Air pollution and the incidence of ischaemic and haemorrhagic stroke in the South London Stroke Register: a case–cross-over analysis

B K Butland, R W Atkinson, S Crichton, B Barratt, S Beever, A Spiridou, U Hoang, F J Kelly, C D Wolfe

ABSTRACT

Background Few European studies investigating associations between short-term exposure to air pollution and incident stroke have considered stroke subtypes. Using information from the South London Stroke Register for 2005–2012, we investigated associations between daily concentrations of gaseous and particulate air pollutants and incident stroke subtypes in an ethnically diverse area of London, UK.

Methods Modelled daily pollutant concentrations based on a combination of measurements and dispersion modelling were linked at postcode level to incident stroke events stratified by haemorrhagic and ischaemic subtypes. The data were analysed using a time-stratified case–cross-over approach. Conditional logistic regression models included natural cubic splines for daily mean temperature and daily mean relative humidity, a binary term for public holidays and a sine–cosine annual cycle. Of primary interest were same day mean concentrations of particulate matter <2.5 and <10 μm in diameter (PM2.5, PM10), ozone (O3), nitrogen dioxide (NO2) and NO2+nitrogen oxide (NOx).

Results Our analysis was based on 1758 incident strokes (1311 were ischaemic and 256 were haemorrhagic). We found no evidence of an association between all stroke or ischaemic stroke and same day exposure to PM2.5, PM10, O3, NO2 or NOx. For haemorrhagic stroke, we found a negative association with PM10, suggestive of a 14.6% (95% CI 0.7% to 26.5%) fall in risk per 10 μg/m3 increase in pollutant.

Conclusions Using data from the South London Stroke Register, we found no evidence of a positive association between outdoor air pollution and incident stroke or its subtypes. These results, though in contrast to recent meta-analyses, are not inconsistent with the mixed findings of other UK studies.

INTRODUCTION

Associations between stroke mortality and morbidity and the short-term exposure to gaseous and particulate air pollutants have been investigated by various studies around the world. A recent meta-analysis by Shah et al.1 based on 94 studies in 28 countries, reported small positive associations between the risk of hospitalisation or mortality for stroke and the same day exposure (lag 0) to each of sulfur dioxide (SO2), carbon monoxide (CO), nitrogen dioxide (NO2) and particulate matter <10 and <2.5 μm in diameter (PM10 and PM2.5, respectively). In terms of stroke subtypes, there were positive associations between ischaemic stroke and ‘overall’ exposure (typically the shortest lag available) to NO2 and PM2.5 and between haemorrhagic stroke and ‘overall’ exposure to NO2. Haemorrhagic stroke is less common than ischaemic stroke leading to lower statistical power and fewer studies considering it as a separate outcome. However, two recently published studies in Taiwan provided evidence of positive associations between hospital admission for haemorrhagic stroke and exposure to PM2.5 (particularly on warm days),4 and between emergency room visits for haemorrhagic stroke and the same day exposure to the PM2.5 components nitrate and elemental carbon.5

Further studies with sufficient information to distinguish between stroke subtypes (eg, ischaemic and haemorrhagic) are therefore required. The use of stroke registry data in this context is relatively uncommon with most studies based on hospital admissions, emergency department/emergency room visits or mortality. Data from a community-based stroke register using multiple sources of case notification will be more complete, accurate and less prone to misclassification.6 7 A study by Henrotin et al.,8 based on the stroke register in Dijon, France, reported a positive association between the previous day exposure (lag1) to ozone (O3) and ischaemic stroke but no associations with haemorrhagic stroke.

The aim of our study is to link data from the South London Stroke Register (SLSR) at postcode level to daily outputs from an urban background pollution model in order to investigate the effects of short-term exposure to gaseous and particulate pollutants on incident stroke and various stroke subtypes using a time-stratified case–cross-over approach.

METHODS

Pollution data

Annual mean pollution concentrations at a spatial resolution of 20 m×20 m were predicted using the King’s College London urban model (KCLurban). The model bases its predictions on a combination of direct measurements from pollution monitors, information from emission data sets and dispersion modelling techniques.9 A full description of the KCLurban model can be found in online supplementary file 1. In a two-stage process, annual average pollutant outputs for each postcode and for each of the years 2005–2012 were first obtained using KCLurban and then modified by pollutant-specific time series 2005–2012 of daily ‘Nowcast’ scaling factors (see online supplementary file 2) to obtain spatially resolved time series of daily mean PM2.5, PM10, O3, NO2 and NO2+nitrogen oxide.
(NO₂, NO₃) concentrations and a daily maximum 8-hour mean O₃ concentration. This method of applying temporal scaling factors to annual model outputs has previously been used in relation to land use regression models. Postcodes were then used to link pollutant time series to individual stroke cases.

