The effect of exhaust and non-exhaust related components of particulate matter on long-term survival after stroke

Cover Title: Particulate matter components and stroke mortality

Anita Desikan, MSc[1], Siobhan Crichton, PhD[1], Uy Hoang, MPH, MBBS, MD[1,3], Benjamin Barratt, PhD[2,3], Sean D Beevers, PhD[2], Frank J Kelly, PhD[2,3], Charles DA Wolfe, MD[1,3,4]

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

Corresponding author:

Anita Desikan

Division of Health and Social Care Research

Faculty of Life Sciences & Medicine

King's College London

5th Floor Addison House

Guy's Campus

London SE1 1UL

Tel number: 02078486623

Email: adesikan3000@gmail.com; anita.desikan@kcl.ac.uk

Word Count: 4856

Key words: stroke; survival analysis; mortality; air pollution; particulate matter

List of Tables and Figures:

Table 1: Average pollutant concentrations

Table 2: Incident stroke cases from 2005-2012 by age, gender and stroke subtype

Table 3: Associations between pollutants and hazard ratios for up to 5 years survival after stroke (all stroke, ischaemic stroke, haemorrhagic stroke)

Figure 1. Kaplan-Meier curves of survival rates for ischaemic, TACI and LACI strokes by $PM_{2.5}$ exposure levels.

Table 4: Associations between pollutants and hazard ratios up to 5 years survival after stroke, broken down by ischaemic aetiological subtype

Abstract

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 post-stroke, especially for pollutants associated with vehicle exhaust.

Methods:

Data from the South London Stroke Register, a population-based register covering an urban, multi-ethnic population was used. Hazard ratios (HR) for a one interquartile range increase in particulate matter <2.5µm diameter ($PM_{2.5}$) and <10µm (PM_{10}) were estimated post-stroke using Cox regression, overall and broken down into exhaust and non-exhaust components. Analysis was stratified for ischaemic and haemorrhagic 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's=0.006) for all strokes (HR=1.28, 95%CI 1.08-1.53) and ischaemic strokes (HR=1.32, 95%CI 1.08-1.62). Within ischaemic subtypes, $PM_{2.5}$ pollution increased mortality risk for total anterior circulation infarcts (TACI) by two-fold (HR=2.01, 95%CI 1.17-3.48, p=0.012) and by 78% for lacunar infarcts (LACI) (HR=1.78, 95%CI 1.18-2.66, p=0.006). PM_{10} pollution was associated with 45% increased mortality risk for LACI strokes (HR=1.45, 95%CI 1.06-2.00, p=0.022). Separating $PM_{2.5}$ and PM_{10} into exhaust and non-exhaust components did not show increased mortality.

Conclusions:

Exposure to certain outdoor particulate matter pollution, particularly particulate matter <2.5μm diameter ($PM_{2.5}$), increased morality risk post-stroke up to 5 years after the initial stroke.

Introduction

Accounting for approximately 9% of all deaths around the world, stroke is a major cause of mortality worldwide[1]. For the patients who survive, stroke continues to be associated with a higher risk of death for years after the event[1, 2, 3, 4]. Outdoor air pollution, a well-known hazard to human health[5, 6], may be particularly harmful to people susceptible to stroke[7] and for survival after stroke[8].

Mortality one month after stroke is about 25%, after six months is about 33%, and after one year is about 50%[1]. Survivors of a first-ever stroke exhibit an over two-fold higher annual mortality rate than people from the general population, even several years after their initial stroke[2, 3]. In one prospective study, 80% of those with first-ever stroke did not survive 10 years later[4].

Several associative studies suggest that the effects of outdoor air pollution may act as a potentially modifiable risk factor on survival rates after suffering a stroke. The onset of stroke has been linked to nitrogen dioxide[9, 10], and acute stroke mortality has been linked to ozone[11], nitrogen dioxide[11], sulphur dioxide[11], and carbon monoxide[11, 12]. Long-term post-stroke mortality has been linked to nitrogen dioxide[8]. However, the strongest evidence supporting a link between air pollution and mortality risks in a post-stroke population comes from studies on particulate matter.

