

Outdoor Fine Particles and Nonfatal Strokes

Systematic Review and Meta-analysis

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Background: Epidemiologic studies find that long- and short-term exposure to fine particles (PM_{2.5}) is associated with adverse cardiovascular outcomes, including ischemic and hemorrhagic strokes. However, few systematic reviews or meta-analyses have synthesized these results.

Methods: We reviewed epidemiologic studies that estimated the risks of nonfatal strokes attributable to ambient PM_{2.5}. To pool risks among studies we used a random-effects model and 2 Bayesian approaches. The first Bayesian approach assumes a normal prior that allows risks to be zero, positive or negative. The second assumes a gamma prior, where risks can only be positive. This second approach is proposed when the number of studies pooled is small, and there is toxicological or clinical literature to support a causal relation.

Results: We identified 20 studies suitable for quantitative meta-analysis. Evidence for publication bias is limited. The frequentist meta-analysis produced pooled risk ratios of 1.06 (95% confidence interval = 1.00–1.13) and 1.007 (1.003–1.010) for long- and short-term effects, respectively. The Bayesian meta-analysis found a posterior mean risk ratio of 1.08 (95% posterior interval = 0.96–1.26) and 1.008 (1.003–1.013) from a normal prior, and of 1.05 (1.02–1.10) and 1.008 (1.004–1.013) from a gamma prior, for long- and short-term effects, respectively, per 10 µg/m³ PM_{2.5}.

Conclusions: Sufficient evidence exists to develop a concentration-response relation for short- and long-term exposures to PM_{2.5} and stroke incidence. Long-term exposures to PM_{2.5} result in a higher risk ratio than short-term exposures, regardless of the pooling method. The evidence for short-term PM_{2.5}-related ischemic stroke is especially strong.

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Health burden assessments of air pollution commonly consider the impact of poor air quality on the risk of premature death, and a subset of these analyses also estimate chronic and acute effects.^{1–4} The causal relation between short-term (a few days up to several weeks) exposure to fine particulate matter (PM_{2.5}) and acute morbidity endpoints (including hospital and emergency room visits for respiratory and cardiovascular diseases) is well established.⁵ A smaller, but growing, literature also finds associations between both short- and longer-term (months to years) exposures to PM and the incidence of chronic cardiovascular diseases including cerebrovascular disease outcomes (such as stroke).^{6–8} The sequelae to stroke may greatly influence the number of years a patient lives with a disability and contribute greatly to lost productivity^{1,9,10}.

The most recent Integrated Science Assessment for Particulate Matter from the US Environmental Protection Agency (EPA)⁵ and a recent American Heart Association literature review¹¹ conclude that short- and long-term exposure to PM_{2.5} are causally related to cardiovascular disease (CVD), including strokes.^{12–19} The literature yields few systematic reviews and meta-analyses of PM_{2.5}-related strokes in particular. This study is distinct from recently published meta-analyses in 2 ways: first, it uses a novel statistical approach and second, it is designed to directly inform air pollution risk assessments.¹⁸

The goals of this article are 2-fold. First, we evaluated the current evidence regarding both short-term and long-term exposure to fine particulate air pollution and the incidence of ischemic stroke (ICD-9 433–444), hemorrhagic stroke (ICD-9 430–432), and cerebrovascular disease (ICD-9 430–438). We assessed the degree to which the literature supports an association between PM_{2.5} exposure and stroke.

Second, we drew upon the epidemiologic evidence to derive quantitative estimates of the risks for each type of stroke that may be included in air pollution risk assessments. We performed a quantitative meta-analysis that proceeds in 2 stages. In the first stage, we evaluate the strength of the epidemiologic evidence supporting the relation between PM_{2.5} and cerebrovascular disease by performing a random-effects meta-analysis to estimate pooled concentration-response relations.²⁰ In the second, we reflect scientifically based conclusions of causality on the epidemiologic evidence by asserting a non-negative prior. We followed this 2-stage approach because (1)

it accounts for our belief, supported by the overall evidentiary base, that $PM_{2.5}$ is unlikely to decrease the risk of stroke, and (2) not imposing this assumption may yield pooled estimates that include a negative lower confidence interval. In this latter case, health impact assessments applying these results will generally also report negative lower confidence intervals—an implausible result that is not consistent with the overall literature and is challenging to characterize.²¹

