Effect of Exhaust- and Nonexhaust-Related Components of Particulate Matter on Long-Term Survival After Stroke

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Background and Purpose—Outdoor air pollution represents a potentially modifiable risk factor for stroke. We examined the link between ambient pollution and mortality up to 5 years poststroke, especially for pollutants associated with vehicle exhaust.

Methods—Data from the South London Stroke Register, a population-based register covering an urban, multiethnic population, were used. Hazard ratios (HR) for a 1 interquartile range increase in particulate matter <2.5 µm diameter (PM$_{2.5}$) and PM <10 µm (PM$_{10}$) were estimated poststroke using Cox regression, overall and broken down into exhaust and nonexhaust components. Analysis was stratified for ischemic and hemorrhagic strokes and was further broken down by Oxford Community Stroke Project classification.

Results—The hazard of death associated with PM$_{2.5}$ up to 5 years after stroke was significantly elevated ($P=0.006$) for all strokes (HR=1.28; 95% confidence interval [CI], 1.08–1.53) and ischemic strokes (HR, 1.32; 95% CI, 1.08–1.62). Within ischemic subtypes, PM$_{2.5}$ pollution increased mortality risk for total anterior circulation infarcts by 2-fold (HR, 2.01; 95% CI, 1.17–3.48; $P=0.012$) and by 78% for lacunar infarcts (HR, 1.78; 95% CI, 1.18–2.66; $P=0.006$). PM$_{10}$ pollution was associated with 45% increased mortality risk for lacunar infarct strokes (HR, 1.45; 95% CI, 1.06–2.00; $P=0.022$). Separating PM$_{2.5}$ and PM$_{10}$ into exhaust and nonexhaust components did not show increased mortality.

Conclusions—Exposure to certain outdoor PM pollution, particularly PM$_{2.5}$, increased mortality risk poststroke up to 5 years after the initial stroke. (Stroke. 2016;47:2916-2922. DOI: 10.1161/STROKEAHA.116.014242.)

Key Words: air pollution • mortality • particulate matter • stroke • survival analysis
to separate PM into source-related components.\textsuperscript{7,15} may prove useful in this regard.

The risk of death associated with air pollution may be unevenly spread throughout the population. There is evidence to suggest that people with a history of myocardial infarction or cardiovascular disease are susceptible to increased mortality risks with higher PM exposure levels.\textsuperscript{16–19} Links between mortality and PM exposure have also been found in diabetics\textsuperscript{13,16} and people with respiratory diseases.\textsuperscript{18,19} Taken together, this evidence suggests that long-term exposure to PM air pollution may be associated with a higher risk of mortality in populations with preexisting health conditions. However, few studies have examined the long-term effects of PM exposure in a poststroke population.

This study combines a stroke register in South London with a high-resolution air quality model to investigate associations between long-term exposure to air pollution and survival after incident stroke.

**Methods**

**Subjects**

Patients in this study come from the South London Stroke Register, a population-based register of incident strokes set up in 1995 among an urban population living in a 2 boroughs of South London. The study had approval from the Ethics Committee of Guy’s and St Thomas’ Hospital Trust, King’s College Hospital, and the subjects gave informed consent. The South London Stroke Register source population consists of 357,308 individuals, of whom 56% were white, 25% were black, 6% were Asian, and 12% were other ethnic group (census 2011). Stroke survival >5 years was examined from 2005 to 2012. Hemorrhagic strokes consisted of primary intracerebral hemorrhage and subarachnoid hemorrhage. Ischemic strokes were subdivided using the Oxford Community Stroke Project classification\textsuperscript{10} as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI), and lacunar infarct (LACI).