There appears to be a causal link between particulate matter (PM) air pollution and an increased risk of morbidity and mortality in humans[13, 14]. Smaller particulate matter below 2.5

μm in diameter ($PM_{2.5}$) may be especially hazardous to human health[13] and PM levels below 10 μm (PM_{10}) have also been implicated. Fewer studies have focused on the association between long-term PM exposures (i.e. concentrations averaged over months or years) and adverse health conditions. There is no evidence to suggest a safe exposure level or threshold to short- or long-term PM air pollution[13]. A study conducted in France, Austria and Switzerland attributed 6% of annual deaths, or an estimated 40,000 deaths per year, to PM_{10} air pollution[14]. One particular concern is how to identify PM sources that may contribute to this link; traffic-related sources are considered a prime candidate[14]. The growing ability of urban air pollution models to separate PM into source-related components[15, 7] 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[16, 17, 18, 19]. Links between mortality and PM exposure have also been found in diabetics[16, 13] and people with respiratory diseases[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 pre-existing health conditions. However, few studies have examined the long-term effects of PM exposure in a post-stroke 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 (SLSR), a population-based register of incident strokes set up in 1995 amongst an urban population living in a two 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 SLSR source population consists of 357,308 individuals of which 56% White, 25% Black, 6% Asian and 12% other ethnic group (census 2011). Stroke survival over 5 years was examined from 2005-2012. Haemorrhagic strokes consisted of primary intracerebral haemorrhage (PICH) and subarachnoid haemorrhage (SAH). Ischaemic strokes were subdivided using the Oxford Community Stroke Project (OCSP) classification[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[20]. Trained fieldworkers collected data as soon as possible after the time of first stroke and a clinician verified the diagnosis of stroke. This study utilised particular data on age, gender, ethnicity (black, white, other), year of stroke, deprivation, transient ischaemic attacks (TIA) before stroke, and stroke severity. Deprivation was measured by the Index of Multiple Deprivation (IMD) and stroke severity was measured by National Institutes of Health Stroke Scale (NIHSS) score. Stroke patients were followed up at 3 months and yearly. Official notification of deaths and death certificates were obtained from the Health and Social Care Information Centre (HSCIC)[20].

Air Pollution

Pollution exposure was represented by averaged annual concentrations related to residential postcode at time of initial stroke (see Table 1). The pollutants considered were nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen oxides (NOx), ozone (O_3), total oxidants

(Ox – O_3+NO_2), and particulate matter (PM). Particulate matter was subdivided into <2.5µm diameter ($PM_{2.5}$) and <10µm (PM_{10}), and the contribution of traffic exhaust and non-exhaust was examined.

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'). The KCLurban model has been previously described[7] and has been well established in public health research[21, 22, 23]. The model provided annual mean concentrations for the pollutants at the geographical centre of each postcode. Traffic exhaust and non-traffic exhaust sources were considered separately for $PM_{2.5}$ and PM_{10}. Inventory exhaust emissions factors were combined with UK specific roadside measurements[24], while non-exhaust emissions were based upon the work of Harrison et al (2012)[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 SLSR participants' place of residence at the time of initial stroke.

Statistical Analysis

Survival time was defined as time between stroke onset and death. Patients who were still alive were censored on 31 December 2012. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated for a one 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 (ischaemic and haemorrhagic), and then by ischaemic subtypes (TACI, PACI, POCI, LACI). Models controlled for the following confounders: age, gender, ethnicity, year of stroke, deprivation (IMD rank subdivided into

