Long-Term Exposure to Particulate Matter Air Pollution Is a Risk Factor for Stroke
Meta-Analytical Evidence

Hans Scheers, MSc; Lotte Jacobs, PhD; Lidia Casas, PhD; Benoit Nemery, MD, PhD; Tim S. Nawrot, PhD

Background and Purpose—Epidemiological studies suggest an association between stroke incidence and stroke mortality and long-term exposure to particulate matter (PM) air pollution. However, the magnitude of the association is still unclear.

Methods—We searched the Pubmed citation database for epidemiological studies and reviews on stroke and PM exposure. Then, we carried out a meta-analysis to quantify the pooled association between stroke incidence and mortality and long-term exposure to PM. Meta-analyses were performed for stroke events and stroke mortality and for PM$_{10}$ and PM$_{2.5}$ separately and jointly.

Results—We identified 20 studies, including a total of >10 million people, on long-term PM exposure and stroke event or stroke mortality. For exposure to PM$_{10}$ (including estimated exposure to PM$_{10}$ from studies using PM$_{2.5}$), the pooled hazard ratio for each 10-$\mu$g/m$^3$ increment in PM$_{10}$ was 1.061 (95% confidence interval, 1.018–1.105) and 1.080 (0.992–1.177) for overall stroke events and stroke mortality, respectively. A stratified analysis by continent revealed that the association between stroke and long-term PM$_{10}$ exposure was positive in North America (1.062 [1.015–1.110]) and Europe (1.057 [0.973–1.148]), but studies in Asia (1.010 [0.885–1.153]) showed a high degree of heterogeneity. Considering exposure to PM$_{2.5}$ (Europe and North America combined), the hazard ratios for a 5-$\mu$g/m$^2$ increment were 1.064 (1.021–1.109) and 1.125 (1.007–1.256) for stroke events and mortality, respectively.

Conclusions—The scientific evidence of the past decade identifies long-term exposure to PM, and PM$_{2.5}$ in particular, as a risk factor for stroke. However, we found some currently unexplained geographical variability in this association. (Stroke. 2015;46:3058-3066. DOI: 10.1161/STROKEAHA.115.009913.)

Key Words: cerebrovascular disorders ■ epidemiology ■ meta-analysis ■ mortality ■ particulate matter

With an incidence rate of 40 to >300 cases per 100000 inhabitants, depending on the region, and a global death rate of 110 per 100000 inhabitants, stroke is one of the most prominent causes of mortality, accounting for 12% of all deaths worldwide. Stroke, an acute event itself, can be triggered by acute events occurring a few hours or days before the stroke onset, such as alcohol abuse or an outburst of anger. However, long-term underlying conditions are even more important predictors of stroke. In a recent study, 90% of all ischemic and hemorrhagic strokes could be attributed to 10 major risk factors, with history of hypertension and current smoking as the most prominent causes.

From the past decade of the 20th century on, numerous epidemiological studies found that respiratory and cardiovascular diseases, as well as general morbidity and mortality, could be associated with increased levels of air pollutants, especially particulate matter (PM). Biological pathways that have been proposed to explain the association between PM and cardiovascular diseases are plausible mechanisms for a link between PM exposure and certain cerebrovascular events as well.

Studies investigating the triggering effect of recent exposure to peak concentrations of PM$_{10}$ or PM$_{2.5}$ (PM with an aerodynamic diameter of <10 $\mu$m or <2.5 $\mu$m, respectively) on stroke were summarized in 3 recent meta-analyses on the short-term effects of PM on stroke hospitalization and mortality. These meta-analyses suggested a small but significant effect of recent PM exposure and the risk of stroke in general and ischemic stroke in particular. In contrast to our knowledge about short-term exposure to air pollution being a trigger of stroke, the record for long-term effects of PM on cerebrovascular disease is much less extensive. Three comprehensive narrative reviews provided a summary of the literature on the topic, but no meta-analyses were conducted. Although studies discussed in these review articles reported fairly mixed results, the overall size and importance of the effect is still unclear. Therefore, we conducted a meta-analysis of the
existing literature to quantify the association between the risk of stroke event and stroke mortality and long-term exposure to PM air pollution. A better understanding of the magnitude of the effect of air pollution on a common cause of death, such as stroke, is important in the light of public health.

Methods

Literature Search
A bibliographic search was carried out by 2 independent reviewers (H.S. and L.J.) in the PubMed database (last accessed on July 20, 2015) to identify original studies analyzing the associations of long-term exposure to PM$_{10}$ or PM$_{2.5}$ with stroke events (both fatal and nonfatal). Details on the search terms used can be found in the online-only Data Supplement. Study designs could be ecological or cohort studies. Experimental studies, case reports, studies on short-term associations between PM and stroke, and publications with no or incomplete results were excluded. Articles not written in English were considered for inclusion. Reviews and the reference lists of eligible studies were screened for additional data. Our meta-analysis complies with the preferred reporting items of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statement for meta-analyses of observational studies.

Data Management
Study results were classified according to the end point of the analysis: stroke event or stroke mortality. When available, preference was given to results obtained by models fully adjusted for covariates. We assessed the quality of the selected studies taking into account the following aspects: study design, number and nature of covariates in the analysis, definition of the end point, and estimation of the exposure (details can be found in the online-only Data Supplement).

