Associations between exhaust and non-exhaust particulate matter and stroke incidence by stroke subtype in South London.

Siobhan Crichton[1,2], Benjamin Barratt[3,4], Anastassia Spiridou[4], Uy Hoang[1,2,4], Shao Fen Liang[1,4], Yevgeniya Kovalchuk[5], Sean D Beevers[3], Frank J Kelly[3,4], Brendan Delaney[6], Charles DA Wolfe[1, 2, 4]

1. Division of Health and Social Care Research, King's College London, London, UK;
2. National Institute of Health Research Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South London, London, UK;
3. Analytical and Environmental Sciences Division and MRC-PHE Centre for Environment and Health, King's College London, UK;
4. NIHR Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust and King's College London, London, UK;
5. NIHR Biomedical Research Centre for Mental Health & Biomedical Research Unit for Dementia, King's College London, UK.
6. Department of Cancer and Surgery, Imperial College, London, UK.

Corresponding author:

Siobhan Crichton

Division of Health and Social Care Research

King's College London

5th Floor Addison House

Guy's Campus

London SE1 1UL

Tel:02078486685 **Words**:4000

Key words: Stroke; Incidence; air pollution

Acknowledgements

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, and the NIHR Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

List of Tables and Figures:

Abstract

Background:

Airborne particulate matter (PM) consists of particles from diverse sources, including vehicle exhausts. Associations between short-term PM changes and stroke incidence have been shown. Cumulative exposures over several months, or years, are less well studied; few studies examined ischaemic subtypes or PM source.

Aims:

This study combines a high resolution urban air quality model with a population-based stroke register to explore associations between long-term exposure to PM and stroke incidence.

Method:

Data from the South London Stroke Register from 2005-2012 were included. Poisson regression explored association between stroke incidence and long-term (averaged across the study period) exposure to $PM_{2.5}$(PM<2.5μm diameter) and PM_{10}(PM<10μm), nitric oxide, nitrogen dioxide, nitrogen oxides and ozone, at the output area level (average population=309). Estimates were standardised for age and sex and adjusted for socio-economic deprivation. Models were stratified for ischaemic and haemorrhagic strokes and further broken down by Oxford Community Stroke Project classification and Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.

Results:

1800 strokes were recorded (incidence=42.6/100,000 person-years). No associations were observed between PM and overall ischaemic or haemorrhagic incidence. For an interquartile

range increase in $PM_{2.5}$, there was a 23% increase in incidence (Incidence rate ratio=1.23 (95%CI:1.03-1.44)) of total anterior circulation infarcts (TACI) and 20% increase for $PM_{2.5}$ from exhausts (1.20(1.01-1.41)). There were similar associations with PM_{10}, overall (1.21(1.01-1.44)) and from exhausts (1.20(1.01-1.41)). TACI incidence was not associated with non-exhaust sources. There were no associations with other stroke subtypes or pollutants.

Conclusion:

Outdoor air pollution, particularly that arising from vehicle exhausts, may increase risk of TACI but not other stroke subtypes.

1 Background

Stroke is a leading cause of mortality and morbidity worldwide. In 2010 it is estimated 17 million first strokes occurred, an increase of 68% since 1990[1]. The contribution of outdoor air pollution to stroke risk has been increasingly studied in recent years[2-14].

Particulate matter (PM) comprises of particles from diverse sources, the proportion of each dependent on weather conditions, local geography and proximity to source. Epidemiological and toxicological studies have shown varying health effects associated with particulate matter, suggesting a role for both its chemical composition and physical properties[15]. Increasingly urban air pollution models are able to separate PM into source-related components[16], providing opportunities to carry out in depth epidemiological studies into associations between health impacts and PM components.

Several studies have found associations between short-term changes in air pollution and stroke risk[5, 6, 10, 11, 13, 17, 18], in particular, PM_{10} and/or $PM_{2.5}$ (PM<10μm and <2.5μm in diameter, respectively). A recent meta-analysis of 19 studies reported short-term changes in $PM_{10,}$ but not $PM_{2.5,}$ were associated with risk of ischaemic but not haemorrhagic strokes[14]. Spikes in ozone concentration have also been shown to increase risk of ischaemic stroke[2, 6]

There has been less focus on long-term exposures, i.e. concentrations averaged over months or years, usually measured at place of residence. Some studies found no associations with stroke risk[3, 7, 8, 12]. The European ESCAPE cohort study found a 5-μg/m3 increase in annual $PM_{2.5}$ exposure associated with 19% increased risk of incident stroke, with similar findings for PM_{10}[19].

