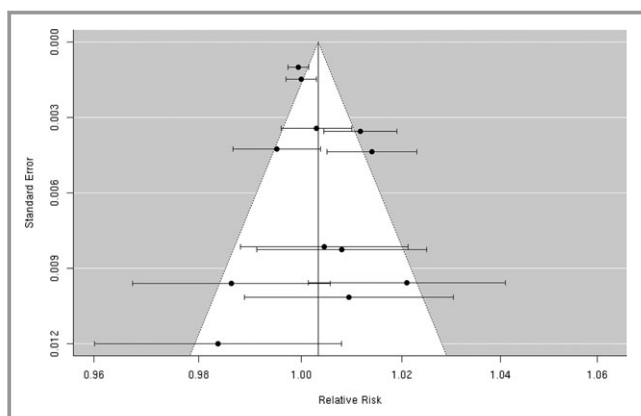


Figure 12. Funnel plot of individual study relative risk (95% CI) for the association between particulate matter PM₁₀ and hospital admissions for cerebrovascular disease (CBVD).

Hemorrhagic stroke

Most,^{32,37,42,58,63} but not all,⁴² studies failed to find any association between short-term exposure to PM₁₀ and

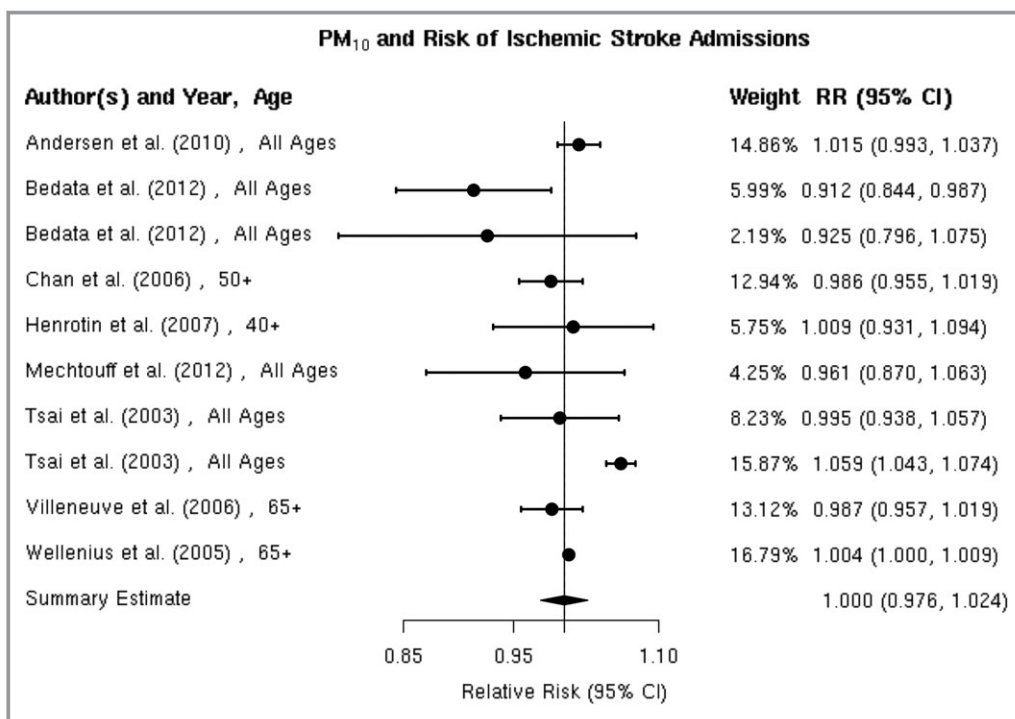


Figure 13. Individual study relative risk (95% CI) for the association between PM₁₀ and hospital admissions for ischemic stroke.^{32,37,42,57,58,61–63}