METHODS

Identifying Cerebrovascular Outcomes

Evidence from clinical and toxicological studies supports a causal relation between exposure to $PM_{2.5}$ and ischemic stroke, hemorrhagic stroke, and cerebrovascular disease.⁵ Ischemic stroke (ICD-9 433–444) characterized by a blood vessel blockage, accounts for about 80% of all cases; hemorrhagic strokes (ICD-9 430–432), characterized by bursting of blood vessels, account for the remaining 20% of cases.²² Cerebrovascular events (ICD-9 430–438) encompass these stroke outcomes and other transient events, as well as sequelae to stroke, including effects on speech and use of limbs.

The evidence for these latter effects is not as strong or consistent as that for cardiovascular disease, especially regarding long-term exposure to $PM_{2.5}$. The reasons for this disparity are not well understood, but some evidence suggests that responses to $PM_{2.5}$ may be modified by differences in exposures, exposure measurement errors, composition of $PM_{2.5}$, and underlying population susceptibility, including use of statin drugs which can offset inflammatory responses.¹²

Indeed, many epidemiologic studies are prone to mischaracterize time of stroke onset and hence misclassify exposure and report a null result.¹¹ To the extent that there is a relation between exposure to fine particles and cerebrovascular outcomes, these studies are likely to underestimate the health risks attributable to air pollution.

Pulmonary oxidative stress and systemic inflammation offer a plausible biological pathway describing the relation between long- and short-term PM exposure and stroke (Figure 1).^{12,13} $PM_{2.5}$ may initiate a systemic inflammatory response even in the case of mild pulmonary inflammation.⁵ The recent Integrated Science Assessment by the US EPA finds that a number of other biological responses can mediate the pathway from systemic inflammation to the onset of stroke, including atherosclerosis, plaque rupture, pro-coagulation effects, and thrombosis.⁵ Determining whether PM and stroke are causally related should account for clinical and toxicological evidence, but developing quantitative risk functions requires epidemiologic literature. The effects of short- and long-term exposures to $PM_{2.5}$ may be complementary, with longer-term exposures exacerbating susceptibility to shorter term $PM_{2.5}$ elevations.²³

Search Procedure

We conducted searches of epidemiologic studies in the medical literature in Medline and PubMed, using the terms “particulate matter” or “air pollution” and “cerebrovascular” or “stroke,” and also reviewed lists of studies included in the US EPA Integrated Science Assessment for Particulate Matter.⁵ This initial search yielded 1801 studies (Figure 2). We