A few studies have looked at ischaemic stroke subtypes[2, 7, 11, 18, 20]. One study of patients admitted to a stroke unit in Italy looked at short-term exposure to a number of pollutants and

risk of stroke categorised using TOAST and OCSP classifications. PM_{10} was associated with risk of lacunar anterior circulatory syndrome, and total anterior circulator syndrome in males only[18]. Other studies have found associations between short-term exposure and risk of strokes due to large artery atherosclerosis[2, 11, 20] and small vessel occlusion[11, 20].

Meta-analysis by the METASTROKE collaboration and review of Genome Wide Association Studies (GWAS) for ischaemic stroke found most genetic variant associations were specific to a subtype, suggesting different subtypes have different risk factor profiles and pathophysiological mechanisms[21, 22].

This study combines a high resolution air quality model with data from the South London Stroke (SLSR) register, a population based register of incident strokes, to investigate associations between long-term exposure to air pollution and stroke incidence, stratified by subtype. This study builds on previous work carried out using data from the SLSR which examined the impact of nitrogen dioxide and PM_{10} on the incidence of ischaemic and haemorrhagic stroke[8] and on ischaemic strokes broken down by stroke severity and stroke subtype[7] and found no significant associations. Previous work utilised pollution levels estimated for a single year, 2002. Since then the air quality model has seen significant improvement and now provides PM levels split by source type and, importantly, the inclusion of $PM_{2.5}$ size fraction. Emissions factors used in the model have been updated, particularly in relation to primary NO_2 emissions and non-exhaust components of PM

2 Methods

2.1 Case identification

Stroke incidence was derived from the South London Stroke Register (SLSR). The SLSR has recorded all first-ever strokes in a defined area since 1995. Methods of data collection have

been described previously[23]. In brief, patients were identified using multiple notification sources and recruited as soon as possible after stroke. World Health Organization criteria were used to define stroke[24]. Pathological subtype was classified as cerebral infarction, primary intracerebral haemorrhage (PICH), subarachnoid haemorrhage (SAH), or unknown. Infarcts were further defined using the Oxford Community Stroke Project definitions as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), posterior circulation infarct (POCI), or infarct unspecified[25]. Aetiological subtype was classified using a modified version of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and strokes were classified as large artery atherosclerosis, cardioembolism, small vessel occlusion, other, undetermined or multiple/concurrent aetiologies[26]. Data from 2005-2012, the period during which pollution data were available, were included.

2.2 Derivation of observed and expected incidence rates

The SLSR source population consisted of 357,308 individuals of which 56% White, 25% Black, 6% Asian and 12% other ethnic group (census 2011). Census output areas (OAs) were the unit of analysis. Each OA includes a recommended minimum of 125 households (absolute minimum=40 households or 100 residents). In 2011 each OA included an average of 309 residents[27]. In 2001 there were 1099 OAs and 1148 in 2011. Of these 1049 were the same at both censuses. To combine population data from the 2001 and 2011 census, 2011 OAs which were a result of 2001 OAs being split were merged while 2001 OAs which were merged in the 2011 census were merged in the 2001 data, resulting in 1089 OAs.

The expected number of strokes in each OA per year were calculated by applying the overall incidence rate in a given year broken down by gender and into five year age bands to the population living within the OA. The population estimates were derived using data from the

2001 and 2011 UK census, with the rate of change in population size within each OA in the years between the census' assumed to be linear. These estimates were then summed to give the total expected strokes in an OA across the study period.

2.3 Air pollution model

Air pollution concentrations were derived using the KCLurban model developed at King's College London as part of the NERC/MRC/SRC/DEFRA/DoH Traffic Pollution and Health in London project ('Traffic'). KCLurban model provided annual mean NO_X, NO_2, O_3, PM_{10} and $PM_{2.5}$ concentrations at the geographical centre of each postcode within the study area, for all sources and separately for traffic exhaust and non-exhaust sources.

The KCLurban model used a kernel modelling technique, based upon ADMS[28, 29], to describe initial dispersion from each emissions source. The contribution from each source was aggregated onto a fixed 20m x 20m grid across London. The model used emissions from the London Atmospheric Emissions Inventory (LAEI)[30] . Inventory exhaust emissions factors were combined with UK specific roadside measurements[31]. Non-exhaust emissions were based upon the work of Harrison[32].

Sources within the model included: road transport (exhaust and non-exhaust), large regulated industrial processes, small regulated industrial processes, large boiler plant, gas heating (domestic and industrial-commercial), oil combustion sources (domestic and commercial), coal combustion sources (domestic and commercial), agricultural and natural sources, rail, ships, airports and others (sewage plant etc.). In modelling the emissions from large industrial processes use was made of emissions data and stack conditions (height, temperature, volume flow rate) for each source.