We needed to standardize reported results to hazard ratios (HRs) for a 10-μg/m$^3$ increment of PM$_{10}$, because HRs of individual studies have been reported for increments of other than 10 μg/m$^3$ (eg, an interquartile range increment) or in comparison with a reference category. Results for PM$_{2.5}$ were converted to estimated results for PM$_{10}$ to be included in the overall analysis. Details on calculations and conversions made to standardize the data can be found in the online-only Data Supplement.

Meta-Analysis
For those studies that provided results on both stroke event and stroke mortality, the most comprehensive data set (ie, on stroke event) was selected for the overall analysis. When a study presented results for both PM$_{10}$ and PM$_{2.5}$ exposure, we selected PM$_{10}$. However, we also performed separate analyses for PM$_{2.5}$ and additional analyses for stroke mortality only. We performed sensitivity analyses per continent and according to the result of the quality assessment. For articles with independent subgroups within 1 study (eg, different cities or different types of stroke), we used the general HR resulting from a meta-analysis by the authors, or, if no general HR was provided, we treated each subgroup as a separate study.

The overall HR and 95% confidence interval were estimated using random-effects models, which is more conservative than a fixed-effect model and accounts for heterogeneity between studies in terms of population and methodology. Heterogeneity and publication bias were tested with the $I^2$ statistic and Egger linear regression method, respectively (details can be found in the online-only Data Supplement).

Results

Selection and Characteristics of Studies
A flow chart of the selection procedure is given in Figure I in the online-only Data Supplement. We included 20 publications on stroke and long-term PM exposure in our meta-analysis. They are listed by region and then chronologically in Table 1. Fourteen studies were cohort studies and included covariates at an individual level; the other 6 made use of registered-based entries of stroke mortality or hospital admission and provided covariates on an ecological scale.

Eight studies were conducted in Europe, 7 in North America, and 5 in Eastern Asia.

The exposure levels reported by the 20 selected studies are shown in Figure 1. The exposure measure was PM$_{10}$ in 9 studies and PM$_{2.5}$ in 7 studies; 4 publications investigated the association of stroke with exposure to both PM$_{2.5}$ and PM$_{10}$. The end point was stroke event (8 studies), stroke mortality (7 studies), or stroke event with separate results for mortality (5 studies). More details on the definition of the outcome can be found in Table I in the online-only Data Supplement.

All publications displayed adjusted results for at least age and, when applicable, sex. Other covariates varied among studies, but the most common variables included in the adjusted models were body mass index, smoking status, alcohol use, and a measure of socioeconomic status (SES) at an individual or area level (Table I in the online-only Data Supplement).

Main Analyses on Long-Term Exposure and Stroke
The overall meta-analysis, including >10 million people and >200,000 stroke events from 20 scientific articles, showed a pooled HR with 95% confidence interval of 1.061 (1.018–1.105) for a 10-μg/m$^3$ increment in long-term PM$_{10}$ or converted PM$_{2.5}$ exposure (Table 2; Figure 2). Twelve of 20 publications presented results on stroke mortality. The result of the analysis was similar to that of stroke event, with a slightly higher HR of 1.080 (0.992–1.177). A stratified analysis by continent revealed that the association between long-term PM exposure and stroke event was positive in North America and Europe (but not statistically significant for the latter) and null in Asia (Table 2).

Sensitivity Analyses
The 3 studies conducted in China reported high ambient PM concentrations (3 to 6× the respective World Health Organization air quality guideline values for long-term exposure to PM$_{2.5}$ or PM$_{10}$). A meta-analysis of these study results revealed a highly significant association between stroke onset and PM exposure (HR, 1.123 [1.010–1.248]). Because the Chinese studies reported such exceptional exposure levels and the 2 Japanese studies were deviant with respect to circumstances, as well as study design and results (Discussion), we excluded the 5 Asian studies from subsequent sensitivity analyses.

For PM$_{10}$ alone (n=9 studies), that is, without the converted PM$_{2.5}$ results from 6 studies, the association between stroke event and PM$_{10}$ exposure disappeared, with an HR of 1.021 (0.975–1.069) for a 10-μg/m$^3$ increase in PM$_{10}$. In contrast, the estimate for PM$_{2.5}$ exposure only was significantly higher than 1: HR, 1.064 (1.021–1.109) for a 5-μg/m$^3$ increase in PM$_{2.5}$ (n=10 studies; Figure 3). A similar difference between PM$_{10}$ and PM$_{2.5}$ exposure, but with generally higher HRs, was found for stroke mortality (Table 3).
Table 1. Characteristics of the Selected Studies on Stroke and Long-Term Exposure to PM