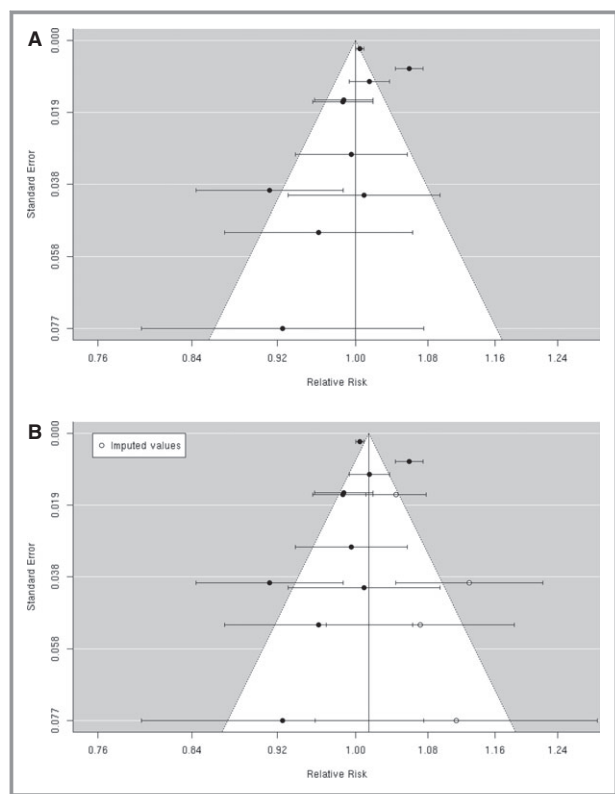


Figure 14. A, Funnel plot of individual study relative risk (95% CI) for the association between particulate matter PM₁₀ and hospital admissions for ischemic stroke; (B) After applying trim and fill methods to adjust for publication bias.

hospital admission for hemorrhagic stroke (Figure 15). The notable exception was the study by Tsai et al in Taiwan, which found a positive and statistically significant association but only on days with a mean temperature $\geq 20^{\circ}\text{C}$. The random-effects summary estimate suggests a 0.9% (95% CI -2.4% to 4.3%) higher risk of hemorrhagic stroke hospital admission per $10\text{-}\mu\text{g}/\text{m}^3$ in PM₁₀ (Figure 2). The pooled studies exhibited considerable heterogeneity ($I^2=78.84\%$, $P=0.0001$). Sensitivity analyses by individual lag subgroups or geographic locations did not materially change the results (Table 3). We did not observe publication bias (Egger regression test, $P=0.22$; Figure 16).

PM₁₀ and Mortality

All^{4,14,3,64–68,74,76,77} studies reported positive associations between PM₁₀ and total cerebrovascular mortality (Figure 17). For example, Hong et al reported a statistically significant 0.7% (0.6% to 0.8%) higher risk of cerebrovascular mortality per $10\text{-}\mu\text{g}/\text{m}^3$ increase in PM₁₀ level in Seoul, Korea. Romieu et al reported a statistically significant 0.4% (95% CI 0.3% to 0.5%) higher risk of cerebrovascular mortality per $10\text{-}\mu\text{g}/\text{m}^3$ increase in PM₁₀ level in 9 Latin American cities, and Li et al found a statistically significant 0.7% (95% CI 0.0% to 1.3%) higher risk of cerebrovascular mortality in Tianjin, China, although only on days with a mean temperature $\geq 20^{\circ}\text{C}$. Similarly, in Helsinki, Finland, Kettunen et al