The KCLurban model is well established for use in public health research[33-35] and has been submitted to the UK Model Inter-comparison Exercise, run by King's on behalf of DEFRA (http://uk-air.defra.gov.uk/library/reports?report_id=777). The model's performance was assessed against long-term fixed air quality monitoring sites that form the London Air Quality Network (http://www.londonair.org.uk). Additional information and validation of the model is available in Supplement 1.

2.4 Derivation of long-term air pollution concentrations

The exposures used in the models were pollutant levels averaged across the full study period. To obtain pollution concentrations, a weighted average was derived. Population counts per postcode at the time of the 2011 census were used to weight the pollution concentration at each postcode and an average calculated within each OA. Applying a weighted average was applied to ensure that the average exposure levels best represented those experiences by the population at risk, and so that postcodes with few residents were given lower weight than those with more residents. An average across years provided an estimate of average pollution levels in each OA across the study period.

2.5 Socio-economic deprivation

The Income Domain of the 2007 Index of Multiple Deprivation (IMD) was used as a measure of socioeconomic deprivation. This is a standard index used by government agencies in England and Wales and is available at the lower super-output area level (LSOA). Each LSOA typically contains 4-6 OAs.

2.6 Statistical Analysis

Poisson models included pollutant concentrations and IMD income scores as continuous variables and logarithm of expected counts as an offset. Robust standard errors were calculated to account for any over dispersion.

We examined all strokes combined and ischemic strokes, PICH and SAHs separately. We repeated analyses for separate ischemic subtypes defined using both OCSP and TOAST classifications. As some pollutants were highly correlated with others, each was examined in a separate model.

Results are expressed as incident rate ratios (IRR) with 95% confidence intervals (CI's), representing the IRR for a one interquartile range (IQR) increase in the level of the pollutant.

The aim of this study was to explore the relationship between pollutants and incidence across several different subtypes and so p-values are not reported. The estimated IRRs instead provide an indication of the pollutants which are likely to have the greatest effect on stroke incidence.

Potential residual spatial autocorrelation was examined for visually using Moran scatterplots in which the deviance residuals from each OA were plotted against the average of the residuals from the four nearest neighbours. Proximity between OAs was determined by using the distance between the population weighted centroid of each output area at the time of the 2011 census[36]. No patterns or evidence of residual autocorrelation in was observed and so models were not further adjusted for spatial autocorrelation.

Analysis was conducted using STATA 13MP.

3. Results

In total 1800 incident strokes were recorded. Overall incidence was 42.6 per 100,000 person years. An average of 1.65 strokes (maximum=8) were recorded per OA. Average age at stroke was 68.8 years (standard deviation=15.8) and just over half were in males (Table 1). Three quarters of strokes were ischaemic, with the most common subtype being PACI (29.6%) followed by LACI (23.2%).

Table 1: Incident stroke cases from 2005-2012 by age, sex and stroke subtype

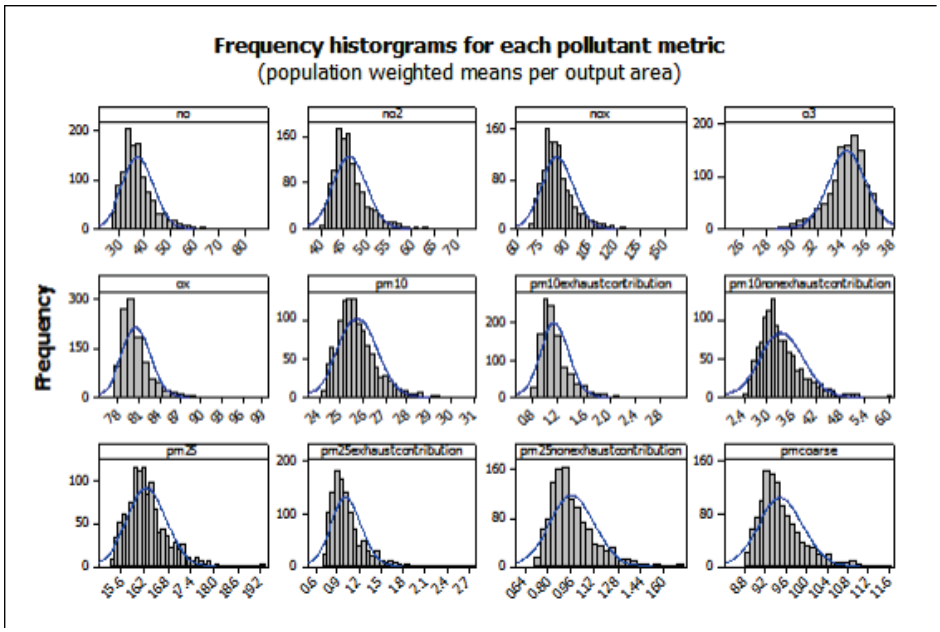
	N(%)
Total	1800
Age, mean(sd)	68.8(15.8)
Age	
<55 years	364(20.2)
55-64 years	300(16.7)
65-74 years	396(22.0)
75-84 years	465(25.8)
>85 years	275(15.3)
Gender	
Male	942(52.3)
Female	858(47.7)
OCSP classification	
TACI	189(10.5)
PACI	532(29.6)
POCI	196(10.9)