<table>
<thead>
<tr>
<th>ID</th>
<th>First Author (Year of Publication)</th>
<th>Area</th>
<th>Study Period</th>
<th>Pollutant Concentration, μg/m³</th>
<th>Study Design</th>
<th>Population (Number)</th>
<th>Stroke Type (as in Publication)</th>
<th>Official Classification</th>
<th>End Point</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Nishiwaki (2013)</td>
<td>9 cities, Japan</td>
<td>1990–2008</td>
<td>PM₁₀ 17.2–43.7†</td>
<td>COH &gt;40 y</td>
<td>(78 057)</td>
<td>Stroke</td>
<td>ICD-10 I60–I69</td>
<td>Mortality</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 cities, Japan</td>
<td></td>
<td>PM₁₀ 17.2–28.7†</td>
<td></td>
<td>(62 142)</td>
<td>Ischemic stroke</td>
<td>ICD-10 I60–I69</td>
<td>Incidence</td>
<td>2181</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Subarachnoid hemorrhage</td>
<td>Incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intracerebral hemorrhage</td>
<td>Incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Qin (2015)</td>
<td>3 cities, China</td>
<td>2006–2008</td>
<td>PM₁₀ 123.1 (14.6)‡</td>
<td>COH 18–74 y</td>
<td>(24 845)</td>
<td>Stroke</td>
<td>Self-reported</td>
<td>Incidence</td>
<td>589</td>
</tr>
<tr>
<td>5</td>
<td>Wong (2015)</td>
<td>Hong Kong, China</td>
<td>1998–2011</td>
<td>PM₂,₃ 35.3 (33.8–37.2)§</td>
<td>COH &gt;65 y</td>
<td>(66 820)</td>
<td>Stroke</td>
<td>Cerebrovascular disease</td>
<td>ICD-10 I60–I69</td>
<td>Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ischemic stroke Unknown 1st/mortality</td>
<td>2610/179</td>
<td>1832/41</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hemorrhagic stroke Unknown 1st/mortality</td>
<td>348/64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Atkinson (2013)</td>
<td>England, United Kingdom</td>
<td>1982–2000</td>
<td>PM₁₀ 19.7 (2.3)‡</td>
<td>ECO 40–89 y</td>
<td>(819 370)</td>
<td>Stroke</td>
<td>ICD-10 I61, I63, and I64</td>
<td>First stroke</td>
<td>13 012</td>
</tr>
<tr>
<td>16</td>
<td>Johnson (2010)</td>
<td>Edmonton, Canada</td>
<td>2003–2007</td>
<td>PM₂,₃ 5.0 (0.2)‡</td>
<td>ECO All (103 4945)</td>
<td>Stroke</td>
<td>Cerebrovascular disease</td>
<td>ICD-10 I60–I68 and G45</td>
<td>First hospital admission</td>
<td>7336</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hemorrhagic stroke Nonhemorrhagic stroke</td>
<td>ICD-10 I60–I62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hemorrhagic stroke TIA</td>
<td>G45</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cerebrovascular disease Stroke</td>
<td>ICD-9 430–438 and 436 ICD-10 I61–I64</td>
<td>Mortality</td>
<td>11 79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PM₁₀ 29.21 (9.73)‡</td>
<td></td>
<td></td>
<td>Stroke</td>
<td>ICD-10 I60–I69</td>
<td>Incidence</td>
<td>11 79</td>
</tr>
</tbody>
</table>
A subanalysis including only studies with a high-quality score (more than the median overall quality score; Table I in the online-only Data Supplement) resulted in a pooled HR of 1.087 (1.023–1.154) for stroke event (n=8) and 1.056 (0.957–1.165) for stroke mortality (n=4), for a 10-μg/m³ increment in PM₂.₅. The corresponding HRs for a 5-μg/m³ increase in PM₁₀, respectively. The dotted lines representing the World Health Organization (WHO) air quality guidelines for long-term exposure to PM₂.₅ and PM₁₀, respectively.

Discussion
Our meta-analysis on risk of stroke event and fatal stroke in association with long-term exposure to PM air pollution includes 20 epidemiological studies, comprising >10 million people and 200,000 stroke events on 3 different continents. We found a positive association between the risk of stroke and PM exposure, with a 2% to 21% excess risk, depending on the definition of exposure, outcome, and population. Considerable geographical variation was observed, with the highest combined HR found in Europe and high heterogeneity in Asia. The 5 studies conducted in Asia were remarkable in various ways. The reported average PM concentrations in Chinese cities were 3- to 10-fold higher than those found in European and North American cities (Figure 2). In addition, the authors found strong associations between stroke and long-term PM exposure. The 2 Japanese studies reported contrasting findings. According to the authors of both publications, stroke incidence in Japan is more prominent in rural areas than in urban areas, and it has been attributed to high salt intake in those low-polluted but socioeconomically lower-rated rural areas. The 2 Japanese publications did not adjust their analysis for diet, and they were the only studies in our systematic review not adjusting for SES indicators. Moreover, they did not account for Asian Dust Storms (ADS). During ADS, a common weather phenomenon in Eastern Asia, dust from the deserts in Mongolia and China is transferred through the atmosphere to countries Japan and Taiwan. Composition of PM in Japan, particularly during ADS, is likely to be different (containing more crust elements and sea salt) from that in Europe and North America. Adverse health effects of ADS have been reviewed in 2010 and many additional epidemiological and experimental studies have confirmed the importance of ADS.
on respiratory and cardiovascular health in more recent years. Therefore, we decided that the 3 Chinese and 2 Japanese studies were too dissimilar from those conducted in North America and Europe to include them in the sensitivity analyses.