Based on a comparison of daily modelled and observed pollutant concentrations from January 2009 to May 2010 across a random sample of London monitoring sites, normalised mean bias was estimated as 9% for PM₁₀ and 8% for NO₂. Further details of model validation (KC UrbAn and ‘Nowcast’ scaling factors) are provided in online supplementary files 1 and 2.

Weather data
Single time series of daily mean temperature and daily mean relative humidity at Heathrow Airport for the years 2005–2012 were obtained from the Meteorological Office. The same time series were used for each postcode within our study area.

Identification of patients with stroke
The SLSR is a population-based register that has prospectively collected information on more than 5000 people of all ages with incident strokes since 1995. It covers a 30.1 km², ethnically diverse area of South London where the base population of 337 308 individuals is composed of 56% white, 25% black, 6% Asian and 12% other ethnicity according to the 2011 census. Patients with first-ever stroke are recruited to the register as soon as possible following stroke onset. They are identified by register nurses and doctors using various sources of notification and the WHO definition of stroke. The detailed methods of case ascertainment and data collection have been described elsewhere. Stroke subtypes are classified into primary intracerebral haemorrhage (PIH), subarachnoid haemorrhage (SAH), lacunar infarct (LACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI) and anterior circulation infarct (TACI), uncategorised and unknown. LACI, PACI, POCI and TACI are defined according to the Oxford Community Stroke Project classification. Other data collected at the time of stroke include sociodemographic characteristics (age at incident stroke, sex, self-definition of ethnic origin, socioeconomic status, living circumstances before stroke) and clinical details at the time of maximal impairment (Glasgow Coma Scale, National Institute of Health Stroke Score, swallowing and urinary incontinence).

Statistical methods
Our data set was constructed to facilitate a time-stratified case–cross-over analysis, in which each case (ie, patient with stroke) acts as its own control. This is achieved by comparing exposure variables (eg, pollutant metrics) between the index day (ie, day of stroke) and a set of control days. For each patient in this study, the control days were chosen so as to be in the same month and day of the week as the event day. The analytical data set therefore resembled that of a 1: M matched case–control study and was analysed as such in STATA12 (StataCorp: Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011) using conditional logistic regression. In terms of covariate adjustment, our regression models included: an indicator variable for public holidays; two natural cubic splines (degrees of freedom=2), one for daily mean temperature averaged over the day and the day prior (mean lags 0–1) and one for daily mean temperature averaged over the 2–6 days prior (mean lags 2–6); two natural cubic splines representing the lagged averages (mean lags 0–1 and mean lags 2–6) of daily mean relative humidity; and in an attempt to adjust for any residual seasonality, the sine–cosine terms needed to incorporate a simple annual cycle. The exposure variables considered were same day (lag 0) daily mean concentrations of PM₁₀, PM₂.5, O₃, NO₂ and NOₓ and the primary outcome variables were all stroke, ischaemic stroke and haemorrhagic stroke. Stroke subtypes TACI, PACI, POCI and LACI were considered as secondary outcomes. Effect modification was explored by including interaction terms in the regression model and testing for improvements in fit using likelihood ratio tests. Three potential effect modifiers were investigated: season, sex and age group (<65, ≥65).

We conducted two sensitivity analyses. First, we used an unconstrained distribution lag model (UDLM) approach to estimate the combined effect on incident stroke of same day (lag 0) and previous day (lag 1) pollutant exposures. Second, we investigated the effects of replacing our postcode-specific modelled pollution concentrations with daily mean pollution measurements from the London Bloomsbury monitoring station of the Automatic Urban and Rural Network (AURN) of the UK Department for Environment, Food and Rural Affairs (http://uk-air.defra.gov.uk).

RESULTS
Between 2005 and 2012, there were 1799 strokes registered on the SLSR database of which 1337 (74%) were ischaemic strokes (ie, TACI, PACI, LACI, POCI and infarct unspecified), 261 (15%) haemorrhagic strokes (ie, PIH or SAH) and 204 (11%) either unclassified or of unknown classification. The 1799 patients with stroke were spread across 1398 postcodes.

Missing data
Missing pollution data on PM₂.₅, PM₁₀, O₃, NO₂ or NOₓ or missing weather data led to the exclusion of 41 strokes from our main analyses, of which 26 were ischaemic and 5 haemorrhagic. Missing information also affected the number of referent or control days per case. Of the 1758 strokes (spread across 1372 postcodes) used in our main analysis, 12 were matched with 2 control days, 1060 were matched with 3 control days and 686 were matched with 4 control days.