LACI	417(23.2)
Infarction unspecified	4(0.2)
PICH	204(11.3)
SAH	57(3.2)
Unknown/undefined	201(11.2)
TOAST Classification *	
Large artery atherosclerosis	179(13.9)
Cardio embolism	310(24.0)
Small vessel Occlusion	344(26.7)
Other/not identified	457(35.4)

*ischaemic strokes only

Abbreviations: TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; LACI, lacunar infarct; POCI, posterior circulation infarct; PCIH, primary intracerebral haemorrhage; SAH, subarachnoid haemorrhage; OCSP, Oxford community stroke project pathological subtype; TOAST, Trial of Org 10172 in acute stroke treatment aetiological subtype

The distribution of each of the pollutants included in the study are displayed in Figure 1 and summarised in Table 2.



Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter below 10 µm; $PM_{2.5}$, particulate matter below 2.5 µm.

Figure 1: Distribution of average pollutant concentrations within each output area

Table 2: Average pollutant concentrations

	Mean(sd) µg m^{-3}	Interquartile range µg m^{-3}	Yearly concentrations minus mean* median (IQR) µg m^{-3}
NO	36.2(5.4)	32.7-38.8	-0.6(-2.1-3.2)
NO_2	45.7(3.3)	43.5-47.0	-0.4(-1.2-1.9)
NO_X	81.9(8.7)	76.3-85.6	-1.0(-3.4-5.2)
O_3	35.6(1.3)	35.0-36.5	0.2(-1.9-1.8)
Ox	81.3(2.0)	80.0-82.0	12.9(-1.6-14.9)
PM_{10}	24.8(0.79)	24.2-25.1	0.2(-1.1-1.0)
PM_{10} exhaust	0.99(0.17)	0.87-1.07	-0.03(-0.15-0.18)_
PM_{10} non-exhaust	3.3(0.51)	3.5-2.9	-0.03(-0.17-0.17)
$PM_{2.5}$	15.4(0.43)	15.1-15.6	-0.03(-0.75-1.30)
$PM_{2.5}$ exhaust	0.89(0.15)	0.78-0.96	-0.02(-0.13-0.16)
$PM_{2.5}$ non-exhaust	0.96(0.14)	0.86-1.02	-0.01(-0.05-0.05)
PM coarse (PM_{10} – $PM_{2.5}$)	9.4(0.39)	9.1-9.6	-0.19(-0.5-0.5)

*Data represents the differences between the yearly concentrations with in an output area and the average concentrations used in the model which were averaged across all years

Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter below 10 µm; $PM_{2.5}$, particulate matter below 2.5 µm.

None of the pollutants were associated with overall, ischaemic or haemorrhagic incidence (Table 3).

Table 3: Associations between pollutants and all stroke, ischaemic stroke, PICH and SAH incidence

	All stroke	Ischaemic	PICH	SAH
N	1800	1338	204	57
Incidence	**IRR(95% CI)**	**IRR(95% CI)**	**IRR(95% CI)**	**IRR(95% CI)**
NO	0.99(0.93-1.05)	0.97(0.91-1.04)	0.95(0.80-1.13)	1.04(0.73-1.47)
NO_2	0.99(0.94-1.04)	0.97(0.91-1.04)	0.96(0.82-1.13)	1.06(0.77-1.44)
NO_X	0.99(0.94-1.05)	0.97(0.91-1.04)	0.96(0.81-1.13)	1.05(0.76-1.44)
O_3	1.00(0.95-1.06)	1.02(0.95-1.09)	1.04(0.88-1.24)	0.95(0.68-1.34)
Ox	0.99(0.94-1.04)	0.97(0.91-1.03)	0.97(0.83-1.12)	1.06(0.79-1.42)
PM_{10}	1.00(0.94-1.06)	0.98(0.92-1.05)	0.97(0.81-1.15)	1.01(0.72-1.43)