Recently, 3 meta-analyses on stroke mortality and hospitalization in association with recent PM exposure have been published. The pooled HR for stroke mortality was 1.014 (1.009–1.019) or 1.013 (1.003–1.024) for a 10-μg/m³ increment in PM₂.₅. These increases in risk per 10-μg/m³ increment are smaller than those we obtained for a 5-μg/m³ increment in long-term exposure, but it should be noted that daily variation in ambient PM levels is usually substantially

### Table 2. Results of Overall Meta-Analyses and Stratified Analyses by Continent

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>End Point</th>
<th>Stratum</th>
<th>No. of Studies</th>
<th>Meta-Analysis</th>
<th>Tests of Heterogeneity</th>
<th>Test of Publication Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM₁₀+converted PM₂.₅</td>
<td>Stroke event</td>
<td>All</td>
<td>20</td>
<td>1.061 (1.018–1.105)</td>
<td>0.005</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asia</td>
<td>5</td>
<td>1.010 (0.885–1.153)</td>
<td>0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Europe</td>
<td>8</td>
<td>1.057 (0.973–1.148)</td>
<td>0.19</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td></td>
<td>North America</td>
<td>7</td>
<td>1.062 (1.015–1.110)</td>
<td>0.009</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Europe+North America</td>
<td>15</td>
<td>1.045 (1.011–1.081)</td>
<td>0.010</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Stroke mortality</td>
<td>All</td>
<td>12</td>
<td>1.080 (0.992–1.177)</td>
<td>0.077</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asia</td>
<td>4</td>
<td>0.986 (0.788–1.234)</td>
<td>0.90</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Europe</td>
<td>5</td>
<td>1.213 (0.955–1.541)</td>
<td>0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>North America</td>
<td>3</td>
<td>1.041 (0.932–1.162)</td>
<td>0.48</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Europe+North America</td>
<td>8</td>
<td>1.085 (1.004–1.172)</td>
<td>0.039</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and PM, particulate matter.

*HR for a 10-μg/m³ increment in PM₁₀ or converted PM₂.₅.

†P value for Cochran Q test.

‡P value for Egger test.

§Too few studies for calculation of bias indicator.

Figure 2. Forest plot of the overall analysis on stroke event and long-term particulate matter (PM) exposure. Hazard ratios (HRs) with 95% confidence intervals (CIs) for a 10-μg/m³ increment in PM₁₀ are presented (including converted HRs from PM₂.₅ exposure). Circles are for PM₁₀, and squares for converted PM₂.₅; symbol size is proportional to the weight of the study in the meta-analysis. Open diamonds represent pooled results from meta-analysis. HEM indicates hemorrhagic stroke; and IS, ischemic stroke. *Weights are calculated as (1/SE²)/Σ(1/SE²)×100 (with SE² the variance of each study effect, and Σ(1/SE²) the sum of inverted variances for all study effects); within continent/overall (sum may differ from 100 because of rounding).
higher than spatial variation within a region. Recent exposure and long-term exposure to PM are different concepts and deserve equal attention. For short-term variation in ambient PM levels, the research question is when adverse events, such as strokes, are most likely to occur, whereas for long-term exposure, the question is rather where people are most at risk. However, although different in concept, the effects of short-term and long-term exposure to PM are not entirely independent from each other because peak elevations of PM (the exposure measure for short-term effects) are likely to occur more frequently in locations with higher long-term ambient PM concentrations.

Other Studies on Stroke and Air Pollution
Two studies on stroke and long-term PM exposure were not included in our meta-analysis because the study cohort was not representative for the general population. Koton et al\(^40\) found no association between stroke and PM\(_{2.5}\) exposure in a cohort of myocardial infarct survivors. Similarly, Maheswaran et al\(^41\) studied a cohort of stroke survivors and found a 52% increased risk of all-cause death for a 10-\(\mu g/m^3\) increase in PM\(_{10}\) concentration.

We restricted our meta-analysis to publications on exposure to PM, but we also found studies quantifying (traffic-related) air pollution by using other pollutants, residential proximity to a major road, or noise as the exposure variable. Most of these studies were reviewed by Ljungman and Mittleman,\(^15\) and they reported positive associations between stroke and long-term exposure to NO\(_x\) or NO\(_2\),\(^22,26,42\) SO\(_2\),\(^18\) or CO.\(^26\) However, null results for NO\(_x\)\(^43\) and ozone\(^18,42\) were found as well. In addition, Maheswaran and Elliott\(^44\) reported higher stroke mortality for living within 200 m of a main road compared with >1000 m; Finkelstein et al\(^45\) published similar results using 50 m for an urban road and 100 m for a highway as the exposure cut-off value.

Overall, these findings support those of our meta-analysis.

Table 3. Results of Sensitivity Analyses

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Pollutant</th>
<th>End Point</th>
<th>No. of Studies</th>
<th>Meta-Analysis Combined HR(\dagger) (95% CI)</th>
<th>P Value (Model)</th>
<th>Tests of Heterogeneity P Value</th>
<th>P% in % (95% CI)</th>
<th>Test of Publication Bias P Value$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (Europe+North America)</td>
<td>PM(_{10})(*)</td>
<td>Stroke event</td>
<td>9</td>
<td>1.021 (0.975–1.069)</td>
<td>0.38</td>
<td>0.016</td>
<td>31.3 (0–66.3)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke mortality</td>
<td>5</td>
<td>1.091 (0.958–1.242)</td>
<td>0.19</td>
<td>0.011</td>
<td>74.5 (3.5–87.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>High-quality score (Europe+North America)</td>
<td>PM(<em>{10})+converted PM(</em>{2.5})(*)</td>
<td>Stroke event</td>
<td>8</td>
<td>1.087 (1.023–1.154)</td>
<td>0.007</td>
<td>0.10</td>
<td>39.6 (0–70.8)</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke mortality</td>
<td>4</td>
<td>1.056 (0.957–1.165)</td>
<td>0.28</td>
<td>0.09</td>
<td>53.9 (0–82.9)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>PM(_{2.5})(*)</td>
<td>Stroke event</td>
<td>5</td>
<td>1.094 (1.038–1.153)</td>
<td>0.001</td>
<td>0.036</td>
<td>8.2 (0–64.1)</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke mortality</td>
<td>4</td>
<td>1.081 (0.981–1.190)</td>
<td>0.12</td>
<td>0.09</td>
<td>54.0 (0–82.9)</td>
<td>0.065</td>
</tr>
</tbody>
</table>