quarters), TIAs before stroke, and stroke severity (NIHSS total). Fewer deaths occurred in ischaemic subtypes than for all strokes; in order to avoid overfitting the model, the number of confounders for ischaemic subtypes was reduced to the following: age, gender, ethnicity, year of stroke, and stroke severity (NIHSS total). This reduced model was also applied to the data on all strokes, ischaemic and haemorrhagic strokes. Estimates hazard ratios for pollutants were similar in the reduced and main models (data not shown). Further models were also fitted in which an interaction term between particulate pollutants and subtype (ischaemic or haemorrhagic, or within ischaemic subtypes) were included. Kaplan-Meier curves were plotted to assess survival probability and $PM_{2.5}$ exposure for ischaemic, TACI and LACI strokes up to 5 years; $PM_{2.5}$ exposure was divided into tertiles (low, middle, 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 75-84 years, and roughly half (52.3%) were male (see Table 2). In the population, 74.3% of strokes were ischaemic (N=1338), 14.5% were haemorrhagic (N=261), and 11.2% were unknown or undefined (N=201). Of the ischaemic strokes, 10.5% of strokes were TACI, 29.6% were PACI, 10.9% were POCI, 23.2% were LACI, and 0.2% were unspecified ischaemic infarcts. Haemorrhagic strokes consisted of PICH (11.3%) and SAH (3.2%) strokes.

Hazard ratios for incident strokes, including subtype analysis

Hazard ratios for all stroke types and separately for ischaemic and haemorrhagic 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, CI: 1.08-1.53, p-value=0.006, see also Figure 1a) and with reduced survival rates by 32% for ischaemic strokes (HR: 1.32, CI: 1.08-1.62, p-value=0.006). No significances were observed for haemorrhagic strokes. Significant interactions between type of stroke (ischaemic or haemorrhagic) and PM_{10} (p=0.0077) and $PM_{2.5}$ (p=0.0095) further suggests that the pollutants may be associated with a higher mortality risk for ischaemic strokes than for haemorrhagic strokes.

Within ischaemic subtypes (see Table 4), $PM_{2.5}$ was associated with a two-fold reduced survival rate for TACI strokes per IQR increase (HR: 2.01, CI: 1.17-3.48, p-value=0.012, see also Figure 1b). For LACI strokes, higher mortality rates were observed for PM_{10} (HR: 1.45, CI: 1.06-2.00, p-value=0.022) and $PM_{2.5}$ (HR: 1.78, CI: 1.18-2.66, p-value=0.006, see also Figure 1b), reducing survival rates by 45% and 78% respectively. No significances were observed for PACI and POCI ischaemic strokes. Separating $PM_{2.5}$ and PM_{10} into exhaust and non-exhaust components did not show increased mortality in either analysis. Interactions between ischaemic 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 morality rate in a post-stroke population, especially for ischaemic 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 interquartile range increase in $PM_{2.5}$, the risk of death after 5 years increased by 28%; for ischaemic stroke patients, the risk of death increased by 32%. Certain

subtypes of ischaemic strokes had particularly high mortality rates associated with $PM_{2.5}$ exposure; the risk of death for TACI stroke patients increased by two-fold for every interquartile range increase in $PM_{2.5}$. For LACI stroke patients, one interquartile range 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[11, 12, 26, 27]; however, the association of air pollution and the risk of death in a stroke population is less well known. To our knowledge only two long-term studies have examined whether stroke patients residing in areas with higher levels of outdoor air pollution have an increased risk of death. Similar to our study, Maheswaran et al (2010) used the South London Stroke Register (SLSR) and reported reduced survival for stroke patients living in areas with higher levels of nitrogen dioxide and PM_{10}. A 10-$\mu g/m^3$ increase in PM_{10} was associated with a 52% increase in risk of death[8]. Wilker et al (2013) used proximity to high-traffic roadways as a proxy for air pollution in the greater Boston area. People who had suffered an ischaemic stroke and were living <100m from high-traffic roadways had a 20% higher mortality rate as compared to post-stroke patients living >400m[28].

Our study suggests that people who have previously suffered an ischaemic stroke, but not a haemorrhagic stroke, may be more vulnerable and at a higher risk of death to chronic, long-term exposure of particulate matter. Several studies support the assertion that air pollution risks may be exacerbated in certain stroke subtypes. Ischaemic but not haemorrhagic strokes have been associated with greater pollution-associated risks for stroke incidence[9, 10, 7], acute stroke mortality[11, 12], and post-stroke mortality[28] but not in all studies[11]. Only a few studies have looked at the link between specific stroke subtypes and air pollutants. Of the two studies that we could find on stroke and air pollution that examined specific subtypes, the onset of TACI and LACI strokes appeared to be associated with PM

pollution[7, 29]. This corresponds with our observations of increased mortality linked to higher PM pollution levels for TACI and LACI strokes.