**Data Collection**

Data collection methods have been described before.\textsuperscript{20} Trained field-workers collected data as soon as possible after the time of first stroke and a clinician verified the diagnosis of stroke. This study utilized particular data on age, sex, ethnicity (black, white, and other), year of stroke, and stroke severity. Deprivation was measured by the Index of Multiple Deprivation, and stroke severity was measured by National Institutes of Health Stroke Scale total. Patients who were still alive were censored on December 31, 2012. Hazard ratios (HR) with 95% confidence intervals (CIs) were estimated for a 1 interquartile range (IQR) increase in each pollutant up to 5 years after initial stroke using a Cox regression model for all-cause mortality. Each pollutant was included separately in the models during the analyses. The analysis was stratified by overall stroke and subtypes (ischemic and hemorrhagic) and then by ischemic subtypes (TACI, PACI, POCI, and LACI). Models controlled for the following confounders: age, sex, ethnicity, year of stroke, deprivation (Index of Multiple Deprivation rank subdivided into quarters), transient ischemic attacks before stroke, and stroke severity (National Institutes of Health Stroke Scale total). Fewer deaths occurred in ischemic subtypes than in all strokes; to avoid overfitting the model, the number of confounders for ischemic subtypes was reduced to the following: age, sex, ethnicity, year of stroke, and stroke severity (National Institutes of Health Stroke Scale total). This reduced model was also applied to the data on all strokes, ischemic and hemorrhagic strokes. Estimate HRs for pollutants were similar in the reduced and main models (data not shown). Further models were also fitted in which an interaction term between particular pollutants and subtype (ischemic or hemorrhagic or within ischemic subtypes) were included. Kaplan–Meier curves were plotted to assess survival probability and PM\textsubscript{2.5} exposure for ischemic, TACI, and LACI strokes up to 5 years; PM\textsubscript{2.5} exposure was divided into tertiles (low, middle, and high). The analysis was conducted using STATA version 13MP.

### Results

#### Demographics of the Study Population

In total, 1800 strokes were recorded between 2005 and 2012. The average age was 68.8 years, with 26% of the individuals aged 75

<table>
<thead>
<tr>
<th>Table 1. Average Pollutant Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) µg/m$^3$</strong></td>
</tr>
<tr>
<td>NO</td>
</tr>
<tr>
<td>NO$_2$</td>
</tr>
<tr>
<td>NO$_x$</td>
</tr>
<tr>
<td>O$_3$</td>
</tr>
<tr>
<td>O$_x$</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
</tr>
<tr>
<td>PM$_{2.5}$ exhaust</td>
</tr>
<tr>
<td>PM$_{2.5}$ nonexhaust</td>
</tr>
<tr>
<td>PM$_{10}$</td>
</tr>
<tr>
<td>PM$_{10}$ exhaust</td>
</tr>
<tr>
<td>PM$_{10}$ nonexhaust</td>
</tr>
<tr>
<td>PM coarse</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; NO, nitric oxide; NO$_2$, nitrogen dioxide; NO$_x$, nitrogen oxides; O$_3$, ozone; Ox, oxidant; PM$_{2.5}$, particulate matter <10 µm; and PM$_{10}$, particulate matter <2.5 µm.

Inventory exhaust emissions factors were combined with UK-specific roadside measurements,\textsuperscript{24} whereas nonexhaust emissions were based on the work of Harrison et al.\textsuperscript{25} Pollution concentrations were then weighted by population counts at each postcode using 2011 census data and averaged across the years of the study period. This provided an estimated average pollution level that could be linked to the South London Stroke Register participants’ place of residence at the time of initial stroke.
to 84 years, and roughly half (52.3%) were men (Table 2). In the population, 74.3% of strokes were ischemic (n=1338), 14.5% were hemorrhagic (n=261), and 11.2% were unknown or undefined (n=201). Of the ischemic strokes, 10.5% of strokes were TACI, 29.6% were PACI, 10.9% were POCI, 23.2% were LACI, and 0.2% were unspecified ischemic infarcts. Hemorrhagic strokes consisted of primary intracerebral hemorrhage (11.3%) and subarachnoid hemorrhage (3.2%) strokes.

