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Air pollution and stroke – an overview of the evidence base

ABSTRACT

Air pollution is being increasingly recognized as a significant risk factor for stroke. There are numerous sources of air pollution including industry, road transport and domestic use of biomass and solid fuels. Early reports of the association between air pollution and stroke come from studies investigating health effects of severe pollution episodes. Several daily time series and case-crossover studies have reported associations with stroke. There is also evidence linking chronic air pollution exposure with stroke and with reduced survival after stroke. A conceptual framework linking air pollution exposure and stroke is proposed. It links acute and chronic exposure to air pollution with pathways to acute and chronic effects on stroke risk. Current evidence regarding potential mechanisms mainly relate to particulate air pollution. Whilst further evidence would be useful, there is already sufficient evidence to support consideration of reduction in air pollution as a preventative measure to reduce the stroke burden globally.

Keywords: air pollution; stroke; epidemiology

1. Introduction

There is increasing interest in the link between air pollution and stroke and an increasing number of studies have been published on this subject. Both air pollution and stroke are common, making the link between these two topics of major public health importance and relevance worldwide. In estimates released in 2014, the World Health Organisation (WHO) estimated that seven million deaths annually worldwide were attributable to the combined effects of outdoor and indoor air pollution (WHO, 2014a). Of particular note is the breakdown of deaths attributed to specific diseases. The WHO estimated that stroke accounted for 40% of all deaths attributable to outdoor air pollution, making stroke the joint leading cause of death attributable to this exposure, along with ischemic heart disease, which was also estimated to account for 40% of all outdoor air pollution related deaths. With regard to deaths attributable to indoor air pollution, stroke was the leading cause of death, accounting for 34%, followed by ischemic heart disease at 26% and chronic obstructive pulmonary disease at 22%.

In this article, a brief overview of air pollution sources and trends in pollution levels is described followed by an outline of the classification and subtypes of stroke. A conceptual model linking air pollution and stroke is presented followed by an outline of epidemiological study designs that may be used to investigate the association between air pollution and stroke. The article then examines the link between air pollution and stroke, focusing on pollution episodes, studies examining daily time series data, studies examining chronic exposure and also the effects of outdoor air pollution on survival following stroke. Potential mechanisms underlying the link between air pollution and stroke are then considered. The article ends with a consideration of the implications for further research and policy.

2. Air pollution – sources and trends

Air pollution has been defined as any undesirable modification of air by substances that are toxic or may have adverse effects on health or that are offensive though not necessarily harmful to health (Last, 1995). These substances may be solids, liquids or gases and not infrequently are a mix of these components. Air pollutants include a wide range of substances including particulate matter, nitrogen dioxide (NO₂), sulphur dioxide (SO₂), carbon monoxide (CO), ozone (O₃), volatile organic compounds and several other pollutants. The main air pollutants that have been investigated in relation to stroke are particulate matter, NO₂, SO₂, CO and O₃.

Particulate matter is a heterogeneous mix of substances, both in terms of size and shape and in terms of chemical composition. Particulate matter less than 10µm in diameter (PM₁₀) comprises respirable particles because these particles can reach the alveoli when inhaled. Within this category, particles are further sub-classified into coarse particles which range from 2.5 to 10µm in diameter, and fine particles which are less than 2.5 µm in diameter (PM_{2.5}). A subcategory of the latter is ultrafine particles which are less than 0.1µm in diameter. In terms of mass, PM_{2.5} generally accounts for approximately 50-70% of PM₁₀. Combustion of fossil fuels is one of the major sources of particulate air pollution. Other

sources include dust storms, resuspension of road dust by moving vehicles, sea salt and volcanic eruptions.

Oxides of nitrogen, including NO₂, are principally formed when fuel is burned at high temperatures. Combustion of carbon fuels, particularly in conditions with a limited oxygen supply or at high temperatures, is a major source of CO. Motor vehicles are the major contributor to outdoor CO concentrations. SO₂ is principally formed by combustion of fossil fuel, with power stations being the major source of outdoor SO₂. Ground level O₃ is classified as a secondary pollutant and is formed by a photochemical reaction involving NO₂ and volatile organic compounds.

In high income countries, road transport and industry are the main sources of outdoor air pollution, although domestic combustion and agriculture also make significant contributions. In the UK, for example, the government estimated that industry accounted for 46% of NO₂ and 36% of PM₁₀ emissions, while road transport accounted for 30% of NO₂ and 18% of PM₁₀ emissions (House of Commons Environmental Audit Committee, 2010). In low and middle income countries, burning of biomass and solid fuels indoors is a significant source of exposure to air pollution and in poorly ventilated areas, very high levels of exposure may be encountered. Industry and road transport are also major contributors to air pollution in an increasing number of low and middle income countries. Other sources include clearance of forests using forest fires which can result in large areas being affected by the pollution haze produced.