Other evidence corroborates a link between air pollution and stroke. Higher levels of PM air pollution have been linked with acute stroke mortality on nationalised death records in Seoul, Korea[11] and Helsinki, Finland[12]. There is also evidence to support an association with stroke incidence for PM_{10} and $PM_{2.5}$[7, 30, 9, 10] though this is not supported in all studies[26]. One study by Zeka, Zanobetti, and Schwartz (2006), examining the effects of PM_{10} on daily mortality of the general population in 20 US cities, assessed whether a diagnosis of stroke would act as an individual effect modifier for mortality. They found that subjects with diagnoses of stroke had more than double the PM_{10}-associated risk of death for both all-cause mortality and for respiratory-related mortality[27].

Possible mechanisms

The adverse health effects of particulate matter have been well documented[13]. The data demonstrating PM's effect on the cardiovascular system are especially strong, and ischaemic stroke and cardiovascular disease share many risk factors, features, and pathophysiological mechanisms[18]. However, unlike cardiovascular disease, the health effects of PM exposure on cerebrovascular diseases like stroke are more uncertain and the mechanisms that may lead to them are less well understood.

Particulate matter is believed to contribute to cardiovascular and cerebrovascular disease by the mechanisms of systemic inflammation, direct and indirect coagulation activation, and direct translocation into systemic circulation[18]. O'Donnell et al (2011) theorised that the health effects of particulate matter and the onset of ischaemic stroke likely differ depending on stroke aetiology and that risk may be greater for non-cardio-embolic than cardio-embolic strokes. It is possible that the physiological mechanisms that define stroke

aetiology onset may also play a role in the mechanisms that influence the risk of death in a post-stroke population to the long-term exposure of particulate matter.

Strengths and limitations

This is the first study that has measured long-term annual pollution exposure and its association with survival rates in a post-stroke population with the following factors: 1) examining overall, exhaust and non-exhaust source contributions for $PM_{2.5}$ and PM_{10}; and, 2) breaking down incident stroke into specific aetiological 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 like: prior TIAs, stroke severity, age, gender, 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. Modelled pollution exposure estimates were assigned to the geographical centres of postcodes, 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 post-stroke population. Previous studies, though, have found that air pollution reduction reduces the risk of death in the general population. Clancy et al (2002) examined the health effects six years before and after a ban on coal sales in 1990 in Dublin, Ireland[6]. The associated drop of deaths after the ban was quite 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 (e.g. survivors of ischaemic stroke, and in particular TACI and LACI stroke), our study may have implications for wider health policies.

Funding Sources

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. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Acknowledgements