Descriptive statistics
Table 1 compares the demographic characteristics and medical history of patients according to stroke classification. Ischaemic and haemorrhagic strokes differed in terms of age and medical history, with haemorrhagic stroke cases tending to be younger and to be less likely to have a history of hypertension, transient ischaemic attack, arterial fibrillation and high cholesterol.

Means, medians and IQRs for study pollutants and weather variables are presented in table 2. Pollutant variables were highly correlated. O₃ was negatively correlated with NO₂ (Spearman’s r=−0.59), NOₓ (r=−0.72), PM₁₀ (r=−0.33) and PM₂.₅ (r=−0.40), whereas NOₓ and NO₂ were positively correlated with both PM₁₀ (r=0.59 and r=0.63, respectively) and PM₂.₅ (r=0.62 and r=0.65, respectively).

Primary outcomes
In single pollutant models, there was no evidence of a positive association of O₃, NO₂, PM₂.₅, PM₁₀ or NOₓ with stroke, ischaemic stroke or haemorrhagic stroke (table 3). For PM₁₀ and haemorrhagic stroke, the association was both negative and statistically significant with an estimated reduction in risk of 14.6% (95% CI 0.7% to 26.5%) per 10 μg/m³ increase in pollutant. This negative association persisted following adjustment for O₃. A significant negative association with haemorrhagic
stroke was also observed for PM$_{2.5}$ but only following adjustment for NO$_X$.

Modifying factors
There was some evidence ($p=0.019$) that any association between O$_3$ and incident stroke may vary with season (table 4). In particular, season-specific estimates appeared to suggest that any negative association between O$_3$ and all stroke was confined to the autumn months.

We found no evidence of effect modification by age group or by sex (data not shown).

Secondary outcomes
In single pollutant models, there was no evidence of an association of PM$_{2.5}$, PM$_{10}$, O$_3$, NO$_2$ or NO$_X$ with TACI, PACI, POCI or LACI (table 5).

Sensitivity analyses
When we incorporated exposures at both lags 0 and 1 (ie, UDLM lag 0–1) in single pollutant models (cf. table 3), we found no evidence of an association of PM$_{2.5}$, PM$_{10}$, O$_3$, NO$_2$ or NO$_X$ with stroke, ischaemic stroke or haemorrhagic stroke (see online supplementary file 3: table S1). Finally, we reran the single pollutant models from table 3 replacing our postcode-specific modelled pollution concentrations with daily mean pollution measurements from a single urban background London (Bloomsbury) monitoring station. In common with our modelled pollution analyses, most estimates of percentage change in risk were negative. As illustrated in online supplementary file 3: table S2, positive estimates were only observed for haemorrhagic stroke and each of O$_3$, NO$_2$ and NO$_X$. However, all associations, whether positive or negative, fell short of statistical significance at the 5% level.

**DISCUSSION**

Main findings
In this study, we found no statistically significant positive associations between exposure to particulate and gaseous air pollutants and incident stroke, whether ischaemic or haemorrhagic. We did, however, find a statistically significant negative association between PM$_{10}$ and haemorrhagic stroke. This did not appear to be due to the confounding effects of O$_3$, nor did it appear to follow any marked seasonal pattern (see table 4) and is therefore difficult to explain. A significant negative association between PM$_{2.5}$ and haemorrhagic stroke only emerged following adjustment for NO$_X$ and, given the strong correlation between NO$_X$ and PM$_{2.5}$ ($r=0.62$), may be spurious and an artefact of collinearity.

Comparison with other findings
Our study findings are in contrast to those of a recent wide-ranging review, and meta-analysis based on 94 studies in 28 countries, of which 25 studies were in Asia, 33 in Europe and 26 in North America. In terms of same day exposures (lag 0), this meta-analysis found small positive associations between the
risk of hospitalisation or mortality for stroke and each of PM$_{2.5}$, PM$_{10}$ and NO$_2$ and in terms of stroke subtypes, positive associations between ischaemic stroke and ‘overall’ exposure (typically the shortest lag available) to PM$_{2.5}$ and NO$_2$ and between haemorrhagic stroke and ‘overall’ exposure to NO$_2$.$^3$ However, our study was relatively small, with our analysis based on 1758 strokes of which 1311 were ischaemic and 256 haemorrhagic. Nevertheless, the 95% CIs surrounding our estimates of percentage change in risk for single pollutant models in table 3, with one exception (PM$_{10}$ and haemorrhagic stroke), extend to include the corresponding estimates and CIs from the meta-analysis referenced above.$^1$