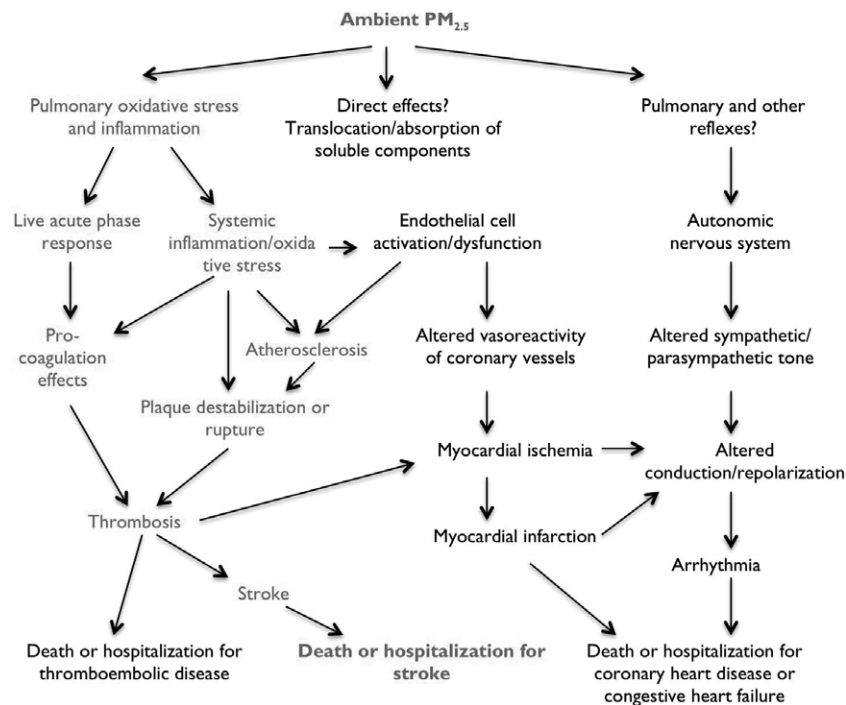


FIGURE 1. Plausible mode of action for $PM_{2.5}$ -related cardiovascular effects (adapted from US EPA).⁵

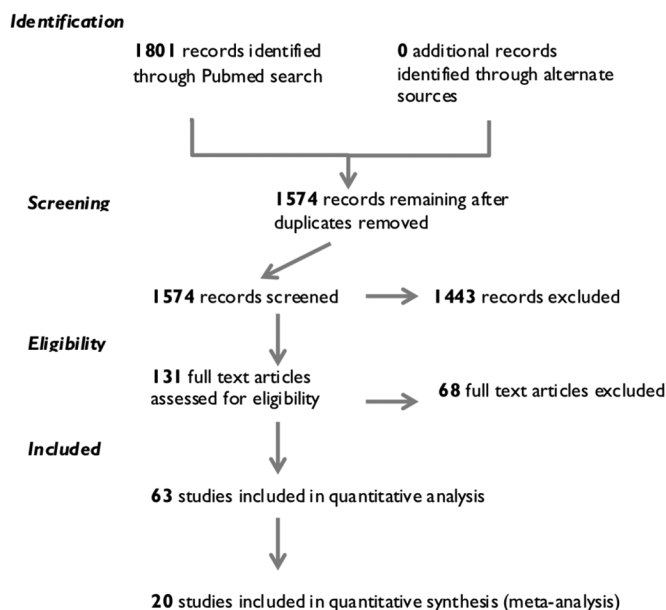


FIGURE 2. Preferred Reporting System for Systematic Reviews and Meta-Analyses (PRISMA) diagram of selection of studies for inclusion.

did not identify any additional studies from alternate sources. From this set of 1801 studies, 1,574 remained after excluding duplicates and those published before 1990. We excluded 1443 studies that did not include fine particulate matter (but rather PM_{10} , total suspended particulate, or black smoke), focused only on second-hand smoke exposures, did not evaluate air pollution, or were not epidemiologic studies. We focused our review on the fine particle fraction because the epidemiologic, clinical and toxicological evidence finds the strongest relation between exposure to this size fraction and adverse health outcomes.⁵ In addition, the current standards for particulate matter in the U.S. and many other countries are based on $PM_{2.5}$ concentrations.

Of the 131 remaining studies, we excluded 111 that lacked quantitative effect estimates (eg, risk ratios, beta coefficients) or that assessed fatal (rather than incident) stroke, leaving 20 studies that were the subject of the quantitative meta-analysis. (See eTable 1 for a list and description of these studies.) These 20 remaining studies reported at least the minimum level of detail regarding the study population, risk estimates, unit change in $PM_{2.5}$, and type of stroke that would enable a quantitative meta-analysis; 1 cross-sectional study reported these minimum data, but upon further investigation the risk ratios proved not to be valid due to insufficient variation in $PM_{2.5}$ across the study area. Certain attributes—including temperature, monitoring data used to quantify population exposure, and the measures the authors used to validate the stroke diagnosis—were reported inconsistently across studies. Other literature has underscored the importance of reporting such data to support quantitative meta-analyses and risk assessments.²⁴