PM_{10} exhaust	0.99(0.93-1.04)	0.97(0.90-1.04)	0.94(0.79-1.12)	0.90(0.64-1.27)
PM_{10} non-exhaust	1.00(0.94-1.06)	0.97(0.90-1.04)	0.98(0.82-1.17)	1.09(0.76-1.57)
$PM_{2.5}$	1.00 (0.95-1.06)	0.99(0.93-1.06)	0.96(0.81-1.14)	0.93(0.67-1.30)
$PM_{2.5}$ exhaust	0.99(0.93-1.04)	0.97(0.91-1.04)	0.94(0.78-1.12)	0.90(0.64-1.28)
$PM_{2.5}$ non-exhaust	0.99(0.94-1.05)	0.97(0.90-1.04)	0.98(0.82-1.16)	1.03(0.72-1.48)
PM coarse	1.00(0.94-1.05)	0.97(0.91-1.04)	0.98(0.83-1.16)	1.10(0.76-1.56)

Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter below 10 μm; $PM_{2.5}$, particulate matter below 2.5 μm.

However, PM_{10} and $PM_{2.5}$ were associated with increased risk of TACIs (Table 4). For a one interquartile range increase in PM_{10}, there was a 21% increase in stroke incidence (IRR=1.21(1.01-1.44)) and an IQR increase in PM_{10} from exhausts associated with a 20% increase in TACI incidence (IRR=1.20(1.01-1.41)), and a slightly weaker (with confidence intervals crossing one) association for non-exhaust (IRR=1.17(0.98-1.39)). There were similar associations with $PM_{2.5}$ overall (IRR=1.23(1.03-1.44)) and $PM_{2.5}$ from exhausts (IRR=1.20(1.01-1.41)) and non-exhausts (IRR=1.17(0.99-1.39)). There were no associations between any other pollutants and OCSP subtypes (Table 4).

Table 4: Associations between pollutants and incidence of stroke broken down by OCSP classification

	TACI	PACI	POCI	LACI
N	189	532	196	417
Incidence	**IRR(95% CI)**	**IRR(95% CI)**	**IRR(95% CI)**	**IRR(95% CI)**
NO	1.15(0.97-1.36)	0.93(0.83-1.05)	1.00(0.80-1.25)	0.93(0.82-1.05)
NO_2	1.13(0.97-1.32)	0.93(0.8	1.00 (0.81-1.23)	0.94(0.84-1.05)

		4-1.04)		
NO_X	1.14(0.97-1.32)	0.94(0.84-1.04)	1.00 (0.81-1.23)	0.94(0.83-1.05)
O_3	0.85(0.71-1.00)	1.06(0.95-1.19)	1.00(0.80-1.26)	1.06(0.94-1.19)
Ox	1.10(0.96-1.27)	0.93(0.84-1.02)	0.99(0.82-1.21)	0.94(0.84-1.04)
PM_{10}	**1.21(1.01-1.44)**	0.94(0.84-1.05)	0.99(0.79-1.24)	0.94(0.82-1.06)
PM_{10} exhaust	**1.20(1.01-1.41)**	0.92(0.82-1.03)	1.02(0.81-1.28)	0.91(0.81-1.03)
PM_{10} non-exhaust	1.17(0.98-1.39)	0.94(0.84-1.05)	0.96(0.77-1.20)	0.92(0.81-1.05)
$PM_{2.5}$	**1.22(1.03-1.44)**	0.95(0.85-1.06)	1.01(0.81-1.27)	0.95(0.85-1.06)
$PM_{2.5}$ exhaust	**1.20(1.01-1.41)**	0.92(0.82-1.04)	1.02(0.81-1.28)	0.91(0.81-1.03)
$PM_{2.5}$ non-exhaust	1.17(0.99-1.39)	0.94(0.84-1.06)	0.96(0.77-1.20)	0.92(0.81-1.04)
PM coarse	1.05 (0.98-1.29)	0.94(0.84-1.05)	0.96(0.77-1.20)	0.93(0.82-1.05)

Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter below 10 μm; $PM_{2.5}$, particulate matter below 2.5 μm; TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; LACI, lacunar infarct; POCI, posterior circulation infarct.

Incident rate ratios for ischemic strokes broken down by TOAST classification are also presented in Table 5. The highest point estimates of the IRR were for risk large artery atherosclerosis associated with particulate matter ranged from 1.09 to 1.11, but the confidence intervals were wide and so no association cannot be ruled out and no other associations were apparent.