None

Conflicts of interest

All the authors declare they have no competing interests

References

1. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet*. 2007;370: 1-12.
2. Dennis MS, Burn JPS, Sandercock PAG, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the oxfordshire community stroke project. *Stroke*. 1993;24:796-800.
3. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Five-year survival after first-ever stroke and related prognostic factors in the perth community stroke study. *Stroke*. 2000;31:2080-2086.
4. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson CS. Ten-year survival after first-ever stroke in the perth community stroke study. *Stroke*. 2003;34:1842-1846.
5. Brunekreef B, Holgate ST. Air pollution and health. *Lancet*. 2002;360:1233-42.
6. Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in dublin, ireland: an intervention study. *Lancet*. 2002;360:1210-1214.
7. Crichton S, Barratt B, Spiridou A, Hoang U, Liang F, Kovalchuk Y, et al. Associations between exhaust and non-exhaust particulate matter and stroke incidence by stroke subtype in South London. *Science of The Total Environment*. 2016;568:278-284.
8. 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.
9. 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.
10. 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;13:1-9.
11. Hong YC, Lee JT, Kim H, Kwon HJ. Air pollution: a new risk factor in ischemic stroke mortality. *Stroke*. 2002;33:2165-2169.
12. Kettunen J, Lanki T, Tiittanen P, Aalto PP, Koskentalo T, Kulmala M, et al. Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. *Stroke*. 2007;38:918-922.
13. WHO. Review of evidence on health aspects of air pollution – revihaap project: Final technical report. 2013.
14. Kunzil N, Kaiser R, Medina S, Studnicka M, Chanel O, et al. Public-health impact of outdoor and traffic-related air pollution: a european assessment. *Lancet*. 2000;356: 795-801.
15. Beevers SD, Kitwiroon N, Williams ML, Kelly FJ, Anderson HR, Carslaw DC. Air pollution dispersion models for human exposure predictions in london. *Journal of exposure science & environmental epidemiology*. 2013;23:647-653.
16. Bateson TF, Schwartz J. Who is sensitive to the effects of particulate air pollution on mortality? a case-crossover analysis of effect modifiers. *Epidemiology*. 2004;15:143-149.
17. Tonne C, Wilkinson P. Long-term exposure to air pollution is associated with survival following acute coronary syndrome. *European Heart Journal*. 2013;34:1306-1311.

18. Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. *J. Med. Toxicology*. 2012;8:166-175.
19. Naess O, Nafstad P, Aamodt G, Claussen B, Rosland P. Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in oslo, norway. *American Journal of Epidemiology*. 2006;165:435-443.
20. Heuschmann PU, Grieve AP, Toschke AM, Rudd AG, Wolfe CDA. 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.
21. Halonen JI, Blangiardo M, Toledano MB, Fecht D, Gulliver J, et al. Is long-term exposure to traffic pollution associated with mortality? A small-area study in london. *Environmental Pollution*. 2016;208:25-32.
22. Kelly F, Anderson HR, 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;155:5-71.
23. Tonne C, Elbaz A, Beevers S, Singh-Manoux A. Traffic-related air pollution in relation to cognitive function in older adults. *Epidemiology*. 2014;25:674-681.
24. 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.
25. 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.
26. O'Donnell M, Fang J, Mittleman M, Kapral MK, Wellenius GA. Fine particulate air pollution (pm2.5) and the risk of acute ischemic stroke. *Epidemiology*. 2011;22:422-431.
27. Zeka A, Zanobetti A, Schwartz J. Individual-level modifiers of the effects of particulate matter on daily mortality. *American Journal of Epidemiology*. 2006;163:849-859.
28. Wilker EH, Mostofsky E, Lue SH, Gold D, Schwartz J, Wellenius G, et al. Residential proximity to high-traffic roadways and poststroke mortality. *Journal of Stroke and Cerebrovascular Diseases*. 2013;22:e366-e372.
29. 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;4:44-48.
30. Maheswaran R, Pearson T, Campbell MJ, Haining RP, McLeod CW, Smeeton N, et al. A protocol for investigation of the effects of outdoor air pollution on stroke incidence, phenotypes and survival using the south london stroke register. International *Journal of Health Geographics*. 2006;5:1-7.

Table 1. Average pollutant concentrations

	Mean (SD) μg m^{-3}	Median (IQR) μg m^{-3}
NO	34.39 (7.15)	33.40 (29.54, 38.40)
NO_2	44.59 (4.29)	44.05 (41.83, 46.87)
NOx	78.98 (11.41)	77.42 (71.42, 85.41)
O_3	36.68 (3.08)	36.98 (34.35, 38.90)
Ox	81.27 (2.45)	81.13 (79.66, 82.38)
PM_{10}	24.84 (1.50)	24.91 (23.63, 25.84)
PM_{10} exhaust	0.90 (0.29)	0.86 (0.71, 1.07)
PM_{10} non-exhaust	3.18 (0.62)	3.06 (2.77, 3.44)
$PM_{2.5}$	15.35 (1.13)	15.26 (14.45, 16.31)
$PM_{2.5}$ exhaust	0.80 (0.26)	0.77 (0.63, 0.95)
$PM_{2.5}$ non-exhaust	0.92 (0.17)	0.89 (0.81, 1.00)
PM coarse	9.49 (0.69)	9.48 (8.92, 9.94)

Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; Ox, oxidant; PM_{10}, particulate matter below 10 μm; $PM_{2.5,}$ particulate matter below 2.5 μm. SD, standard deviation; IQR, interquartile range.