Statistical Pooling

We used 2 statistical pooling approaches to reflect the 2 goals of this analysis. In the first procedure, we performed a traditional random-effects meta-analysis (ie, the frequentist approach), using the risk estimates reported in each study to characterize the overall strength of the evidence regarding the risk of $PM_{2.5}$ -related stroke.²⁵ The random-effects meta-analysis also allowed us to evaluate between-study variation in the association between $PM_{2.5}$ exposure and various cerebrovascular outcomes. However, when the number of study estimates pooled is small, this procedure too often fails to reject the null hypothesis of no heterogeneity—thus yielding an unrealistic characterization of uncertainty attributed completely to sampling error.²⁶

To address this limitation, we introduce a Bayesian random-effects meta-analysis with 2 models. The first Bayesian approach treats the unknown overall risk and heterogeneity both as random variables; this is a typical model with a normal prior for the overall risk and an inverse-gamma prior for the heterogeneity. We favor this approach mainly due to its computational ease. However, the dispersion of the uncertainty distribution could become unrealistically large when only a small number of studies are available for analysis and can include negative values, implying a probability that increases in $PM_{2.5}$ may decrease incidence of stroke. Risk analyses generally develop quantitative risk functions that permit both negative and positive risk estimates, regardless of the biological plausibility for such an outcome; the result can be health impact estimates whose quantitative bounds include substantial negative tails, implying that decreases in air pollution result in increases in strokes. To the extent that this is not biologically plausible, this would be a misleading result and not useful in informing policy decisions.

For these reasons, we propose the second model, which is a new meta-analytic method that combines features of both the frequentist and Bayesian approaches by adding our prior belief to the data.²⁷ Specifically, we believe that the overall evidence supports a positive uncertainty risk distribution, reflecting the biological implausibility of stroke incidence decreasing as $PM_{2.5}$ exposures increase. Thus, we assume a gamma prior with positive support to characterize the uncertainty distribution. In addition, the estimate of the heterogeneity from a noninformative prior is too imprecise to support pooling risk estimates; to overcome this, we use an empirical prior. The dispersion of the estimated uncertainty distribution is bounded above by the observed variation in study-specific risk estimates, a property of the frequentist approach. In this respect, the model blends classical and Bayesian approaches. For both pooling approaches, we drew from the literature review described above.

In our primary analysis, we preferentially selected risk estimates associated with distributed or cumulative lags in days of ambient $PM_{2.5}$ exposure. Where this lag structure was unavailable and the author reported risk estimates associated with 2 or more lag periods, we selected the largest risk

estimate available; we took this approach under the premise that the lag associated with the greatest effect estimate was capturing the critical window of exposure.²⁸ Put differently, the unknown true lag structure between exposures to onset of strokes may not be in days but in hours.¹¹ For example, if the true lag were 18 hours (ie, 0.75 day), the highest risk estimate would be observed for PM_{2.5} with 1 day lag. The question of lag structure is not relevant to long-term studies, which generally detect differences in risk between locations rather than over time. To the extent that a study reported risk estimates stratified by copollutant, we selected risk estimates associated with single-pollutant models, as the studies specified this model most frequently; by doing so we maximized the number of study-specific estimates available for pooling. After this approach to selecting risk estimates yielded 4 risk ratios from long-term studies and 221 risk ratios from short-term studies.

We evaluated the sensitivity of the results to several study attributes. We first characterized the sensitivity of the pooled risk estimate to the selection of risk estimates from single-pollutant models by performing a mixed-effects analysis in which we pooled risk estimates within each copollutant. We also applied a mixed-effects model to pool effect estimates by geographic area and age. Finally, using the random-effects meta-regression models, we attempted to predict risk levels based on study attributes, including the years in which the study was performed, as well as PM_{2.5} and temperature levels. Due to the limited number of studies with sufficient information on covariates, the meta-regression models were not sufficiently powered to detect whether any variables modified the PM_{2.5}-stroke relation (results not shown).