Table 5: Associations between pollutants and incidence of stroke broken down by TOAST classification

	Large artery atherosclerosis	Cardio embolic	Small vessel occlusion
N	179	310	344
Incidence	IRR(95% CI)	IRR(95% CI)	IRR(95% CI)
NO	1.03(0.9-1.14)	1.01(0.91-1.11)	0.97(0.91-1.07)
NO2	1.04(0.92-1.13)	1.02(0.93-1.10)	0.97(0.92-1.06)
NOX	1.05(0.92-1.14)	1.02(0.92-1.10)	0.96(0.91-1.06)
O3	0.96(0.88-1.1)	1.04(0.93-1.11)	0.99(0.92-1.07)
Ox	1.02(0.94-1.08)	0.98(0.94-1.05)	1.01(0.95-1.06)
PM10	1.11(0.92-1.19)	1.07(0.93-1.14)	0.97(0.90-1.08)
PM10 exhaust	1.11(0.91-1.2)	1.05(0.92-1.14)	0.98(0.90-1.09)
PM10 non-exhaust	1.09(0.91-1.19)	1.05(0.91-1.14)	0.98(0.90-1.09)
PM2.5	1.10(0.92-1.18)	1.06(0.93-1.13)	0.97(0.91-1.07)
PM2.5 exhaust	1.09(0.91-1.19)	1.05(0.92-1.14)	0.96(0.90-1.08)
PM2.5 non-exhaust	1.09(0.91-1.19)	1.04(0.91-1.14)	0.96(0.90-1.08)
PM coarse	1.00(0.75-1.33)	0.99(0.79-1.26)	1.03(0.83-1.23)

Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter below 10 μm; $PM_{2.5}$, particulate matter below 2.5 μm;

4. Discussion

This study looked at the association between air pollutants and incidence of stroke. The level of detail in the stroke and air pollution database allowed this association to be explored across a large number of pollutants and stroke subtypes. While no associations were observed overall, when ischaemic strokes were broken down by subtype, particulate matter was associated with increased risk of total anterior circulatory infarcts (TACI). The incidence rate ratio for $PM_{2.5}$ was similar to that of PM_{10}, and was slightly higher for exhaust compared to non-exhaust

related components of PM_{10} and $PM_{2.5}$. Risk of mortality from stroke in the UK has previously been shown to be associated with proximity of residential address to main roads[37]. The potential differential effect of particulate matter from exhaust and non-exhaust sources is an areas which warrants further investigation.

The lack of association observed between long-term exposure and risk all ischaemic or haemorrhagic stroke is in line with findings from previous studies[3, 4, 8]. Only one study of the long-term effects found a significant increased risk of haemorrhagic stroke associated with long-term exposure to $N0_2$ in Japan[12].

Few studies have looked at pollutants and specific types of stroke. Corea et al examined the associations between multiple pollutants and hospitalisation for acute stroke by Oxford Community Stroke Project (OCSP) and Trial of Org Acute Stroke treatment (TOAST) classifications. They found an increased risk of lacunar anterior circulatory syndrome (LACI) associated with PM_{10} levels on day of admission and increased risk of TACI in males but not females. There were no associations found by TOAST classification. Other studies have found associations between short-term exposure and increased risk of stroke due to large artery atherosclerosis[2, 11, 20] and small vessel occlusion[11, 20].

One study looked at the long-term effect of exposure and risk of stroke by ischaemic subtypes[7]. Data from the SLSR from 1995-2007 was used but no associations found between PM_{10} or $N0_2$ and risk of ischaemic subtypes. In the current study, data were available for a number of new pollutants, including particulate matter by source as a result of advancements in the model used to generate the pollutant database.

4.1 Possible mechanism

Particulate material has been shown to impair respiratory and cardiovascular systems through a combination of autonomic, haemostatic, inflammatory, and vascular endothelial disturbances with consequent changes in cardiac and vascular function[11, 14]. However, the effect of exposure to particulate matter on cerebral vessels is more uncertain and the mechanism by which any effect on cerebral vascular disease is mediated is yet to be elucidated.

Researchers have postulated that PM's effect on ischemic stroke might be regulated by systemic inflammation and activation of the coagulation system, leading to atherosclerosis, vasoconstriction, increase of fibrinogen and acceleration the formation of acute thrombus[14].

The association between PM and TACI shown in this study suggests mechanisms involving large-artery atherosclerosis, although while there was an elevated risk of large artery atherosclerosis observed in this study, the associated confidence intervals were wide. Long term effects tend to be characterised by progression of atherosclerosis[38] . Short term effects, or spikes in pollutant levels, may trigger events such as disruption of a vulnerable atherosclerotic plaque with subsequent thrombosis and/or downstream embolism leading to ischaemic stroke or rupture of an aneurysm resulting in haemorrhagic stroke [20, 38]. It is also hypothesised that the effects of short term changes in air pollution repeatedly over a period of time could explain associations observed between long term exposures and stroke where spikes recur repeatedly in an area resulting in high average levels of pollution in that area[38],

4.2 Strengths and limitations

To our knowledge this is the first study looking at long-term exposure to PM from exhausts and non-exhausts, and the risk of stroke by subtype. While the majority of the existing studies use admissions to hospitals or stroke units to identify cases, this study used data from a population-based register collecting data on all strokes within a defined area. It is estimated

that the completeness of case ascertainment is 88%[23] and includes those not-admitted to hospital.