\(*\)HR for a 10-\(\mu g/m^3\) increment in PM\(_{10}\).
\(\dagger\)HR for a 5-\(\mu g/m^3\) increment in PM\(_{2.5}\).
\(\dagger\)P value for Cochran \(Q\) test.
\(\times\)P value for Egger test.

The 5 Asian studies\(^29,32,35–37\) were excluded from the sensitivity analyses. CI indicates confidence interval; HR, hazard ratio; and PM, particulate matter.

Figure 3. Forest plot of the subanalysis on stroke event and long-term particulate matter (PM\(_{2.5}\)) exposure. Hazard ratios (HRs) with 95% confidence intervals (CIs) for a 5-\(\mu g/m^3\) increment in PM\(_{2.5}\) are presented. Symbol size is proportional to the weight of the study in the meta-analysis. Open diamonds represent pooled results from meta-analysis. HEM indicates hemorrhagic stroke; and IS, ischemic stroke.

*Weights are calculated as \((1/SE^2) / (\sum 1/SE^2) \times 100\) (with SE\(^2\) the variance of each study effect, and \(\sum 1/SE^2\) the sum of inverted variances for all study effects): within continent/overall (sum may differ from 100 because of rounding).
Biological Mechanisms

Ambient air pollution is a mixture of several pollutants, but epidemiological and experimental evidence suggests that PM explains the harm caused by air pollution best. By selecting PM_{2.5} as a common indicator, we may capture all effects of different sources and components of PM. Four recent reviews\(^{6,7,9,10}\) summarized the literature concerning biological pathways of the relationship between exposure to PM air pollution and cardiovascular disease. Chronic inhalation of pollutants may cause chronic pulmonary and systemic oxidative stress and inflammation that are critical and well-documented factors leading to the manifestation of endothelial dysfunction, vasoconstriction, and atherosclerosis at the vasculature level and coagulation and thrombosis at the blood tissue level.\(^{9,10,46,47}\) These processes in turn are key factors in the development of chronic or acute cardiovascular diseases, and similarly, they are critical for the onset of cerebrovascular events, such as stroke, especially ischemic stroke. Moreover, the neural cells of the brain are also vulnerable to long-term PM exposure. Particulates can impair the blood–brain barrier, either directly (after having penetrated into the circulatory system) or through the inflammatory processes mentioned above, and subsequently cause chronic inflammation and oxidative stress within the neural cells.\(^{11}\)

Strengths and Limitations

In this comprehensive literature review, we pooled data of 20 different studies from several geographical regions in 1 meta-analysis, thus increasing the statistical power and allowing an investigation of regional patterns. Furthermore, all these studies were published in the past decade (and even 14 of 20 in the past 4 years), indicating that data on both the exposure and the outcome are recent and relevant. By recalculating results for PM_{2.5} to estimated results for PM_{10}, we were able to pool studies using PM_{10} and those using PM_{2.5} as the exposure measure in the main analysis, in addition to separate analyses for both fractions.

This recalculation implies the use of a conversion factor. We opted for a conversion factor of 0.74\(^{8}\) because PM_{2.5}/PM_{10} ratios in the range of 0.5 to 0.8 have been reported, depending on region or city.\(^{38}\) Although the estimated values may not reflect the true PM_{10} concentration for the studies in question, changing the conversion factor to 0.5, 0.8, or a region-specific value did not at all influence the overall result. In our sub-analyses of PM_{2.5} data only, the estimated effects were always higher than those in the corresponding analyses using PM_{10} and converted PM_{2.5}, indicating the importance of measuring PM_{2.5} directly and confirming the hypothesis that the PM_{2.5} fraction is more hazardous than the coarse fraction (PM_{2.5–10}) of PM_{10}.\(^{8}\)

By pooling data for ischemic stroke and hemorrhagic stroke, we might have underestimated the true association between PM exposure and the onset of ischemic stroke. Indeed, evidence found in the literature suggests that the PM-related risk of ischemic stroke is higher than the risk of hemorrhagic stroke.\(^{11,15}\) This is not surprising because ischemic stroke is related to general cardiovascular disease, whereas hemorrhagic stroke has a different pathogenesis. Unfortunately, only 4 of 20 publications in our meta-analysis published results for ischemic and hemorrhagic stroke separately.

Two other potential limitations concern the methodology of the original studies. First, the estimation of exposure was based on data obtained by central monitor stations. All authors made efforts to approach the personal exposure by using data from the monitor station closest to the home of the study subject, sometimes excluding subjects living too far from a station, or by applying spatial interpolation models. However, it is clear that the true exposure, taking into account time spent outdoors versus indoors, in traffic, at work, or in other regions can never be measured at an individual level in large-scale cohort or population-based studies. Moreover, 3 studies\(^{21,27,28}\) extrapolated air pollution data recorded in 1 year to an estimate for the whole-study period, thereby neglecting possible long-term trends.