As briefly discussed above, in the second pooling approach, we specified that the true uncertainty distribution of risk follows a gamma distribution, implying that risk must be positive. This model specification reflects our understanding, which is based on the overall PM_{2.5} health-effects literature, that exposure to PM_{2.5} cannot be protective and that negative estimates are biologically implausible. The observed study-specific logarithm of the risk estimate is assumed to be normally distributed with a gamma-distributed mean. The focus of the Bayesian meta-analysis is to estimate the mean and variance of the gamma distribution given the observed risks and underlying assumptions on the distributions of the unknown parameters. As part of the Bayesian approach, prior distributions of the mean and variance of the gamma distribution need to be specified, and a numerical value of the mean and variance of these prior distributions also needs to be provided. Typically we have no direct information on the value of these quantities; we thus supply a large (noninformative) value. However, when the number of studies examined is small, noninformative values yield very large, and often unreasonable, estimates of the gamma distribution variance. To bound this variance, we select the variance of the prior variance distribution to be no larger than the observed variation in the study-specific risk estimates, a property of the frequentist approach (S.H.H., unpublished

data, 2013). In this manner, we are combining features of both the Bayesian and frequentist approaches to meta-analysis. Details of the pooling methodology are provided in the eAppendix (<http://links.lww.com/EDE/A823>).

RESULTS

After removing articles focused on second-hand smoke, mortality, and other measures of PM, we identified 20 studies investigating a relation between ambient PM_{2.5} and nonfatal stroke or cerebrovascular disease.^{6,29-45} Of these 20 cerebrovascular disease or stroke studies, 4 investigated the effects of long-term PM_{2.5} exposures,^{6,36,37,44} whereas the remaining 16 investigated short-term exposures. Some studies estimated the risks for strokes and total cerebrovascular disease separately; in others, only a combined cerebrovascular disease risk estimate was provided. In instances where both are available, we focus on the ischemic or hemorrhagic stroke risk estimates (and not cerebrovascular) because they are more clearly defined health outcomes and because they exclude transient and reversible effects. The risk estimates for each of the 20 studies are provided in Figure 3 and basic study attributes as shown in eTable 1 (<http://links.lww.com/EDE/A823>). Because of important differences between the long- and short-term studies of population exposure in the distributions, we pool these 2 sets of studies separately.

Long-term Studies

Four cohort studies characterized the relation between long-term PM_{2.5} exposures and cerebrovascular disease. The first is the Women's Health Initiative (WHI) study, which estimated the effect of PM_{2.5} on both stroke and total cerebrovascular disease among postmenopausal women and examined time to onset of stroke as the outcome measure.⁶ The WHI study found a strong significant association between long-term PM_{2.5} exposures and first onset of stroke. The second is an analysis of the California Teacher's Cohort comprising current and former female public school teachers; it assessed the risk of cerebrovascular disease due to PM_{2.5} exposure.⁴⁴ This study found particularly strong risks among postmenopausal women. The third study followed a cohort of patients receiving treatment from general practices in England, using modeled air quality data to predict population exposure.⁴⁵ This study found weak relations between long-term PM_{2.5} exposure and the risk of cerebrovascular disease. Finally, Kloog and coauthors³⁶ used a land-use regression model in concert with remote sensing techniques to estimate exposure among a cohort of Medicare recipients, finding an increased risk of stroke from short- and long-term exposures.

Using the frequentist approach, pooling the 4 risk estimates from these 4 studies yields a pooled risk ratio estimate of 1.06 (95% confidence interval = 1.00–1.13) (Figure 4). A funnel plot analysis provides little evidence of asymmetry ($P_{\text{Egger}} = 0.25$). The trim-and-fill method imputed 2 hypothetically missing studies, slightly attenuating the risk. However, because the overall number of long-term studies is small, the