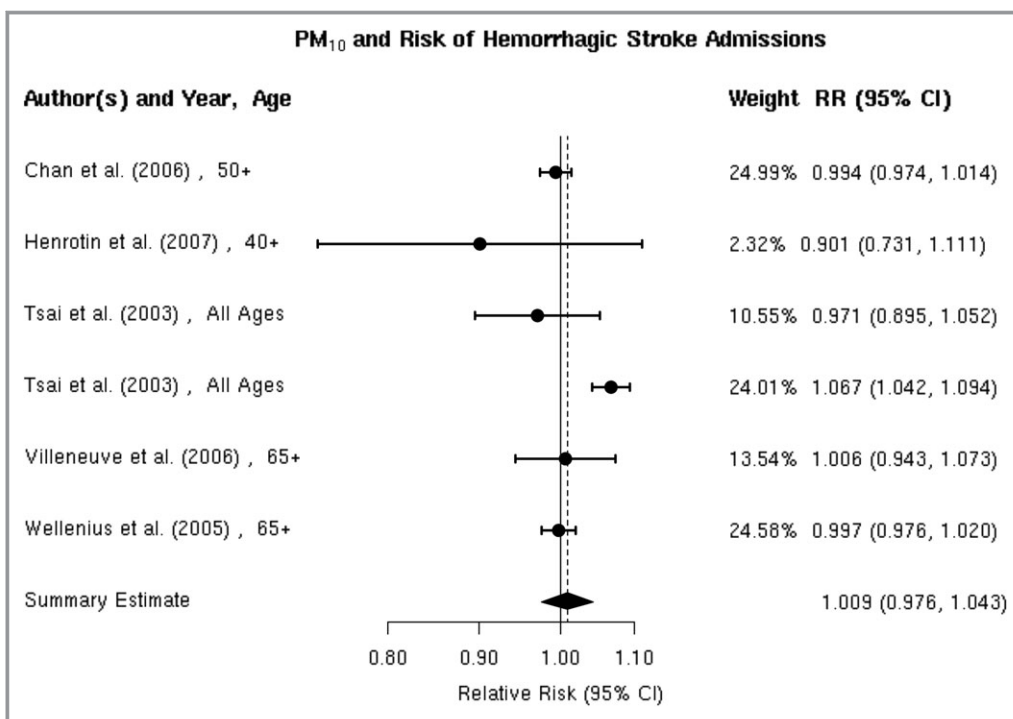


Figure 15. Individual study relative risk (95% CI) for the association between particulate matter PM₁₀ and hospital admissions for hemorrhagic stroke.^{32,37,42,58,63}

reported a positive and statistically significant association between PM₁₀ and cerebrovascular mortality only in the warm season (May to October). The random-effects summary of 0.5% (95% CI 0.3% to 0.7%) higher risk of cerebrovascular mortality per 10-μg/m³ increase in PM₁₀ supports the presence of a statistically significant association between PM₁₀ and cerebrovascular mortality (Figure 2). These studies were heterogeneous (*I*²=84.25%, *P*<0.0001), and there is evidence suggestive of publication bias (Egger regression test, *P*=0.05; Figure 18A). When we applied trim and fill

methods to adjust for publication bias (estimated 3 missing studies), we no longer observed publication bias (Egger regression test, *P*=0.99; Figure 18B), but these studies remained heterogeneous (*I*²=40.72%, *P*=0.01). The results did not materially change in sensitivity analyses pooling point estimates by individual lag subgroups or excluding 2 studies that defined total cerebrovascular mortality using ICD-10: 60 to 61, 63 to 64⁴¹ or ICD-10: 61, 63, and 69⁷² (Table 3). The associations did not vary by geographic locations (Table 3).

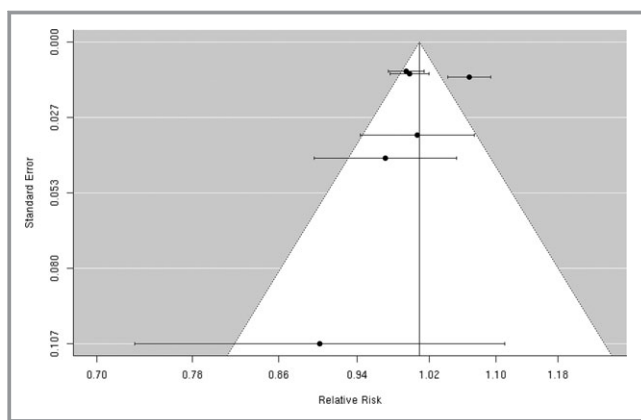


Figure 16. Funnel plot of individual study relative risk (95% CI) for the association between particulate matter PM₁₀ and hospital admissions for hemorrhagic stroke.

PM_{2.5-10} and Hospital Admission

Total cerebrovascular disease

We found 4 studies^{36,39,50,52} that examined the association between PM_{2.5-10} and hospital admission for cerebrovascular diseases, and the results were heterogeneous (Figure 19). Two of these studies^{36,52} reported a positive, but not statistically significant, association, while the other 2 studies^{39,50} reported a negative but not statistically significant association. We did not include the study by Peng et al, because they did not report the association between PM_{2.5-10} and cerebrovascular hospital admission. The random-effects summary of -0.9% (95% CI -5.4% to 3.8%) excess relative risk suggests that short-term exposure to PM_{2.5-10} is not associated with hospital admissions for total