In this study long-term exposure was defined as average pollution concentration in the area resided in at time of stroke. Concentrations were available at the postcode level for each year of the study. Due to the relatively low number of strokes per year recorded by the SLSR, to explore the association between pollutants and stroke incidence it was necessary to average within output areas and across the study period. Pollutant levels within each output area are highly correlated from one year to the next and so the areas with the highest pollution levels are likely to remain the same across the study period. However, due to the averaging it is possible some trends could be missed due to the loss of detail.

As some of the pollutants considered in this study were highly correlated with each other, single pollutant models were used to explore associations and so the lack of adjustment for levels of other pollutants is a potential source of bias. Further, estimates were age and sex adjusted and models adjusted for area level deprivations but it was not possible to take into account the effect of other potential confounders in the models. While information on demographic characteristics and the prevalence of risk factors is available for participants in the SLSR, in order to adjust for these factors, detailed information from the non-stroke population would also be required.

No information was available on how long the participant had been resident in the area at the time of stroke or what proportion of time is spent in their home. Detailed information on day to day activities would be required for more accurate measures of exposure over time, but would not be feasible in a cohort such as the SLSR.

4.3 Summary

This study explored associations between air pollutants and incidence of stroke. Findings suggest that long term exposure to pollutants may contribute more to the risk of particular stroke subtypes than to others. The majority of studies of stroke and air pollution to date have considered ischaemic strokes as a single group. Further large scale studies are needed to explore the hypothesis that there is a differential contribution of pollutants, in particular particulate matter, to the risk of different subtypes of ischaemic stroke.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: Findings from the global burden of disease study 2010. *The Lancet*. 2014;383:245-255
2. Henrotin J-B, Besancenot J-P, Bejot Y, Giroud M. Short-term effects of ozone air pollution on ischaemic stroke occurrence: A case-crossover analysis from a 10-year population-based study in dijon, france. *Occupational and environmental medicine*. 2007;64:439-445
3. Johnson JY, Rowe BH, Allen RW, Peters PA, Villeneuve PJ. A case-control study of medium-term exposure to ambient nitrogen dioxide pollution and hospitalization for stroke. *BMC public health*. 2013;13:368
4. Johnson JY, Rowe BH, Villeneuve PJ. Ecological analysis of long-term exposure to ambient air pollution and the incidence of stroke in edmonton, alberta, canada. *Stroke*. 2010;41:1319-1325
5. Leiva G MA, Santibañez DA, Ibarra E S, Matus C P, Seguel R. A five-year study of particulate matter (pm2. 5) and cerebrovascular diseases. *Environmental Pollution*. 2013;181:1-6
6. Lisabeth LD, Escobar JD, Dvonch JT, Sánchez BN, Majersik JJ, Brown DL, et al. Ambient air pollution and risk for ischemic stroke and transient ischemic attack. *Annals of neurology*. 2008;64:53-59
7. Maheswaran R, Pearson T, Beevers SD, Campbell MJ, Wolfe CD. Outdoor air pollution, subtypes and severity of ischemic stroke-a small-area level ecological study. *International Journal of Health Geographics*. 2014;13:23
8. Maheswaran R, Pearson T, Smeeton NC, Beevers SD, Campbell MJ, Wolfe CD. Outdoor air pollution and incidence of ischemic and hemorrhagic stroke a small-area level ecological study. *Stroke*. 2012;43:22-27
9. Maheswaran R, Pearson T, Smeeton NC, Beevers SD, Campbell MJ, Wolfe CD. Impact of outdoor air pollution on survival after stroke population-based cohort study. *Stroke*. 2010;41:869-877
10. Qian Y, Zhu M, Cai B, Yang Q, Kan H, Song G, et al. Epidemiological evidence on association between ambient air pollution and stroke mortality. *Journal of epidemiology and community health*. 2013:jech-2012-201096
11. Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P, et al. Ambient air pollution and the risk of acute ischemic stroke. *Archives of internal medicine*. 2012;172:229-234
12. Yorifuji T, Kashima S, Tsuda T, Ishikawa-Takata K, Ohta T, Tsuruta K-i, et al. Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in shizuoka, japan. *Science of the Total Environment*. 2013;443:397-402