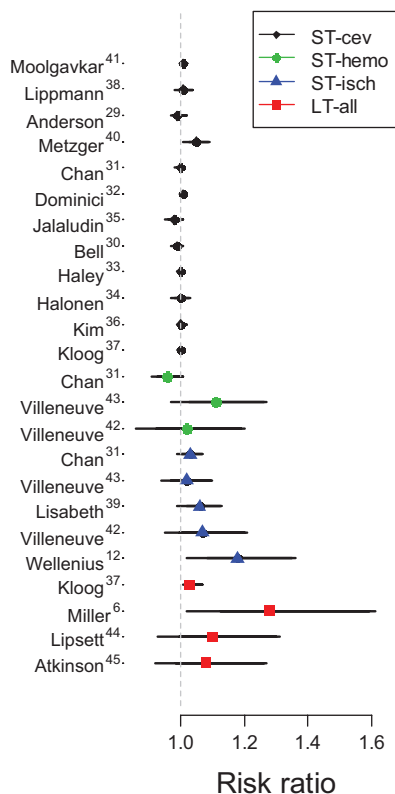


FIGURE 3. Association of short- and long-term exposure to PM_{2.5} (per 10 μg/m³) with nonfatal stroke.

funnel plot analysis is not highly informative and so we did not include a figure here.

In addition to the classical frequentist approach, we used a Bayesian approach to the meta-analysis to account for all potential uncertainty by exploring 2 prior assumptions, normal or gamma distribution, for the unknown true study-specific risk.^{20,46} For the 4 estimates, the gamma prior returns the posterior mean of 1.05 (95% posterior interval [PI] = 1.02–1.10), whereas the normal prior yields the posterior mean of 1.08 (0.96–1.27). Note that the normal prior used noninformative distributions for all parameters involved in the model, assuming no previous knowledge on the study-specific risk and the mean risk. However, the gamma prior used a semi-informative distribution that required the risk to be positive. More details on statistical differences between normal and gamma priors can be found in the eAppendix (<http://links.lww.com/EDE/A823>).

Short-term Studies

Of the 16 short-term studies, we selected 221 risk estimates (202 of which were drawn from the Dominici et al³² multi-city study) that met the inclusion criteria we noted above. Of these 221 risk estimates, 141 were positive; 12 estimates were negative and statistically significant, whereas 23 were positive and statistically significant. Of the 16 studies examining short-term exposures, 10 were conducted in North America, 2 in Asia, 2 in Europe, and 1 in Australia. Although 14

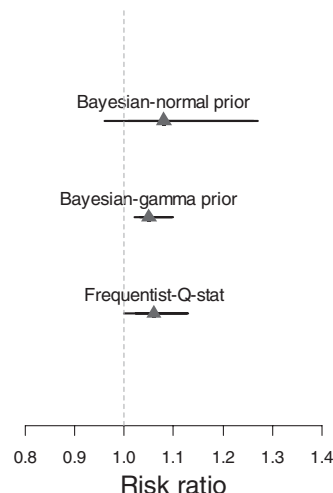


FIGURE 4. Pooled estimates of long-term PM_{2.5}-related cerebrovascular, hemorrhagic, and hemorrhagic and ischemic stroke.

of the studies used time-series or case-cross over approaches, 1 study followed a 2-stage modeling technique in which the authors first estimated city-specific risks and then pooled estimates across cities.³⁰ Single-city estimates were available in the report by Dominici and colleagues,³² and so we pooled the 202 single-city estimates from this article with the single-city estimates from the remaining 15 studies. We discuss this procedure further below.

We first pooled the individual city time-series and case-crossover study estimates across the stroke endpoints, generating a pooled estimate (risk ratio) of 1.007 (95% confidence interval = 1.003–1.01) (Figure 5A). In our mixed-effects model, where we pooled within each stroke outcome, we find that the pooled ischemic stroke risk ratio is 1.04 (1.01–1.07), the cerebrovascular estimate was 1.006 (1.002–1.01), and the hemorrhagic estimate was 1.012 (0.92–1.11). In another mixed-effects model, where we pooled studies according to the continent in which they were performed, we generate a positive and significant pooled estimate (risk ratio) of 1.008 (1.004–1.013) for North America, a negative estimate for Europe, and a negative estimate for Asia (results not shown). The funnel plot analysis (Figure 5B) provides some evidence of asymmetry ($P_{\text{Egger}} = 0.0607$).⁴⁷ The trim-and-fill method imputed 18 hypothetically missing study estimates, slightly attenuating the risk estimate (results not shown).