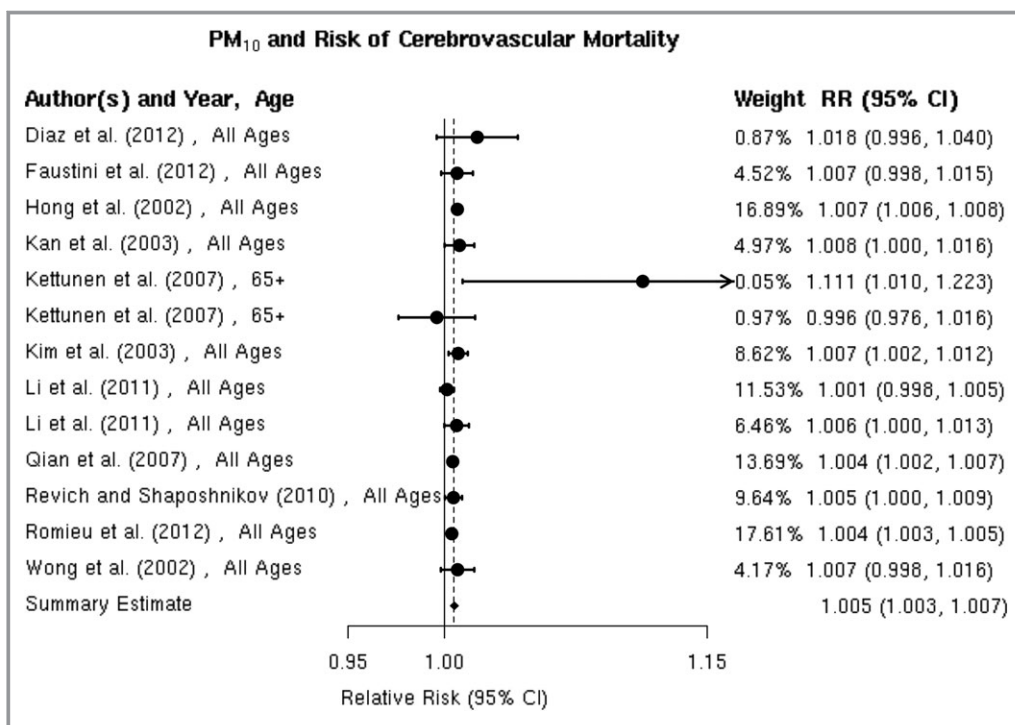


Figure 17. Individual study relative risk (95% CI) for the association between particulate matter PM₁₀ and mortality for cerebrovascular disease (CBVD).^{41,43,64–69,74,76,77}

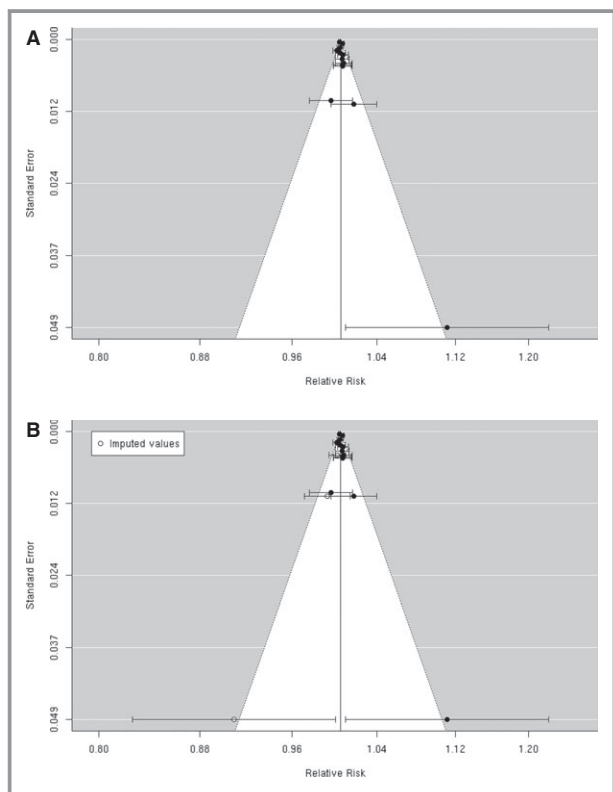


Figure 18. A, Funnel plot of individual study relative risk (95% CI) for the association between particulate matter PM₁₀ and mortality for cerebrovascular disease (CBVD); (B) After applying trim and fill methods to adjust for publication bias.

cerebrovascular disease (Figure 2). We observed no publication bias (Egger regression test, $P=0.74$; Figure 20), and these studies were heterogeneous ($I^2=80.12\%$, $P=0.01$). Sensitivity analyses by geographical locations or excluding hospital admissions defined by ICD-10: 60 to 61, 63 to 64³⁹ did not materially change the results (pooled relative risk 0.996 [95% CI 0.926 to 1.071]; data not shown in Table 3).