**HRs for Incident Strokes, Including Subtype Analysis**

HRs for all stroke types and separately for ischemic and hemorrhagic strokes are presented in Table 3. Five years after an initial stroke, PM$_{2.5}$ was associated with reduced survival rates by 28% per IQR increase for all strokes (HR, 1.28; 95% CI, 1.08–1.53; $P=0.006$; see also Figure [A]) and with reduced survival rates by 32% for ischemic strokes (HR, 1.32; 95% CI, 1.08–1.62; $P=0.006$). No significances were observed for hemorrhagic strokes. Significant interactions between type of stroke (ischemic or hemorrhagic) and PM$_{2.5}$ ($P=0.0095$) further suggest that the pollutants may be associated with a higher mortality risk for ischemic strokes than for hemorrhagic strokes.

Within ischemic subtypes (Table 4), PM$_{2.5}$ was associated with a 2-fold reduced survival rate for TACI strokes per IQR increase (HR, 2.01; 95% CI, 1.17–3.48; $P=0.012$; see also Figure [B]). For LACI strokes, higher mortality rates were observed for PM$_{10}$ (HR, 1.45; 95% CI, 1.06–2.00; $P=0.022$) and PM$_{2.5}$ (HR, 1.78; 95% CI, 1.18–2.66; $P=0.006$; see also Figure [B]), reducing survival rates by 45% and 78%, respectively. No significances were observed for PACI and POCI ischemic strokes. Separating PM$_{2.5}$ and PM$_{10}$ into exhaust and nonexhaust components did not show increased mortality in either analysis. Interactions between ischemic subtypes and PM$_{10}$ ($P=0.3985$) and PM$_{2.5}$ ($P=0.4128$) were not statistically significant.

**Discussion**

Long-term annual exposure to the pollutant PM$_{2.5}$ is associated with an increase in the long-term mortality rate in a post-stroke population, especially for ischemic strokes. Although the difference between subtypes was not statistically significant, there was also some indication that PM$_{2.5}$ exposure may increase risk of TACI and LACI more than POCI and PACI. For every IQR increase in PM$_{2.5}$, the risk of death after 5 years increased by 28%; for patients with ischemic stroke, the risk of death increased by 32%. Certain subtypes of ischemic strokes had particularly high mortality rates associated with PM$_{2.5}$ exposure; the risk of death for patients with TACI stroke increased by 2-fold for every IQR increase in PM$_{2.5}$.

**Table 2. Incident Stroke Cases From 2005 to 2012 by Age, Sex, and Stroke Subtype**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. of Strokes (%)</th>
<th>No. of Deaths</th>
<th>Cumulative Survival, % (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1800</td>
<td>729</td>
<td>87.1 (86.2–88.0)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>364 (20.2)</td>
<td>52</td>
<td>83.9 (79.1–87.7)</td>
<td></td>
</tr>
<tr>
<td>55–64</td>
<td>300 (16.7)</td>
<td>53</td>
<td>77.8 (71.6–82.9)</td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>396 (22.0)</td>
<td>149</td>
<td>55.2 (49.2–60.8)</td>
<td></td>
</tr>
<tr>
<td>75–84</td>
<td>465 (25.8)</td>
<td>264</td>
<td>31.1 (25.9–36.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;85</td>
<td>275 (15.3)</td>
<td>211</td>
<td>9.5 (5.4–15.0)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>942 (52.3)</td>
<td>336</td>
<td>56.2 (52.2–60.0)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>858 (47.7)</td>
<td>393</td>
<td>45.6 (41.5–49.6)</td>
<td></td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TACI</td>
<td>189 (10.5)</td>
<td>105</td>
<td>39.3 (31.3–47.2)</td>
<td></td>
</tr>
<tr>
<td>PACI</td>
<td>532 (29.6)</td>
<td>241</td>
<td>45.7 (40.5–50.7)</td>
<td></td>
</tr>
<tr>
<td>POCI</td>
<td>196 (10.9)</td>
<td>70</td>
<td>53.9 (44.8–62.1)</td>
<td></td>
</tr>
<tr>
<td>LACI</td>
<td>417 (23.2)</td>
<td>134</td>
<td>59.3 (53.4–64.7)</td>
<td></td>
</tr>
<tr>
<td>Infarction unspecified</td>
<td>4 (0.2)</td>
<td>2</td>
<td>50.0 (5.8–84.5)</td>
<td></td>
</tr>
<tr>
<td>PICH</td>
<td>204 (11.3)</td>
<td>98</td>
<td>50.5 (42.6–57.9)</td>
<td></td>
</tr>
<tr>
<td>SAH</td>
<td>57 (3.2)</td>
<td>16</td>
<td>71.2 (57.3–81.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown/undefined</td>
<td>201 (11.2)</td>
<td>63</td>
<td>49.7 (38.3–60.0)</td>
<td></td>
</tr>
</tbody>
</table>