Pooling the 221 estimates across all 3 health endpoints using the Bayesian approach, we obtained a posterior mean risk ratio of 1.008 (95% posterior interval = 1.004–1.013) from the gamma prior and 1.008 (1.003–1.013) from the normal prior (Figure 6). For all cerebrovascular disease combined (213 estimates), the Bayesian approach again returned very similar results: the posterior mean of the risk ratio 1.007 (1.004–1.012) from the gamma prior and 1.007 (1.002–1.012) from normal prior. Cerebrovascular disease is the dominant cause of stroke and covers more than 95% of all estimates—and for

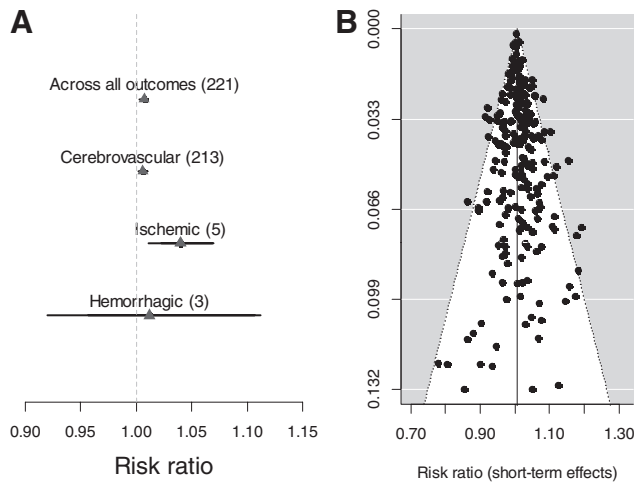


FIGURE 5. A, Pooled estimates of short-term PM_{2.5}-related stroke outcomes by classical frequentist's approach: cerebrovascular, hemorrhagic, and hemorrhagic and ischemic stroke. B, A funnel plot for 4 studies of short-term exposure to PM_{2.5} and stroke outcomes (per 10 μg/m³).

this reason, the results for total cerebrovascular disease (n = 213) and all stroke types (n = 221) do not differ substantially (Figure 6).

However, for ischemic and hemorrhagic strokes, the risk ratio was much wider than for cerebrovascular disease. The posterior mean risk ratio of ischemic stroke was 1.05 (95% posterior interval = 1.01–1.09) from the gamma prior and 1.05 (0.99–1.14) from the normal prior. The risk ratio of hemorrhagic stroke was a bit lower but with wider credible interval than ischemic stroke: the posterior mean of 1.02 (1.00–1.06) from the gamma prior and 1.01 (0.84–1.25) from the normal prior. Figure 7 displays the difference over cause (ischemic versus hemorrhagic strokes) and over prior distribution (normal versus gamma distributions).

To assess the influence of the 202 city risk ratios from the study by Dominici et al,³² we excluded these values and then pooled across the remaining study risk estimates (n = 19) and for the cerebrovascular endpoint alone (n = 11). The results are displayed in eFigure 1 (<http://links.lww.com/EDE/A823>). Both prior distributions, normal and gamma, returned comparable posterior medians (represented by dots), but the normal prior returned much wider posterior intervals that cover unrealistic negative risk values.

DISCUSSION

After examining 3 types of stroke—cerebrovascular, ischemic, and hemorrhagic—we conclude that the evidence supports a causal relation between PM_{2.5} exposure and cerebrovascular disease (strokes), particularly ischemic strokes associated with short-term exposure to PM_{2.5}. Our conclusions are generally consistent with several other recent reviews.¹⁹ Both pooling approaches—frequentist and Bayesian—yield small, nonzero short- and long-term risk estimates. The results of

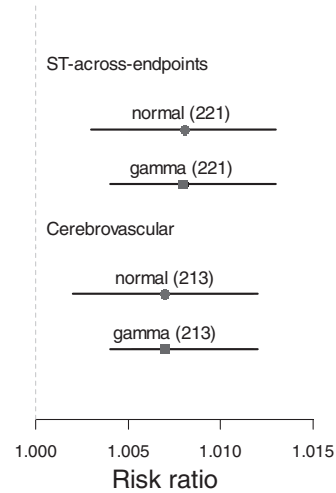


FIGURE 6. Pooled estimates of short-term PM_{2.5}-related stroke outcomes by Bayesian approach with 2 prior distributions: Across-all strokes and cerebrovascular.

