Citation for published version (APA):
Air pollution and the incidence of ischaemic and haemorrhagic stroke in the South London Stroke Register: a case–cross-over analysis

B K Butland,1 R W Atkinson,1 S Crichton,2 B Barratt,3,4 S Beevers,3 A Spiridou,2,4 U Hoang,2,4 F J Kelly,3,4 C D Wolfe2,4

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 (PM$_{2.5}$, PM$_{10}$), ozone (O$_3$), nitrogen dioxide (NO$_2$) and NO$_2$+nitrogen oxide (NO$_x$).

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 PM$_{2.5}$, PM$_{10}$, O$_3$, NO$_2$ or NO$_x$. For haemorrhagic stroke, we found a negative association with PM$_{10}$ suggestive of a 14.6% (95% CI 0.7% to 26.5%) fall in risk per 10 μg/m$^3$ 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.1–3 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 (SO$_2$), carbon monoxide (CO), nitrogen dioxide (NO$_2$) and particulate matter <10 and <2.5 μm in diameter (PM$_{10}$ and PM$_{2.5}$, respectively). In terms of stroke subtypes, there were positive associations between ischaemic stroke and ‘overall’ exposure (typically the shortest lag available) to NO$_2$ and PM$_{2.5}$ and between haemorrhagic stroke and ‘overall’ exposure to NO$_2$. 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 PM$_{2.5}$ (particularly on warm days),4 and between emergency room visits for haemorrhagic stroke and the same day exposure to the PM$_{2.5}$ 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 (lag 1) to ozone (O$_3$) 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 measurements and dispersion 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 PM$_{2.5}$, PM$_{10}$, O$_3$, NO$_2$ and NO$_x$+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 pollu-
tant 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 (KCLurban 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, ethnic-
ally diverse area of South London where the base population of 
357 308 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 notifica-
tion 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 haem-
orrhage (SAH), lacunar infarct (LACI), partial anterior circula-
tion infarct (PACI), posterior circulation infarct (POCI) and 
anterior circulation infarct (TACI), unspecified 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, socio-
-economic status, living circumstances before stroke) and clinical 
details at the time of maximal impairment (Glasgow Coma 
Score, 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 their own control. This is achieved by comparing 
exposure variables (eg, pollutant metrics) between the index day 
(i.e., 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 (StatCorp: Stata 
Statistical Software: Release 12. College Station, TX: StataCorp 
LP; 2011) using conditional logistic regression. In terms of cov-
ariate 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 PM₂.₅, PM₁₀, O₃, 
NO₂ and NOₓ and the primary outcome variables were all 
stroke, ischaemic stroke and haemorrhagic stroke. Stroke sub-
types TACI, PACI, POCI and LACI were considered as second-
ary 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 esti-
mate the combined effect on incident stroke of same day (lag 0) 
and previous day (lag 1) pollutant exposures. Second, we inves-
tigated the effects of replacing our postcode-specific modelled 
pollution concentrations with daily mean pollution measure-
ments 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 
(i.e., TACI, PACI, LACI, POCI and infarct unspecified), 261 
(15%) haemorrhagic strokes (i.e., 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 haemor-
rhagic. 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), NO₂(r=−0.72), PM₁₀(r=−0.33) and 
PM₂.₅ (r=−0.40), whereas NOₓ and NO₂ were positively corre-
lated 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 pol-
lutant. This negative association persisted following adjustment 
for O₃. A significant negative association with haemorrhagic
stroke was also observed for PM2.5 but only following adjustment for NOX.

Modifying factors

There was some evidence (p=0.019) that any association between O3 and incident stroke may vary with season (table 4). In particular, season-specific estimates appeared to suggest that any negative association between O3 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 PM2.5, PM10, O3, NO2 or NOX 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 PM2.5, PM10, O3, NO2 or NOX 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 O3, NO2 and NOX. 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 PM10 and haemorrhagic stroke. This did not appear to be due to the confounding effects of O3, nor did it appear to follow any marked seasonal pattern (see table 4) and is therefore difficult to explain. A significant negative association between PM2.5 and haemorrhagic stroke only emerged following adjustment for NOX and, given the strong correlation between NOX and PM2.5 (r=0.62), may be spurious and an artefact of collinearity.18

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.1 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 PM2.5, PM10 and NO2 and in terms of stroke subtypes, positive associations between ischaemic stroke and ‘overall’ exposure (typically the shortest lag available) to PM2.5 and NO2 and between haemorrhagic stroke and ‘overall’ exposure to NO2. 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 (PM10 and haemorrhagic stroke), extend to include the corresponding estimates and CIs from the meta-analysis referenced above.

Our findings are not, however, out of place when viewed in the context of other UK studies. A study of transient ischaemic attack and minor stroke cases within two prospective cohorts, one in Manchester and one in Liverpool, 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 PM10, NO, NO2,
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. While an earlier study in Birmingham did report a statistically significant positive association between PM₁₀ and same day admission for acute cerebrovascular disease, an earlier study in London found no evidence of an association with previous day exposure to O₃, NO₂ or SO₂. 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. Our choice of same day exposures (ie, lag 0) was based primarily on observations from reviews and meta-analyses. 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 NOₓ became positive but no associations were statistically significant (table S1). The findings of a study in Okayama, Japan, suggested that for PM₁₀ the critical exposure period is in the hours, rather than days, prior to the onset of cerebrovascular disease. 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. 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. 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. 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. 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. 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.

### 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, 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 33.3%) for PM₂.₅ and 2.5% (95% CI −12.4% to 19.9%) for PM₁₀. However, the CIs were again particularly wide.

### 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,
NO$_2$ or NO$_X$. 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.

This observation and that of Shah et al., who noted that for PM$_{10}$ and NO$_2$ 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 (ie, 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 (NO$_2$) 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 x 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, NO$_2$ or NO$_X$ 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.

**Acknowledgements** The authors acknowledge the use of weather measurement data from the UK Meteorological Office through the British Atmospheric Data Centre (BADC)—badc.nerc.ac.uk.

**Funding** The research was funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London.

**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 COMEPA 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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*J Epidemiol Community Health* 2017 71: 707-712 originally published online April 13, 2017
doi: 10.1136/jech-2016-208025

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