Second, the ecological nature of register-based studies makes it difficult to account for confounding factors, such as smoking status and SES, because these data are generally not provided in the databases from which stroke events are retrieved. The 6 register-based studies included an estimate of SES on the area level (eg, a deprivation index), but only 1 included data on smoking status. In contrast, all 14 cohort studies adjusted for smoking and 9 adjusted for individual SES, by using educational level, household income, employment status, or a combination of these factors as an indicator of SES. Notably, the 2 studies not adjusting for the important confounder SES were those conducted in Japan,\(^{29,35}\) which is another reason to interpret their study results with greater care. Because of these important differences in study design and methodology, we created a quality index based on the design, exposure measurement, and inclusion of important covariates.

All high-quality studies had a prospective cohort design and measured air pollution exposure over the whole-study period. In addition, all but one used spatial interpolation models to estimate personal exposure instead of raw data from monitor stations. Including only high-quality studies resulted in higher pooled estimates for stroke event but lower HRs for stroke mortality than the corresponding overall analyses.

Implications for Public Health

The Global Burden of Disease (GBD) 2010 study\(^{49}\) provided global statistics on attributable deaths and disability-adjusted life years for 67 risk factors, including environmental air pollution. Worldwide, 3.7 million deaths and 3.1% of global disability-adjusted life years were attributed to air pollution, placing it in the top 10 of risk factors. Cardiovascular and circulatory diseases (including stroke) accounted for the majority of deaths attributed to air pollution. According to the subsequent GBD 2013 study,\(^{1}\) stroke was the third cause of death, with a death rate of 110 per 100,000 inhabitants, resulting in >6 million deaths worldwide in 2013. Burnett and et al\(^{10}\) developed an integrated exposure–response function for the GBD 2010 study and calculated population attributable fractions for stroke and PM exposure. Regional population attributable fractions varied from 1% to 43% for stroke, with a frequency peak value of ≈3% and a second peak value of ≈15%, but no overall global figure was given. These values are similar to the population attributable fractions for alcohol use, diabetes mellitus, and psychological stress, published in the INTERSTROKE study, a global case–control study of risk factors for stroke.\(^{5}\)
Given the high incidence of stroke and stroke-attributed mortality,\textsuperscript{1,2} a substantial reduction of exposure to PM may result in an equally substantial decrease in stroke incidence and stroke mortality, not only in areas with extremely high exposures to PM, such as many cities in China, but also in areas with substantially lower ambient concentrations (although still higher than the World Health Organization guideline values), such as many regions in Western Europe and North America. A reduction of ambient PM concentrations requires urgent attention in many areas of the world. Indeed, in large cities worldwide, annual mean PM\textsubscript{10} concentrations of 30 (Los Angeles), 60 (Sofia, Bulgaria), 70 (Santiago, Chile), 100 (Johannesburg, South Africa), or even 120 \(\mu\text{g} / \text{m}^3\) (Beijing, China) have been reported.\textsuperscript{2} The argument that it is difficult to meet standards in densely populated areas ignores the fact that the importance of a factor with respect to public health increases in proportion to the number of people who are exposed to it. Several cities in North America, Scandinavia, and the United Kingdom prove that ambient PM\textsubscript{10} concentrations of <20 \(\mu\text{g} / \text{m}^3\), as recommended by the World Health Organization,\textsuperscript{3,4} are realistic, even in an urban environment.

Measures taken to reduce the emissions of PM will not only decrease the risk of cerebrovascular disease but also, and to an even greater extent, that of cardiovascular and pulmonary disease.\textsuperscript{5,6} Furthermore, such measures will lead to a decline in the occurrence of peak days with high levels of air pollution and, hence, to a decrease in acute effects caused by short-term exposure, such as stroke,\textsuperscript{7,8} cardiovascular and respiratory events, and all-cause mortality.\textsuperscript{9,10}

### Conclusions

In addition to the recognition of PM air pollution as a causal factor in the progression and triggering of cardiovascular disease, our meta-analysis provides evidence for a positive association between the risk of stroke and long-term PM exposure. Given the fact that the whole population is exposed, air pollution is an important risk factor for stroke, and among other diseases, stroke incidence and stroke mortality would substantially decrease when measures are taken to reduce ambient air pollution levels.

### Sources of Funding

This work was supported by grants from the Fund for Scientific Research (Vlaanderen) and the European Research Council (grant no. ERC-2012-StG 310898).

### Disclosures

None.

### References

Long-Term Exposure to Particulate Matter Air Pollution Is a Risk Factor for Stroke: Meta-Analytical Evidence

Hans Scheers, Lotte Jacobs, Lidia Casas, Benoit Nemery and Tim S. Nawrot

Stroke. 2015;46:3058-3066; originally published online October 13, 2015;
doi: 10.1161/STROKEAHA.115.009913

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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Long-term exposure to particulate matter air pollution is a risk factor for stroke: the meta-analytical evidence

Meta-analysis on particulate matter and stroke

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Supplemental Methods and Results

Literature search and selection of studies

We used the following search terms in the Pubmed database, without the use of quotation marks:

- air pollution stroke
- air pollution cerebrovascular disease
- air pollution stroke mortality
- air pollution cerebrovascular disease mortality
- air pollution stroke hospital admissions
- air pollution cerebrovascular disease hospital admissions
- particulate matter stroke
- particulate matter cerebrovascular disease
- particulate matter stroke mortality
- particulate matter cerebrovascular disease mortality
- particulate matter stroke hospital admissions
- particulate matter cerebrovascular disease hospital admissions

A flow chart of the selection procedure is given in Figure I. Of the 596 studies identified after our initial search, 572 were excluded for various reasons. Of 24 included publications, six were further excluded because they reported findings based on the same population as another included study. Two initially undetected studies were added on the basis of references and reviews. Thus, we eventually included 20 publications on stroke and long-term PM exposure in our meta-analysis.1-20

The definition of the endpoint varied slightly among publications. Both terms ‘cerebrovascular disease’ and ‘stroke’ were found. All but four studies10,11,14,15 defined stroke type based on the International Classification of Diseases (ICD) provided by the World Health Organization (WHO). Hence, it was possible to distinguish between all strokes (ICD-9 430-438 or ICD-10 I60-I69), ischemic strokes (ICD-9 434 or ICD-10 I63) and hemorrhagic strokes (ICD-9 430-432 or ICD-10 I60-I62). However, too few studies reported results for ischemic stroke or hemorrhagic stroke separately to allow analyses by stroke type. On the other hand, one study14 did not show combined results for all strokes, but only for ischemic and hemorrhagic stroke separately, and we included both HRs in the meta-analysis. Seven studies published results on stroke mortality only. The other 13 papers included non-fatal strokes and defined the outcome as ‘stroke incidence’ (6), ‘first stroke’ (4 publications), ‘hospital admission’ (2), or ‘first hospital admission’ (1). Five out of these 13 studies conducted a subanalysis on stroke mortality (see Figure I).

Variation in PM$_{2.5}$ values in the Edmonton study5 was low, which resulted in a HR with a very large CI, thus having virtually no weight in the meta-analysis. Qin et al.15 presented no overall HR, but only results for stratified analyses by body weight class (normal, BMI<25; overweight, 25<BMI<30; obese, BMI>30). We included these stratified analyses as separate study results in the meta-analysis.
Quality of studies and standardization of results

We assessed quality of the selected studies taking into account the following aspects: study design, number and nature of covariates in the analysis, estimation of the exposure, and definition of the endpoint. Scores for each of these aspects and the overall quality score are presented in Table I. Studies with an overall quality score above the median were included in the subanalyses of high quality studies. After removing the five Asian studies from the list, the cut-off was a score of 7 for overall stroke event (N=15 studies) and 6.75 for the mortality subset (N=8).

We standardized reported results to hazard ratios (HR) for a 10 µg/m³ increment of PM$_{10}$ in three steps. First, whenever the HR or relative risk (RR) was not presented on a continuous scale, but as a HR or RR for each exposure quantile with the lowest quantile as a reference, we calculated the difference (D) between the means of the highest and the lowest quantile and treated the HR for the highest quantile compared to the lowest as a HR for a D µg/m³ increment of PM (HR$_D$).

Second, each HR$_D$ and each HR for an interquartile range (IQR) increment (HR$_{IQR}$) was recalculated to a HR per 10 µg/m³ increment (HR$_{10\mu g}$) with the formula HR$_{10\mu g} = HR_D^{10/D}$ or HR$_{10\mu g} = HR_{IQR}^{10/IQR}$ for PM$_{10}$ and, analogously, to a HR per 5 µg/m³ increment for PM$_{2.5}$: HR$_{5\mu g} = HR_D^{5/D}$ or HR$_{5\mu g} = HR_{IQR}^{5/IQR}$.

Third, since we aimed to insert study results for both PM$_{10}$ and PM$_{2.5}$ in a single meta-analysis, we transformed results for PM$_{2.5}$ to estimated results for PM$_{10}$ by applying a conversion factor assuming that, on average, PM$_{10}$ consists of 70% of PM$_{2.5}$ (HR$_{PM10}$ = HR$_{PM2.5}^{0.7}$). However, proportions of 50% to 80% have been reported in studies measuring both fractions in the same environment.

Hazard ratios (HR), 95% confidence intervals (CI), and tests for heterogeneity and publication bias proved to be robust against changes in the conversion factor (Table II).

Heterogeneity and publication bias

The overall HR and 95% confidence interval (CI) was estimated using a random-effects model. To check the assumption of substantial heterogeneity among studies, we applied Cochran’s Q test and calculated the I$^2$ statistic. I$^2$ values of ≤25%, 25-75% and ≥75% indicate low, moderate and high heterogeneity, respectively. Publication bias was assessed by visual inspection of funnel plots and by formal testing with Egger’s linear regression method.

Statistics on heterogeneity among studies and publication bias are shown in Tables 2 and 3. Our a priori choice for random effects models was justified, given the considerable heterogeneity. Cochran’s Q test was significant in most main and subgroup meta-analyses, and I$^2$ values indicated moderate to high heterogeneity.

Figure II to Figure IV show the funnel plots for the inspection of publication bias in the overall analysis (15 studies from Europe and North America, Figure II), the analysis of stroke...
mortality data only (8 studies, Figure III) and the analysis of PM$_{2.5}$ exposure data only (10 studies, Figure IV). Severe departure from symmetry around the meta-estimate (indicated by the vertical axis) suggests publication bias towards negative (left) or positive (right) study results.