PM_{2.5-10} and Mortality

Three^{70,73,75} studies reported effect estimates for the association between short-term exposure to PM_{2.5-10} and total cerebrovascular disease mortality (Figure 21). In 47 US cities, Zanobetti and Schwartz 2009 found a 0.8% (95% CI 0.1% to 1.6%) higher risk of total cerebrovascular disease mortality per 10- $\mu\text{g}/\text{m}^3$ increase in PM_{2.5-10} over 2 days before deaths. The summary estimate of 0.7% (95% CI -0.5% to 1.9%) excess relative risk does not yet support the presence of a statistically significant association between PM_{2.5-10} and cerebrovascular mortality (Figure 2). These studies were not heterogeneous ($I^2=46.83\%$, $P=0.12$), and we did not observe publication bias (Egger regression test, $P=0.21$; Figure 22). Sensitivity analysis limited to the European studies yielded a summary estimate of 1.1% (95% CI -2.2% to 4.5%) higher risk of total cerebrovascular disease per 10- $\mu\text{g}/\text{m}^3$ increase in PM_{2.5-10}.

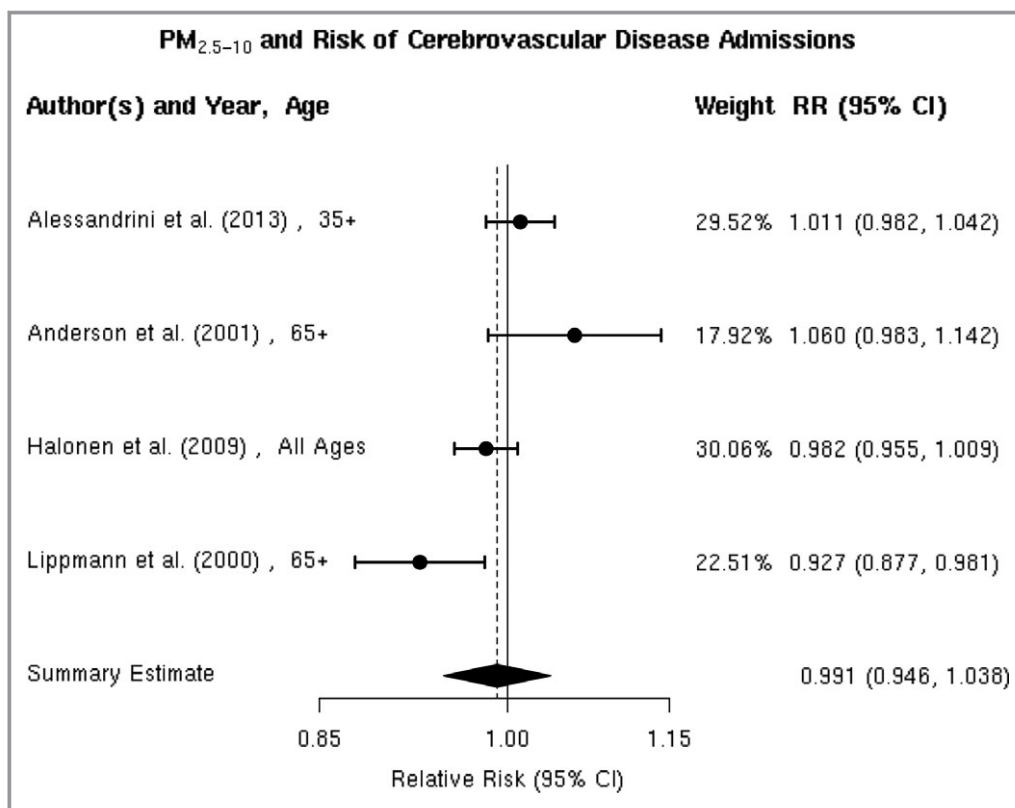


Figure 19. Individual study relative risk (95% CI) for the association between particulate matter $PM_{2.5-10}$ and hospital admissions for cerebrovascular disease (CBVD).^{36,39,50,52}