With regard to trends in pollution levels, there has been a striking decline in outdoor pollution levels over the last four decades in several high income countries. Figure 1, for example, illustrates the fall in black smoke levels between the 1960s and the 1980s in London, UK using data from a central monitoring station. The decline in outdoor pollution levels have, however, plateaued off in recent years in the UK, which is struggling to meet some European Union air quality standards, especially in London (King's College London, 2016). In the USA, there have been similar decreases in air pollution concentrations over recent decades (United States Environmental Protection Agency, 2015).

In many low and middle income countries worldwide, however, the situation regarding air quality is deteriorating. The WHO monitors air pollution concentrations in a large number of cities, around 1600 cities in 91 countries worldwide, and air pollution concentrations have increased in several cities, including those in the Americas, Asia and Africa (WHO, 2014b).

3. Stroke – classification and subtypes

Stroke is the term used to describe an episode of acute neurological dysfunction caused by ischemia or haemorrhage which persists for over 24 hours or until death. The precise definitions of different types of stroke are described elsewhere (Sacco et al., 2013). The incidence of stroke in 2010 was estimated to range from 60/100,000 person-years in Kuwait to 504/100,000 person-years in Lithuania (Feigin et al., 2014). The incidence decreased in high income countries between 1990 and 2010 but has increased in low and middle income countries (Feigin et al., 2014).

Stroke is a major cause of mortality and morbidity worldwide. It accounts for 9% of all deaths worldwide and 10-12% of deaths in high income countries (Donnan et al., 2008). In terms of morbidity, it is the sixth most common cause of disability adjusted life years lost (Donnan et al., 2008).

There are two main stroke types – ischemic stroke and haemorrhagic stroke. Ischemic stroke may be caused by a thrombus or an embolus resulting in diminution or occlusion of the blood supply to part of the brain and damage to brain tissue. Haemorrhagic stroke may be due to a primary intracerebral haemorrhage or a subarachnoid haemorrhage, with the latter typically caused by a ruptured cerebral aneurysm.

There are two main classification systems used to classify stroke subtypes and both include more detailed subtypes of ischemic stroke, useful for more detailed examination of the link between air pollution and ischemic stroke. The Oxford classification is primarily a clinical classification and the relevant categories include total anterior circulation infarct, partial anterior circulation infarct, posterior circulation infarct and lacunar infarct (Bamford et al., 1991). The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification is based on aetiology and the three main ischemic stroke subtypes are stroke due to atheroma of large vessels, stroke caused by small vessel disease, and cardioembolic stroke, which is stroke caused by an embolus from the heart (Adams et al., 1993).

4. Conceptual framework linking air pollution and stroke

Investigating the link between an exposure and an outcome forms the basis of studies in environmental epidemiology. Before going into the epidemiological evidence base on the link between air pollution and stroke, it is useful to have a conceptual framework for this link. However, such a framework has not been articulated in the literature previously and a basic framework is provided in Figure 2. There are two aspects to exposure to air pollution in this context – acute exposure and chronic exposure. In addition, there are also two aspects to the outcome – acute effects and chronic effects on stroke risk.

Acute exposure describes short-term or transient increases in pollution concentrations as illustrated in Figure 3. The daily variation in pollution levels examined in time series studies would be the typical example in this category of exposure. Pollution episodes which last for a number of consecutive days would also fall into this category of exposure.

Chronic exposure describes sustained exposure to high levels of pollution. Typically, this will be months or years of sustained high average exposure. Chronic exposure is typically examined using cohort studies but may also be investigated using ecological correlation studies, and case-control studies using average exposure levels.

An acute effect refers to the occurrence of a clear point effect such as plaque rupture or thrombus formation causing ischemic stroke, and rupture of an aneurysm or micro-aneurysm causing haemorrhagic stroke. These acute effects may be triggered by an acute increase in exposure to pollution, such as pollution spikes that occur during day to day variation in pollution levels. Acute effects will also include transient increases in blood

coagulability or blood pressure which are potential mechanisms mediating the acute effects of air pollution on stroke risk.

Whilst it may be intuitive to link acute effects with acute increases in exposure (indicated by Pathway 1 in Figure 2), chronic exposure as measured using average pollution exposure levels could also be linked to acute effects. This is because high average pollution levels may be an indication of relatively constant high levels or may be the result of numerous spikes of pollution resulting in high average levels. This point is important because the mechanism underlying chronic exposure effects of air pollution on stroke observed in cohort and ecological studies could potentially be explained by numerous acute exposure spikes (indicated by Pathway 3 in Figure 2).