Number of incident strokes and deaths by age, sex, and stroke subtype. Cumulative survival at 5 years was calculated and compared across groups using the log-rank test. CI indicates confidence interval; LACI, lacunar infarct; PACI, partial anterior circulation infarct; PICH, primary intracerebral hemorrhage; POCI, posterior circulation infarct; SAH, subarachnoid hemorrhage; and TACI, total anterior circulation infarct.
For patients with LACI stroke, 1 IQR increase in PM_{2.5} was associated with a 78% increase in the risk of death; for PM_{10}, the associated increased risk of death was 45%.

The link between air pollution and stroke as a cause of death has been studied before; however, the association increased risk of death was 45%.

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stroke cause onset may also play a role in the mechanisms that influence the risk of death in a poststroke population to the long-term exposure of PM.

**Strengths and Limitations**

This is the first study that has measured long-term annual pollution exposure and its association with survival rates in a poststroke population with the following factors: (1) examining overall, exhaust, and nonexhaust source contributions for PM$_{2.5}$ and PM$_{10}$ and (2) breaking down incident stroke into specific causal subtypes. One of the positives of our study was that it was carefully controlled and attempted to reduce the influence of factors associated with stroke deaths such as previous transient ischemic attacks, stroke severity, age, sex, stroke ethnicity, and deprivation status.

One limitation of our study is that we did not quantify individual pollution exposure but used pollution levels at residential postcode addresses as a proxy for individual exposure to pollutants. Modeled pollution exposure estimates were assigned to the geographical centers of postcodes and then averaged across the years of the study. Information on how long the participant stayed in their residence, how far away their residence was located from the postcode centroid, and what the day-to-day activities of the participants were as they relate to pollutant exposure levels was not available.

Another potential point of criticism is that we only measured associations between long-term annual pollution exposure and mortality, and therefore it is hard to make a definitive statement of whether reducing air pollution would reduce mortality in a poststroke population. Previous studies, although, have found that air pollution reduction reduces the risk of death in the general population. Clancy et al. examined the health effects 6 years before and after a ban on coal sales in 1990 in Dublin, Ireland. The associated drop of deaths after the ban was stark; 116 fewer respiratory deaths and 243 fewer cardiovascular deaths occurred in Dublin after the coal ban. This indicates that air pollution reduction has the ability to reduce deaths. By identifying the groups that are particularly vulnerable to air pollution–associated mortality (eg, survivors of ischemic stroke and, in particular, TACI and LACI stroke), our study may have implications for wider health policies.

**Sources of Funding**

The research was funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy’s and St Thomas’ National Health Service (NHS) Foundation Trust and...
King’s College London, and the NIHR Collaboration for Leadership in Applied Health Research and Care South London at King’s College Hospital NHS Foundation Trust.

Disclosures

None.

References


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Stroke. 2016;47:2916-2922; originally published online November 3, 2016; doi: 10.1161/STROKEAHA.116.014242

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