Discussion

Findings of key epidemiologic studies and the meta-analyses presented here suggest that particulate matter air pollution is associated with a statistically significant higher risk of cerebrovascular disease mortality, with weaker evidence for the presence of associations with different types of strokes

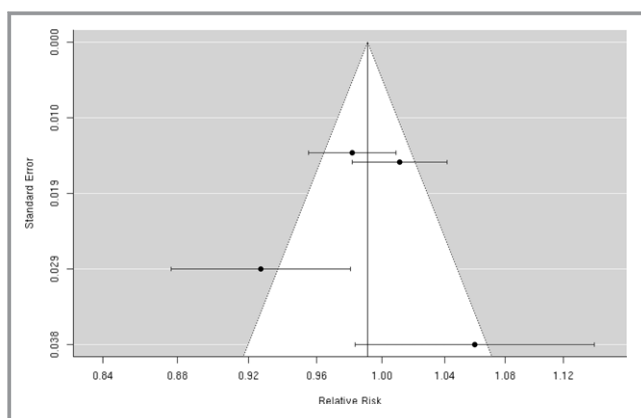


Figure 20. Funnel plot of individual study relative risk (95% CI) for the association between particulate matter $PM_{2.5-10}$ and hospital admissions for cerebrovascular disease (CBVD).

such as ischemic and hemorrhagic strokes. Specifically, we found a summary estimate of 1.4% (95% CI 0.9% to 1.9%) higher risk of cerebrovascular mortality per $10\text{-}\mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$. Several studies suggest that hospital admission for total cerebrovascular disease or ischemic stroke may be associated with $PM_{2.5}$, but the weight of the published evidence does not yet show a positive and statistically significant association, as suggested by the summary estimates of 0.3% (95% CI -0.5% to 1.2%) and 1.3% (95% CI -4.2% to 7.0%) excess relative risk, respectively. Only 2 studies have specifically considered hemorrhagic stroke, but these studies do not suggest that risk of hemorrhagic stroke is associated with $PM_{2.5}$ levels.

Results for PM_{10} were similar to those for $PM_{2.5}$. Specifically, we found a summary estimate of 0.5% (95% CI 0.3% to 0.7%) higher risk of cerebrovascular mortality per $10\text{-}\mu\text{g}/\text{m}^3$ increase in PM_{10} . The evidence for the presence of an association between PM_{10} and hospital admission for total cerebrovascular disease or ischemic stroke remains inconsistent, as suggested by the summary estimates of 0.3% (95% CI -0.1% to 0.8%) and 0.0% (95% CI -2.4% to 2.4%) excess risk per $10\text{-}\mu\text{g}/\text{m}^3$ increase in PM_{10} , respectively. Additional large studies will be needed to convincingly demonstrate the presence or absence of these associations in future meta-