Table 2. Incident stroke cases from 2005-2012 by age, gender and stroke subtype

	Number of strokes (%)	Number of deaths	Cumulative survival. % (95% CI)	p-value
Total	1800	729	87.1 (86.2-88.0)	
Age, mean(SD)	68.8 (15.8)	-	-	
Age				<0.0001
<55 years	364 (20.2)	52	83.9 (79.1-87.7)	
55-64 years	300 (16.7)	53	77.8 (71.6-82.9)	
65-74 years	396 (22.0)	149	55.2 (49.2-60.8)	
75-84 years	465 (25.8)	264	31.1 (25.9-36.5)	
>85 years	275 (15.3)	211	9.5 (5.4-15.0)	
Gender				<0.0001
Male	942 (52.3)	336	56.2 (52.2-60.0)	
Female	858 (47.7)	393	45.6 (41.5-49.6)	
Subtype				<0.0001
TACI	189 (10.5)	105	39.3 (31.3-47.2)	
PACI	532 (29.6)	241	45.7 (40.5-50.7)	
POCI	196 (10.9)	70	53.9 (44.8-62.1)	
LACI	417 (23.2)	134	59.3 (53.4-64.7)	
Infarction unspecified	4 (0.2)	2	50.0 (5.8-84.5)	
PICH	204 (11.3)	98	50.5 (42.6-57.9)	
SAH	57 (3.2)	16	71.2 (57.3-81.3)	
Unknown/ undefined	201 (11.2)	63	49.7 (38.3-60.0)	

Number of incident strokes and deaths by age, gender and stroke subtype. Cumulative survival at 5 years was calculated and compared across groups using the log rank test.

Abbreviations: TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct; PICH, primary intracerebral haemorrhage; SAH, subarachnoid haemorrhage; SD, standard deviation

Table 3. Associations between pollutants and hazard ratios (HR) up to 5 years survival after stroke (all stroke, ischaemic stroke, haemorrhagic stroke)

	All stroke		Ischaemic		Haemorrhagic	
N	1800		1338		261	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
NO	0.96 (0.85-1.08)	0.466	1.00 (0.88-1.15)	0.952	0.75 (0.53-1.06)	0.105
NO_2	0.97 (0.87-1.08)	0.556	1.01 (0.89-1.14)	0.929	0.80 (0.59-1.10)	0.173
NO_X	0.96 (0.85-1.08)	0.498	1.00 (0.88-1.15)	0.942	0.77 (0.55-1.08)	0.127
O_3	1.07 (0.87-1.33)	0.517	0.99 (0.78-1.27)	0.962	1.55 (0.86-2.80)	0.147
Ox	0.97 (0.88-1.08)	0.614	1.01 (0.90-1.13)	0.907	0.82 (0.61-1.12)	0.223
PM_{10}	1.12 (0.98-1.29)	0.102	1.16 (0.99-1.36)	0.069	0.77 (0.51-1.18)	0.239
PM_{10} exhaust	0.98 (0.84-1.15)	0.804	1.05 (0.89-1.25)	0.564	0.73 (0.46-1.16)	0.181
PM_{10} non-exhaust	0.95 (0.86-1.04)	0.262	0.98 (0.88-1.09)	0.697	0.80 (0.59-1.07)	0.131
$PM_{2.5}$	**1.28 (1.08-1.53)**	**0.006**	**1.32 (1.08-1.62)**	**0.006**	0.89 (0.53-1.49)	0.667
$PM_{2.5}$ exhaust	0.98 (0.84-1.14)	0.791	1.05 (0.89-1.25)	0.573	0.72 (0.45-1.15)	0.173
$PM_{2.5}$ non-exhaust	0.94 (0.85-1.03)	0.190	0.97 (0.87-1.08)	0.571	0.79 (0.57-1.07)	0.124
PM coarse	0.98 (0.87-1.10)	0.694	1.00 (0.87-1.14)	0.952	0.73 (0.51-1.06)	0.102