13. Yorifuji T, Suzuki E, Kashima S. Cardiovascular emergency hospital visits and hourly changes in air pollution. *Stroke*. 2014;45:1264-1268
14. Yu X-B, Su J-W, Li X-Y, Chen G. Short-term effects of particulate matter on stroke attack: Meta-regression and meta-analyses. *PloS one*. 2014;9:e95682
15. WHO. Review of evidence on health aspects of air pollution – revihaap project: Final technical report. 2013
16. Beevers SD, Kitwiroon N, Williams ML, Kelly FJ, Ross Anderson H, Carslaw DC. Air pollution dispersion models for human exposure predictions in london. *Journal of exposure science & environmental epidemiology*. 2013
17. Carlsen HK, Forsberg B, Meister K, Gíslason T, Oudin A. Ozone is associated with cardiopulmonary and stroke emergency hospital visits in reykjavík, iceland 2003–2009. *Environmental health*. 2013;12:28
18. Corea F, Silvestrelli G, Baccarelli A, Giua A, Previdi P, Siliprandi G, et al. Airborne pollutants and lacunar stroke: A case cross-over analysis on stroke unit admissions. *Neurology international*. 2012;4
19. Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: Results from 11 european cohorts within the escape project. *Environmental health perspectives*. 2014;122:919-925
20. O'Donnell MJ, Fang J, Mittleman MA, Kapral MK, Wellenius GA. Fine particulate air pollution (pm2. 5) and the risk of acute ischemic stroke. *Epidemiology (Cambridge, Mass.)*. 2011;22:422
21. Markus HS, Bevan S. Mechanisms and treatment of ischaemic stroke [mdash] insights from genetic associations. *Nature Reviews Neurology*. 2014;10:723-730
22. Traylor M, Farrall M, Holliday EG, Sudlow C, Hopewell JC, Cheng Y-C, et al. Genetic risk factors for ischaemic stroke and its subtypes (the metastroke collaboration): A meta-analysis of genome-wide association studies. *The Lancet Neurology*. 2012;11:951-962
23. Heuschmann PU, Grieve AP, Toschke AM, Rudd AG, Wolfe CD. Ethnic group disparities in 10-year trends in stroke incidence and vascular risk factors the south london stroke register (slsr). *Stroke*. 2008;39:2204-2210
24. Hatano S. Experience from a multicentre stroke register: A preliminary report. *Bulletin of the World Health Organization*. 1976;54:541-553
25. Bamford J, Sandercock P, Dennis M, Warlow C, Burn J. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *The Lancet*. 1991;337:1521-1526
26. Hajat C, Coshall C, Rudd A, Patel M, Bhalla A, Howard R, et al. The inter-and intraobserver reliabilities of a new classification system for ischaemic stroke: The south london stroke register. *Journal of the neurological sciences*. 2001;190:79-85
27. ONS.2015
28. CERC. Adms 4 and roads user guides. 2004
29. CERC. Adms-roads an air quality management system user guide. Cambridge environmental research consultants ltd, cambridge. 2006;2012
30. (GLA) GLA. The london atmospheric emissions inventory 2010. 2010;2015
31. Carslaw DC, Beevers SD, Tate JE, Westmoreland EJ, Williams ML. Recent evidence concerning higher no x emissions from passenger cars and light duty vehicles. *Atmospheric Environment*. 2011;45:7053-7063
32. Harrison RM, Jones AM, Gietl J, Yin J, Green DC. Estimation of the contributions of brake dust, tire wear, and resuspension to nonexhaust traffic particles derived from atmospheric measurements. *Environmental science & technology*. 2012;46:6523-6529
33. Halonen JI, Blangiardo M, Toledano MB, Fecht D, Gulliver J, Ghosh R, et al. Is long-term exposure to traffic pollution associated with mortality? A small-area study in london. *Environmental Pollution*. 2015

34. Kelly F, Anderson H, Armstrong B, Atkinson R, Barratt B, Beevers S, et al. The impact of the congestion charging scheme on air quality in london. Part 1. Emissions modeling and analysis of air pollution measurements. *Research report (Health Effects Institute)*. 2011:5-71
35. Tonne C, Elbaz A, Beevers S, Singh-Manoux A. Traffic-related air pollution in relation to cognitive function in older adults. *Epidemiology (Cambridge, Mass.)*. 2014;25:674
36. ONS.2016
37. Maheswaran R, Elliott P. Stroke mortality associated with living near main roads in england and wales a geographical study. *Stroke*. 2003;34:2776-2780
38. Maheswaran R. Air pollution and stroke–an overview of the evidence base. *Spatial and Spatio-temporal Epidemiology*. 2016