Our findings are not, however, out of place when viewed in the context of other UK studies.$^{19-22}$ A study of transient ischaemic attack and minor stroke cases within two prospective cohorts, one in Manchester and one in Liverpool,$^1$ found a significant positive association with NO but only in Manchester and only at lag 3, having investigated a total of six pollutants and four different lags (0, 1, 2, 3). At lag 0, relative risk estimates were both non-significant and below 1 for PM$_{10}$, NO, NO$_2$,
SO2 and CO in Manchester and for PM10, O3 and SO2 in Liverpool. A study based in the west Midlands conurbation, which includes Birmingham, found no evidence of a positive association between the average of same day and previous day exposure to PM2.5, PM10, NO2, SO2 or CO and hospital admission for stroke in those aged 65 and over, with relative risk estimates below 1 and statistically significant in the case of SO2.20

While an earlier study in Birmingham did report a statistically significant positive association between PM10 and same day admission for acute cerebrovascular disease,21 an earlier study in London found no evidence of an association with previous day exposure to O3, NO2 or SO2.22 From this latter study (assuming 1 ppb = 2.0 μg/m3 for O3 and 1 ppb = 1.88 μg/m3 for NO2), the estimated change in risk per 10 μg/m3 increase in pollutant was −0.30% (−0.90% to 0.25%) for O3 and −0.27% (−0.57% to 0.08%) for NO2.22

Our choice of same day exposures (ie, lag 0) was based primarily on observations from reviews and meta-analyses.1 2 When in sensitivity analyses we included previous day and same day exposures in our single pollutant models (UDLM lag 0–1), the association between haemorrhagic stroke and NO2 became positive but no associations were statistically significant (see online supplementary file 3: table S1). The findings of a study in Okayama, Japan, suggested that for PM2.5 the critical exposure period is in the hours, rather than days, prior to the onset of cerebrovascular disease.23 Similarly, a study in Boston, USA, reported a positive association between PM2.5 and ischaemic stroke which was most marked for PM2.5 levels12–14 hours prior to stroke onset.24 However, although within the SLSR, time of day of stroke is recorded, these times were only considered to be definite for 44% of strokes, 44% of ischaemic strokes and 48% of haemorrhagic strokes.

### Study strengths and limitations

A major strength of our study lies in the use of data from a designated community-based stroke register rather than from an administrative database.7 In particular, we would point to the method of case definition which involves the identification of cases from various sources by registry doctors and nurses and the collection of sufficiently detailed information to facilitate the classification of cases into various stroke subtypes.10

In terms of exposure information, one advantage of using modelled rather than monitored pollution data is that we can obtain temporally resolved daily pollutant outputs at fine spatial resolution such as postcode of residence with limited missing data. However, both monitored and modelled pollution are likely to be subject to measurement error.25 Measurement error is a particular problem in air pollution studies where individual-level exposure is not measured directly and is estimated based on distant pollution monitors or pollution modelling. If this measurement error is additive and classical, then on average, we would expect our OR estimates to be biased towards the null (ie, closer to 1), although for any single study this could equate to an increased likelihood of obtaining an OR estimate below 1.

Our study was based on a time-stratified case–cross-over design. This type of analysis compared with a Poisson regression time-series approach may lead to reduced statistical power.26 However, it has the advantage that it automatically adjusts for time-invariant individual-level potential confounders such as sex, age, current smoking status and previous medical history. The possibility that our findings are subject to residual confounding is also reduced by our choice of control days which help to adjust for time trends and seasonality (including day of the week effects), and the inclusion of time-varying covariates (ie, daily mean temperature and daily mean relative humidity) in our conditional logistic regression models. Another advantage of the case–cross-over approach is that it facilitates the easy investigation of potential modifying factors.15

### Stroke subtypes

**Differences between our results and those of other studies from around the world may be due to geographical variations in the prevalence of stroke subtypes.** Ischaemic stroke is a relatively broad category including TACI, PACI, LACI and POCI and risk factors for these stroke subtypes may vary. Although few studies are able to consider these disease categories separately, a small study in Mantua, Italy,27 found evidence of a positive association between PM10 exposure and same day hospital admission for TACI in men only and for LACI in men and women. When we investigated these stroke subtypes in our analysis (table 5), we found small non-significant, though positive, associations between TACI (number of cases=187) and both PM2.5 and PM10, with the percentage increase in risk per 10 μg/m3 increase in pollutant estimated at 5.9% (95% CI −15.9% to 23.6%) for PM2.5 and 2.5% (95% CI −2.4% to 19.9%) for PM10. However, the CIs were again particularly wide.