The chronic effect classically describes progression of atherosclerosis. This effect could be caused by chronic exposure to high pollution levels leading to progression of atherosclerosis (Pathway 4 in Figure 2). Even in this apparent chronic exposure situation however, it may potentially be repeated acute exposure spikes that cause progression of atherosclerosis (Pathway 2 in Figure 2).

Theoretically, a single acute pollution spike could also trigger the atherosclerotic process (Pathway 2 in Figure 2). This would be analogous to a single acute exposure to radiation initiating carcinogenesis. However, there is at present little epidemiological or experimental evidence to suggest that this is a potential pathway.

5. Epidemiological study designs for investigating air pollution and stroke

A range of epidemiological study designs may be used to examine the association between air pollution and stroke.

Acute exposure effects may be investigated using daily time-series studies, case-crossover studies or studies of pollution episodes. Conceptually, daily time series studies are ecological studies whilst case-crossover studies are individual level studies, where exposures on a case-day are compared with exposures on control or referent days. Although studies generally examine daily pollution levels, the investigation could focus on a finer time scale e.g. using hourly pollution exposures.

The effects of chronic exposure may be investigated using cohort studies, case-control studies where average pollution exposures are used, ecological correlation studies or cross-sectional studies. However, it should be noted that these studies would in general examine the effects of combined acute and chronic exposure and cannot distinguish between these two effects for the reasons explained previously. Cross-sectional studies are not ideal for examining effects on stroke risk as prevalent cases would exclude severe stroke cases that resulted in death and possibly miss mild stroke cases that have fully recovered. Cross-sectional studies may, however, be useful to investigate potential underlying mechanisms, such as associations between blood pressure or measures of coagulability and average pollution concentrations in population samples.

Panel studies, also referred to as repeated measures studies, are not typically included under epidemiological studies but are another study design that may be used to examine, for example, the correlation between variation in blood pressure or coagulation and variation in exposure to pollution over time, and would provide stronger evidence of a link between air pollution and these potential mechanisms than cross-sectional studies. Intervention studies, typically of 'natural experiments' where an intervention has been introduced to reduce air pollution levels, are also a study design which would give stronger evidence for a causal link than other study designs providing there are adequate comparison groups to control for confounding and other temporal trends. This design may also provide evidence to evaluate the impact of interventions to control pollution levels on stroke risk.

This overview is limited to studies of pollution episodes, daily time series studies and case-crossover studies for examining acute exposure effects, and cohort and ecological correlation studies for examining chronic exposure effects.

6. Early studies of air pollution episodes

This section illustrates early studies of air pollution episodes using publications examining two early pollution episodes. The first concerns the London smog episode which occurred in the winter of 1952. This is the classic example of a clearly documented pollution episode which was caused by a temperature inversion over the London region (Logan 1953). The pollution episode lasted five days and black smoke concentrations rose from around 300 $\mu\text{g}/\text{m}^3$ to a peak of around 2,500 $\mu\text{g}/\text{m}^3$. The pollution episode also featured large rises in SO_2 and other toxic chemicals. The relative risk of mortality from stroke during the week containing the pollution episode was 1.25 (95% CI, 1.03-1.47) compared with stroke mortality in the previous week.

During the same pollution episode, requests for admission to hospital for cerebral haemorrhage were also investigated (Abercrombie, 1953). The information was presented graphically and showed no apparent increase in requests for admission for cerebral haemorrhage. Although the diagnosis of cerebral haemorrhage was presumably based on clinical diagnosis as advanced imaging methods were not available then, the data nevertheless hint that any association was largely confined to ischemic stroke. It is also interesting to note that the association with stroke mortality was modest compared with relative risks of around 8 associated with respiratory mortality (Logan, 1953).

Stroke mortality was also examined in a pollution episode which occurred in New York in 1966 (Glasser et al., 1967). The pollution episode lasted three days during which SO_2 concentrations and the coefficient of haze were elevated. The information was presented graphically. Mean SO_2 concentrations were around 0.5 ppm compared with mean concentrations of around 0.2 ppm during corresponding periods in the previous five years. Similarly, the coefficient of haze was around 6.0 during the pollution episode compared with values around 2.0 during the control periods. Mortality from stroke during the week containing the pollution episode was compared with a combination of control periods before

and after the pollution episode and in the preceding five years and yielded a relative risk for stroke mortality of 1.24 (1.04-1.44).

7. Time-series and case-crossover studies

Studies examining the effects of short-term changes in exposure to air pollution on stroke risk have typically examined daily variation in pollution levels using time-series and case-crossover study designs. A large number of these studies have been carried out and three systematic reviews have examined and synthesised the evidence.