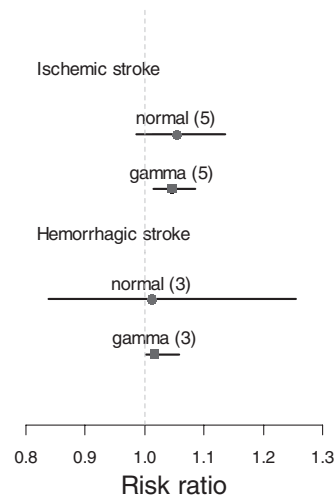


FIGURE 7. Pooled estimates of short-term PM_{2.5}-related stroke outcomes by Bayesian approach with 2 prior distributions: ischemic and hemorrhagic stroke.

the short-term risk were fairly consistent across the 2 pooling methods; with both the frequentist and Bayesian approaches, there are increases in excess risk ratio, but they are small. The frequentist and Bayesian techniques each report a small positive estimate for ischemic stroke. Although the frequentist and Bayesian gamma models generate a small pooled estimate for ischemic stroke, the Bayesian normal prior does not. Taken together, these results suggest a stronger relation between short-term PM_{2.5} exposure and ischemic stroke than the other 2 strokes. Both the long- and short-term studies demonstrate a limited degree of funnel plot asymmetry, suggesting that these results are not greatly influenced by publication bias. The fact that about 90 percent of the short-term estimates came from a single study is a source of bias, as it reduces the level of between-study heterogeneity. However, the population

in that study of those estimates were distributed throughout the United States, were composed of multiple ethnic backgrounds, and were exposed to a range of PM_{2.5} levels.

Differences in the pooled risk estimates for the short- and long-term studies may be attributed to the time periods caused by these studies. For example, the long-term studies integrated the effects of the most recent exposure (in hours or days), as well as chronic exposures to air pollution that affect the underlying cardiovascular pathologies, which in turn increase a person's propensity to suffer a stroke; these studies will also account for stroke events triggered by other acute causes on days in which air quality is good. For these reasons, long-term studies tend to observe much larger effects if air pollution causes chronic cardiovascular pathologies, such as atherosclerosis. Given that the long- and short-term studies are observing different effects, it would be inappropriate for risk assessors to use both pooled effect estimates in the same health impact analysis—doing so would likely incorrectly estimate effects.

This article demonstrates how the frequentist and Bayesian approaches may be applied in a complementary manner to produce pooled risk estimates that may inform air pollution risk assessments. In this analysis, we applied the frequentist approach as a first step, probing the extent to which PM_{2.5} exposure was associated with various stroke outcomes; we found a positive relation between long- and short-term exposure and stroke. These findings—and the strong evidence that exposure to PM_{2.5} could not be health-protective—then informed our prior belief that the PM_{2.5}-related risks of stroke may be positive, but not zero or negative, arguing for the use of the Bayesian model. Such an approach may prove useful in future air pollution meta-analyses—particularly those in which there are a small number of estimates or those for which the estimates are substantially skewed. However, given the somewhat inconsistent support for a positive, non-zero effect, the use of the proposed Bayesian gamma model may place too much weight on strictly positive risk estimates, and thus future approaches should explore the feasibility of applying both zero and gamma prior models.

This Bayesian approach exhibits 2 key strengths that make it particularly well suited to generating risk distributions that inform air pollution health impact assessments. First, it offers an opportunity to inform the shape of the risk distribution with prior knowledge about the biological plausibility of air pollution affecting health without distorting that distribution. Conversely, alternative approaches to adjusting the uncertainty distribution—for example, ignoring negative values or centering the distribution on zero—distort the distribution. Second, this approach ensures that if the evidence was not sufficient to support a strictly positive distribution, then the model would not converge.

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