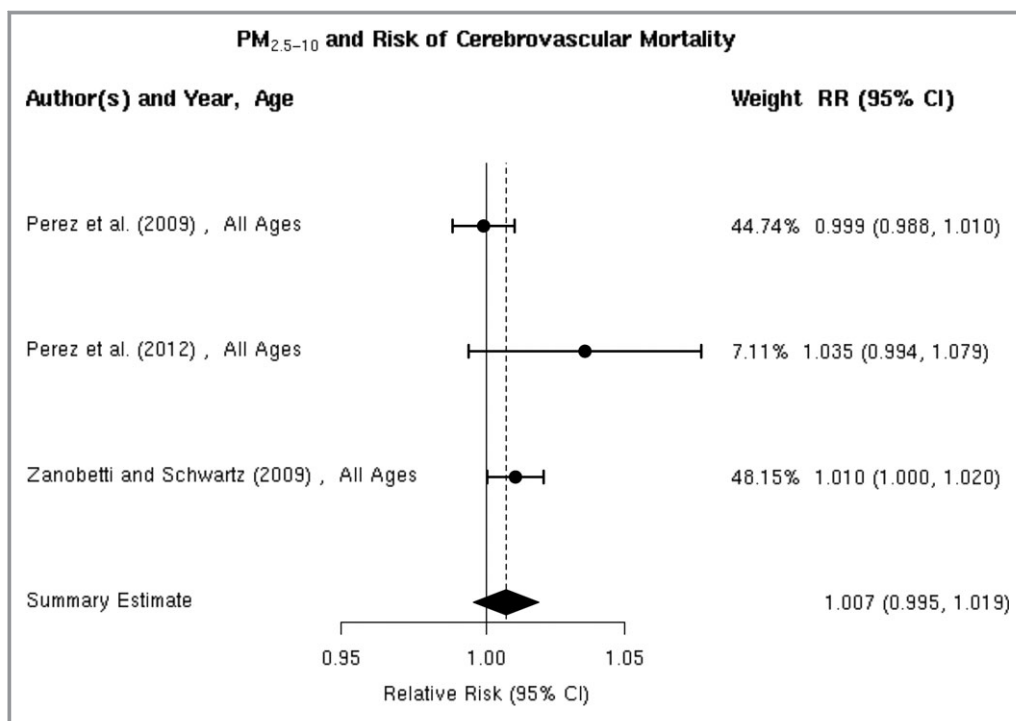


Figure 21. Individual study relative risk (95% CI) for the association between particulate matter $PM_{2.5-10}$ and mortality for cerebrovascular disease (CBVD).^{70,73,75}

analyses. The few available studies do not clearly suggest an association between PM_{10} and hospital admissions for hemorrhagic stroke.

Substantially fewer studies have considered the association between $PM_{2.5-10}$ and cerebrovascular mortality or morbidity and the evidence currently available does not indicate the presence of such associations, as suggested by summary estimates of 0.9% (95% CI 5.4% to 3.8%) and 0.7% (95% CI -0.5% to 1.9%) excess risk per $10\text{-}\mu\text{g}/\text{m}^3$ increase in $PM_{2.5-10}$, respectively. We found no studies relating $PM_{2.5-10}$

specifically with risk of ischemic stroke or hemorrhagic stroke hospitalization.

The meta-analytic summary estimates often masked considerable variability among studies, even where we did not find statistically significant heterogeneity. There are likely multiple sources that may explain this underlying variability in results across studies. First, ambient particulate matter is a heterogeneous mixture of various compounds (eg, organic and elemental carbon, metals, sulfates, nitrates, and microorganisms) from multiple sources (eg, traffic, manufacturing, power generation). The role of each component or source—individually or in conjunction—as an acute trigger of cardiovascular events including stroke remains unclear.⁷⁸

Second, exposure misclassification may bias effect estimate toward the null⁷⁹ and may arise from different strategies used to assess PM exposure at the community level and the type of air pollution monitoring network accessible to researchers. For example, O'Donnell et al estimated city-specific associations between ischemic stroke hospital admission and $PM_{2.5}$ using measurements from 19 monitors in cities of various sizes in Ontario, Canada. They found a -0.7% (95% CI -6.3% to 5.1%) decrease in hospital admission for ischemic stroke when including monitoring data from all cities. After only including cases with monitoring data from the 4 largest cities, where >1 single monitor in each city was used, they found a 1.1% (95% CI -4.0% to 6.5%) higher risk of hospital admission for ischemic

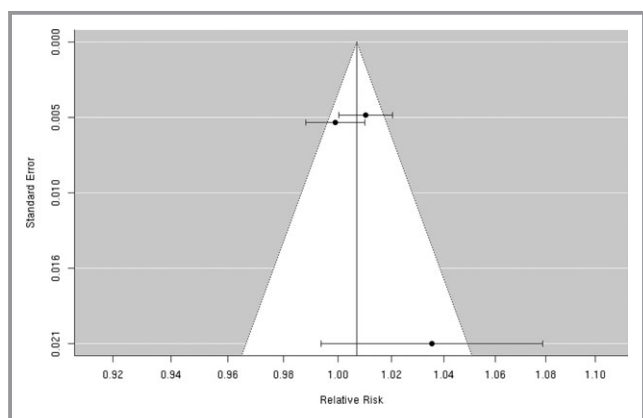


Figure 22. Funnel plot of individual study relative risk (95% CI) for the association between particulate matter $PM_{2.5-10}$ and mortality for cerebrovascular disease (CBVD).

stroke, perhaps due to reduction of exposure misclassification. In addition, delay times from stroke onset to hospital presentation can lead to exposure misclassification, which may bias the results toward the null.⁷⁹