Confounders: age, sex, ethnicity (black, white, other), NIHSS, deprivation score, previous TIA, and year of stroke

Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; O_3, ozone; Ox, oxidant; PM_{10}, particulate matter below 10 μm; $PM_{2.5}$, particulate matter below 2.5 μm; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

Figure 1. Kaplan-Meier curves of survival rates for ischaemic, TACI and LACI strokes by $PM_{2.5}$ exposure levels.

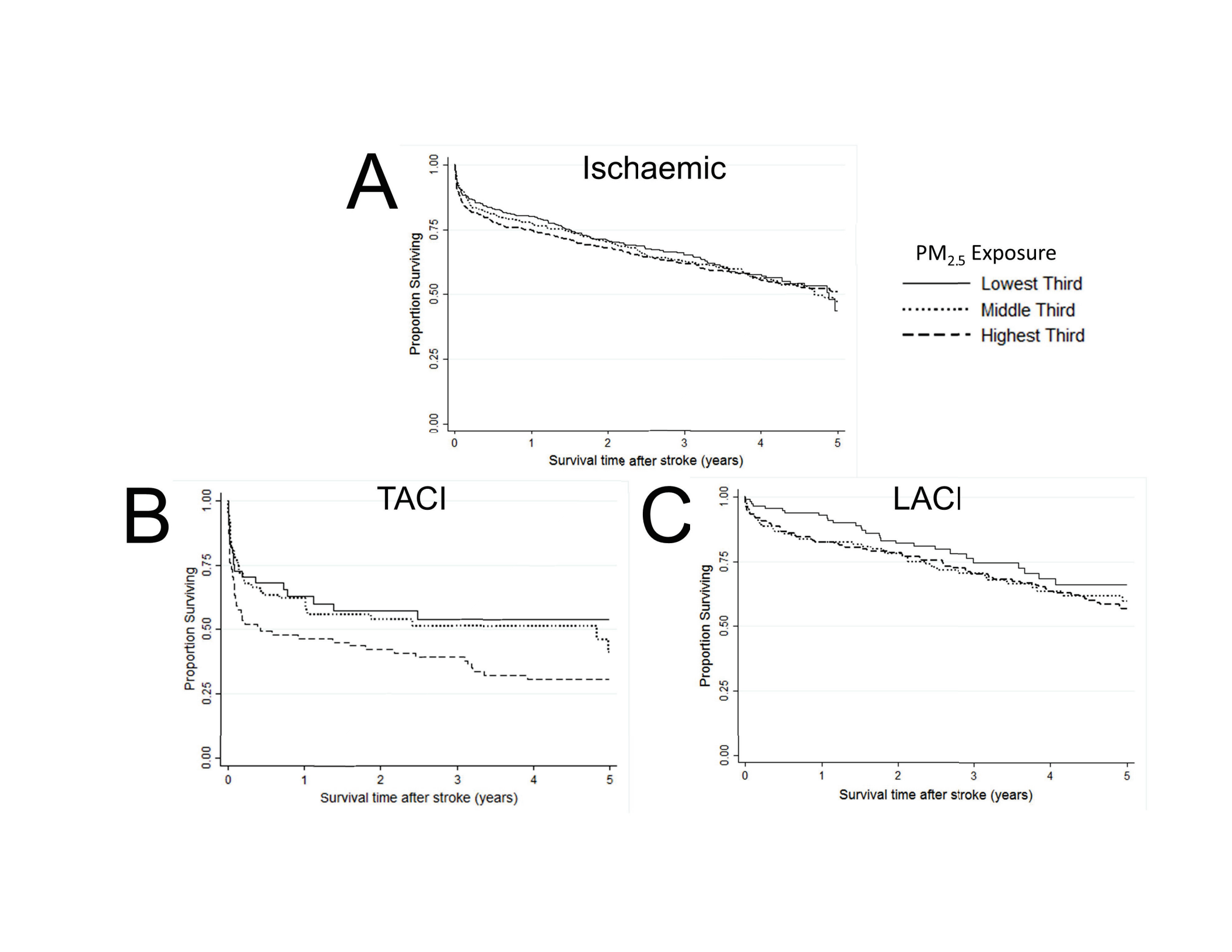
Proportion of survival over 5 years for ischaemic strokes (A) and two ischaemic subtypes, TACI (B) and LACI (C). $PM_{2.5}$ exposure levels adjusted by interquartile range were divided into thirds (low, middle, high) for the Kaplan-Meier curve.