### Table 5 Estimating the percentage change in risk (95% CI) per 10 μg/m3 increase in pollutant: single pollutant regression models*

<table>
<thead>
<tr>
<th>Daily mean Pollutant</th>
<th>Subtypes of ischaemic stroke</th>
<th>Single pollutant regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TACI (number of cases=187), per cent change (95% CI)</td>
<td>PACI (number of cases=520), per cent change (95% CI)</td>
</tr>
<tr>
<td>PM2.5</td>
<td>5.9 (−15.9 to 33.3)</td>
<td>−9.6 (−22.1 to 5.0)</td>
</tr>
<tr>
<td>PM10</td>
<td>2.5 (−12.4 to 19.9)</td>
<td>−4.8 (−13.9 to 5.3)</td>
</tr>
<tr>
<td>O3</td>
<td>3.1 (−9.5 to 17.4)</td>
<td>−1.2 (−8.7 to 6.9)</td>
</tr>
<tr>
<td>NO2</td>
<td>−6.2 (−18.8 to 8.4)</td>
<td>−3.6 (−11.9 to 5.4)</td>
</tr>
<tr>
<td>NOx</td>
<td>−1.0 (−4.9 to 3.1)</td>
<td>−0.7 (−3.5 to 2.3)</td>
</tr>
</tbody>
</table>

*The conditional logistic regression model fits the pollutants at lag 0 and adjusts for two natural cubic splines (df=2) for temperature (lags 0–1 and 2–6), two natural cubic splines (df=2) for humidity (lags 0–1 and 2–6), public holidays and a sine/cosine annual cycle.

LACI, lacunar infarct; NO2, nitrogen dioxide; NOx, NO2+nitrogen oxide; O3, ozone; PACI, partial anterior circulation infarct; PM10, particulate matter <10 μm in diameter; PM2.5, particulate matter <2.5 μm in diameter; POCI, posterior circulation infarct; TACI, anterior circulation infarct.

### Conclusion

In a study set in South London (UK) of the association between short-term pollution exposure and incident stroke, we found no evidence of any positive associations of stroke or stroke subtype (ie, ischaemic or haemorrhagic) with any of PM2.5, PM10, O3,
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NO₂ or NOₓ. While these findings are in contrast to those of large reviews and meta-analyses, they are not inconsistent with the rather mixed findings of other UK studies.⁵⁻⁻⁷ This observation and that of Shah et al.,³ who noted that for PM₁₀ and NO₂ associations with incident stroke were stronger in low-income to middle-income countries than high-income countries, may indicate geographical differences in risk. Future studies that investigate such geographical differences and obtain greater certainty about the timing of event in relation to the relevant exposure metric (e.g., hours or days) are therefore required.

What is already known on this subject

- Evidence of weak positive associations between same day exposure to carbon monoxide, sulfur dioxide, nitrogen dioxide (NO₂) and particulate air pollution and incident stroke comes from various studies around the world. Fewer studies have considered stroke subtypes.

What this study adds

- We linked via postcode 1758 incident strokes recorded on the South London Stroke Register to air pollutants modelled at 20 m×20 m resolution. We found no statistically significant positive association between all stroke, haemorrhagic stroke, ischaemic stroke, or ischaemic stroke subtypes and same day exposure to particulate matter <2.5 and <10 μm in diameter, ozone, NO₂ or NO₃+nitrogen oxide. While these findings are in contrast to those of large reviews and meta-analyses, they are not inconsistent with the rather mixed findings in other UK studies.

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Contributors

BK8 conducted the statistical analysis and took the lead in drafting the paper. The contribution of RWA was to study inception and co-authorship of the paper. SC and UH were responsible for the management and formatting of the SLSR—led the informatics development on data paper. SC and UH were responsible for the management and formatting of the SLSR. BKB conducted the statistical analysis and took the lead in drafting. LC and NH were responsible for the management and formatting of the SLSR. AS led the informatics development on data paper. SC and UH were responsible for the management and formatting of the SLSR. BKB conducted the statistical analysis and took the lead in drafting.

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Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests

BK8 owns shares in Royal Dutch Shell and Scottish and Southern Energy. Her work on this project was funded by King’s College London. RWA reports grants from King’s College London during the conduct of the study and personal fees from COMEAP outside the submitted work. FJK and AS report grants from NIHR during the conduct of the study.

Ethics approval

The study was approved by the Ethics Committees of Guy’s and St Thomas’ NHS Foundation Trust, King’s College Hospital Foundation Trust, St George’s University Hospital, National Hospital for Nervous Diseases, and Westminster Hospital.

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