Third, cerebrovascular disease and stroke are composite end points that include strokes of different etiologies (eg, ischemic versus intracerebral hemorrhage versus subarachnoid hemorrhage). It seems plausible that PM would have different associations with risk of acute ischemic stroke versus intracerebral hemorrhage. Even ischemic stroke is a heterogeneous disease with multiple potential etiologies including large artery atherothrombosis, small vessel disease, cardioembolic events, and other less common ischemic stroke etiologies. Indeed, there is limited evidence to suggest that some etiologic subtypes of ischemic stroke may be more strongly associated with PM.⁵⁹ As the distribution of ischemic stroke etiologies varies across populations, even specifically considering studies of ischemic stroke leaves considerable room for heterogeneity in outcome.

Fourth, studies using ICD-9/10 codes to ascertain ischemic or hemorrhagic stroke often lead to outcome misclassification and is expected to have biased effect estimates toward the null hypothesis of no association.⁸⁰ Stroke registries in which cases are ascertained by medical record review can be valuable source for identifying cases particularly for studying stroke of different etiologies.

Fifth, current epidemiologic studies often account for temporal or meteorologic confounders in different ways. Finally, differences in demographic characteristics of underlying population (eg, percent of participants younger than 65 years old), local meteorology, average PM levels, or quality control of ascertainment of stroke and subtypes (eg, interindividual variations between medical coders during stroke ascertainment) may also contribute to heterogeneity of results across studies including the observed geographic variations of the association between PM_{2.5} and hospital admission for total cerebrovascular disease. For example, the elderly and those with certain comorbid conditions are thought to be more susceptible to cardiovascular effects of air pollution.⁷⁸ To the extent that population demographics and the distribution of stroke risk factors and comorbid conditions vary greatly across study populations, this may contribute substantially to the heterogeneity of results across studies.

Research Gaps and Recommendations

These results highlight a number of important gaps in the current literature. First, most prior studies have evaluated a composite end point of cerebrovascular events, but additional large studies specifically considering ischemic stroke, ischemic stroke subtypes, and hemorrhagic stroke are still needed.

Second, few studies to date have evaluated whether the association between PM and stroke varies by PM composition or source. Studies to identify PM components or sources most relevant to stroke mortality and morbidity are needed. Third, most studies have focused on PM_{2.5} and PM₁₀ but study of PM_{2.5-10} is also warranted for its relevance to morbidity, as evidenced in prior studies of association with cardiovascular disease.⁵⁶ We did not have sufficiently large sample size to draw a conclusion for PM_{2.5-10} in this study. Fourth, given the heavy reliance of prior studies on administrative data, outcome misclassification due to the use of ICD codes is prevalent in current studies particularly for stroke subtypes. More epidemiologic studies based on registry data or using medical record review for outcome ascertainment should be carried out to replicate current results. Additionally, history of prior stroke is an important risk factor for stroke, but few studies have considered recurrent versus first stroke.⁵⁵ Studies are needed to evaluate the association between stroke recurrence and particulate matter. Fifth, few studies have identified subgroups of the population that may be at increased risk of stroke mortality and morbidity. In addition, studies are needed to identify whether or not patients with non-cardioembolic (large-artery atherosclerosis, small-vessel disease) or cardioembolic ischemic stroke are at greater risk of hospital admission for ischemic stroke associated with PM₁₀. Sixth, most available studies of ischemic stroke and subtypes or hemorrhagic stroke suffer from exposure misclassification due to the use of date of hospital admission rather than date and time of stroke symptom onset. Novel epidemiologic study design or statistical methods of data analysis that address this issue may help minimize such misclassification. Seventh, given the inconsistent results for an association between PM₁₀ and hospital admission for total cerebrovascular diseases, additional large studies are needed to replicate the current results for PM₁₀. Eighth, given a borderline significant increase in risk of hospital admission for ischemic stroke associated with PM_{2.5} within 24 hours but not 48 hours of onset, more studies are needed to evaluate the temporal window of PM_{2.5} exposure most relevant to ischemic stroke and subtypes. To conclude, more studies, particularly large studies that simultaneously leverage statistical correction of exposure or outcome errors, case ascertainment via physician diagnosis and accurate exposure data for PM components or PM_{2.5-10} are warranted to further elucidate the association between short-term change in ambient particulates and stroke.

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