Table 4. Associations between pollutants and hazard ratios (HR) up to 5 years survival after stroke, broken down by ischaemic aetiological subtype

	TACI		PACI		POCI		LACI	
N	189		532		196		417	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
NO	0.86 (0.63-1.18)	0.360	0.96 (0.77-1.19)	0.696	0.90 (0.62-1.29)	0.554	1.19 (0.93-1.53)	0.172
NO_2	0.88 (0.66-1.18)	0.397	0.98 (0.79-1.21)	0.840	0.90 (0.64-1.27)	0.561	1.13 (0.90-1.43)	0.289
NO_X	0.87 (0.64-1.18)	0.373	0.96 (0.78-1.20)	0.748	0.90 (0.63-1.29)	0.555	1.17 (0.92-1.49)	0.211
O_3	1.15 (0.66-2.01)	0.622	1.16 (0.77-1.74)	0.475	1.20 (0.61-2.35)	0.600	0.70 (0.43-1.13)	0.149
Ox	0.85 (0.64-1.14)	0.279	1.02 (0.84-1.24)	0.817	0.91 (0.65-1.26)	0.551	1.08 (0.87-1.33)	0.482
PM_{10}	1.33 (0.89-1.99)	0.168	1.01 (0.80-1.28)	0.927	1.00 (0.61-1.64)	0.991	**1.45 (1.06-2.00)**	**0.022**
PM_{10} exhaust	0.92 (0.61-1.37)	0.676	1.02 (0.78-1.32)	0.907	0.85 (0.50-1.44)	0.545	1.28 (0.91-1.80)	0.151
PM_{10} non-exhaust	0.89 (0.69-1.15)	0.380	0.96 (0.80-1.14)	0.632	0.80 (0.57-1.12)	0.187	1.11 (0.91-1.36)	0.302
$PM_{2.5}$	**2.01 (1.17-3.48)**	**0.012**	0.95 (0.71-1.28)	0.751	1.40 (0.76-2.59)	0.286	**1.78 (1.18-2.66)**	**0.006**
$PM_{2.5}$ exhaust	0.92 (0.62-1.37)	0.683	1.01 (0.78-1.32)	0.916	0.85 (0.50-1.44)	0.535	1.28 (0.91-1.80)	0.150
$PM_{2.5}$ non-exhaust	0.88 (0.68-1.14)	0.321	0.95 (0.80-1.14)	0.608	0.77 (0.54-1.09)	0.137	1.11 (0.90-1.36)	0.333
PM coarse	0.93 (0.67-1.28)	0.635	1.06 (0.87-1.30)	0.562	0.79 (0.54-1.16)	0.225	1.11 (0.83-1.46)	0.485

Confounders: age, sex, ethnicity (black, white and other), NIHSS, and year of stroke

Abbreviations: NO, nitric oxide; NO2, nitrogen dioxide; NOX, nitrogen oxides; O3, ozone; Ox, oxidant; PM10, particulate matter below 10 μm; PM2.5, particulate matter below 2.5 μm; NIHSS, National Institutes of Health Stroke Scale


A
Ischaemic
Proportion Surviving
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
5
Survival time after stroke (years)
PM2.5 Exposure
Lowest Third
Middle Third
Highest Third
B
TACI
Proportion Surviving
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
5
Survival time after stroke (years)
C
LACI
Proportion Surviving
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
5
Survival time after stroke (years)