We found no indications of publication bias in most analyses. However, Egger’s test results and funnel plots of the main analyses for Europe and North America taken together suggest a bias towards positive results for studies with large CIs ($p=0.018$ for stroke event and $p=0.040$ for stroke mortality) (Table 2 in main paper). When considering only the high quality studies, moderate publication bias was found only in the subset of stroke mortality with PM$_{2.5}$ exposure.
## Supplemental Tables

### Table I. Quality assessment of studies included

<table>
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<tr>
<th>Reference</th>
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<th>Other&lt;sup&gt;f&lt;/sup&gt;</th>
<th>Exposure measurement</th>
<th>Definition of stroke&lt;sup&gt;i&lt;/sup&gt;</th>
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Prospective cohort with personal baseline questionnaire of all subjects: 2 points; Cohort study with questionnaire organized later: 1 point; Register-based ecological study: 0 points

Adjusted for age and sex: 0.5 points each (in cohort studies on men or women only, the 0.5 points were awarded)

Adjusted for personal habits: 1 point for smoking status; 1 point for at least two of: alcohol consumption, diet, physical activity, occupational exposure.

Adjusted for health: 1 point for BMI plus at least one of: blood pressure (hypertension, medication), cholesterol, diabetes, family history of cardiovascular disease

Adjusted for SES: 1 point for estimation of SES at an individual level (at least one of: income, education, employment status), 0.5 points for area-level estimation (e.g. deprivation index)

Measured during the whole study period: 1 point; Measured during 1 year and extrapolated to whole period: 0 points; Measured during >1y but less than study period: 0.5 points

Interpolation model used (e.g. land-use regression model): 1 point; Raw data from nearest monitor station: 0 points

Based on CD-9 or ICD-10 coding: 0.5 points; First stroke (i.e. individuals with stroke history excluded): 0.5 points

Sum of scores

* Included in the overall subanalysis on high-quality studies (Europe and North America only)
† Included in the mortality subanalysis on high-quality studies (Europe and North America only)
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<th>Pollutant</th>
<th>Endpoint</th>
<th>Conversion factor for PM$_{2.5}$</th>
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<th>Meta-analysis</th>
<th>Tests of heterogeneity</th>
<th>Test of publ. bias</th>
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</table>

In bold the conversion factor and related results chosen by the authors of the present paper.

*HR for a 10 µg/m³ increment in PM$_{10}$ or converted PM$_{2.5}$.

†For the six studies concerned, the conversion factor was 0.6, 0.6, 0.36, 0.67, 0.6, and 0.6, respectively.
Supplemental Figures

Figure I. Flowchart of the literature search.

596 studies identified
(PubMed search)

572 studies excluded
- 276 not relevant (did not study either air pollution or stroke)
- 144 other approach (short-term exposure, patient cohort)
- 35 other pollutant than PM
- 77 no data analysis (reviews, comments, letters)
- 40 experimental studies (human, animal, \textit{in vitro})

24 studies selected for inclusion

6 studies excluded because of duplicate with the same population

18 studies included

2 additional studies identified from reviews and reference lists

20 studies included on long-term PM exposure and stroke:
- 7 on stroke mortality only
- 8 on stroke event without separate data on mortality
- 5 on stroke event with separate data on mortality
Figure II. Funnel plot of individual study hazard ratio (presented on a natural log scale) for the association between stroke event and PM$_{10}$ (including converted PM$_{2.5}$) exposure (N=15 studies, North America + Europe).

Figure III. Funnel plot of individual study hazard ratio (presented on a natural log scale) for the association between stroke mortality and PM$_{10}$ (including converted PM$_{2.5}$) exposure (N=8 studies, North America + Europe).
Figure IV. Funnel plot of individual study hazard ratio (presented on a natural log scale) for the association between stroke event and PM2.5 exposure (N=10 studies, North America + Europe).
Supplemental References


Abstract

粒子状物質による大気污染への長期曝露は脳卒中の危険因子である
メタ解析のエビデンス

Long-Term Exposure to Particulate Matter Air Pollution Is a Risk Factor for Stroke
Meta-Analytical Evidence

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背景および目的：脳卒中の発生率および死亡率と粒子状物質（PM）による大気汚染への長期曝露との関連がいくつかの疫学研究で示唆されている。しかし、その関連性の程度については不明である。

方法：PubMedデータベースで脳卒中とPM曝露に関する疫学研究を検索した。次に、脳卒中の発生率および死亡率とPMへの長期曝露を統合した関連性をメタ解析によって定量化した。脳卒中イベントおよび脳卒中死亡率とPM₂.⁵およびPM₁₀について、個別および複合してメタ解析を行った。

結果：PMへの長期曝露は脳卒中イベントもしくは脳卒中死亡率に関して合計1,000万例以上を調べた20項の調査を特定した。PM₂.⁵曝露（PM₂.⁵を用いた調査からPM₂.⁵曝露数を予測した調査も含む）における10µg/m³増加毎の統合ハザード比は、全脳卒中イベントでは0.96【95%信頼間（CI）：1.018～1.105】脳卒中死亡率では0.890（0.992～1.177）。脳卒中イベントをHans Scheers, MSc, Lotte Jacobs, PhD, Lidia Casas, PhD, et al.に基づく。

Stroke 2015;46:3058-3066. DOI: 10.1161/STROKEAHA.115.009913.