Shah et al investigated publications reporting on the effects of CO, SO₂, NO₂, O₃ and particulate matter on hospital admissions and mortality (Shah et al., 2015). They included 94 studies in their meta-analysis, 78 of which examined particulate matter. They found that increases in both admissions and mortality from stroke were associated with increases in CO, SO₂, NO₂, PM_{2.5} and PM₁₀ concentrations. Only weak associations were seen with O₃. The strongest associations were observed for exposures with a 0-day lag. Fewer studies examined the effects on ischemic and hemorrhagic stroke separately. NO₂ was associated with both ischemic and haemorrhagic stroke. PM_{2.5} was only associated with ischemic stroke.

Wang et al confined their systematic review to studies examining the effect of short-term changes in particulate matter on stroke admission and mortality (Wang et al., 2014). They included 45 studies in their analysis. They found that increases in both PM_{2.5} and PM₁₀ were associated with increased stroke mortality. Associations were less consistent in relation to stroke admissions. There were fewer studies examining ischemic and haemorrhagic stroke separately and overall, there were no significant associations.

Yang et al included studies investigating both particulate and gaseous pollutants (Yang et al., 2014). They included 34 studies in their meta-analysis. They found significant increases in stroke associated with particulates, SO₂, CO and NO₂. Associations were more apparent for ischemic stroke.

8. Cohort studies

Two recent reviews which included cohort studies examining the effects of long-term exposure to air pollution on stroke risk have been published. Ljungman and Mittleman identified six cohort studies examining the effects of long-term exposure to air pollution on stroke mortality (Ljungman and Mittleman, 2014). Four of these studies reported significant increases in stroke mortality associated with increases in air pollutants – three in relation to NO₂ and one in relation to particulate matter. They also identified six cohort studies examining the effects of long-term exposure to air pollution on hospitalisation for stroke, which is a proxy for stroke incidence. Three of these six studies reported significant increases in hospitalization for stroke associated with increases in air pollutants – two in relation to particulate matter and one in relation to NO₂.

Scheers et al carried out a meta-analysis of studies examining the effects of long-term exposure to air pollution on stroke risk, and confined their analysis to the effects of particulate matter (Scheers et al., 2015). They identified 15 cohort studies examining these effects. In analyses focussed on cohort studies examining the association with PM_{2.5}, the authors found that the hazard ratio was 1.06 (1.02-1.11) for a stroke event associated with a 5ug/m³ increase in PM_{2.5}.

9. Ecological studies

A smaller number of ecological studies examining the association between air pollution and stroke have been carried out. These include studies in the UK (Maheswaran and Elliott, 2003; Maheswaran et al., 2005, 2012), USA (Hu et al., 2008; Kloog et al., 2012) and Canada (Johnson et al., 2010). The evidence is mixed, with possibly stronger evidence of association in relation to stroke mortality than with hospitalization for stroke. One study subsequently examined the link between air pollutants and ischemic stroke subtypes and severity (Maheswaran et al., 2014). There were no significant associations with clinical or aetiological ischemic stroke subtypes but there was a suggestion that air pollution exposure was more likely to be linked with mild rather than severe stroke.

10. Effects of air pollution on survival after stroke

It is important to distinguish between the effects of air pollution on the incidence of stroke and the effects of air pollution on survival after a stroke. Studies limited to examining stroke mortality rates cannot easily distinguish between these two scenarios. Most published studies to date have not specifically examined survival following a stroke.

The first study to examine the effects of air pollution on survival after stroke used a population based stroke cohort in South London (Maheswaran et al., 2010). This cohort study followed up 3320 stroke patients and used PM₁₀ and NO₂ concentrations modelled at a very fine spatial scale to estimate exposure to outdoor air pollution. Median survival was 3.7 years. Survival was significantly lower amongst patients living in areas with higher levels of outdoor air pollution and reduced survival was observed throughout the follow-up period, indicating that the adverse effect was not due to a short-term 'harvesting' type effect. The association between air pollution and reduced post-stroke survival has been replicated in a subsequent study (Wilker et al., 2013).

11. Potential mechanisms mediating the link between air pollution and stroke

There are a number of potential mechanisms which could potentially mediate the link between air pollution and stroke. These mechanisms can be grouped into two categories – those which could potentially explain the acute effects of air pollution on stroke and those which could potentially explain the chronic effects of air pollution on stroke. The majority of

the evidence to date largely relates to ischemic stroke and in terms of pollutants, the work largely centres on the actions of particulate matter.

The mechanisms which could explain acute effects include thrombosis pathways, vasoconstriction, plaque rupture and acute rises in blood pressure. These potential mechanisms have been summarised in a recent review (Newby et al., 2015). Activation of platelets, impaired fibrinolytic function and an increase in the thrombotic response have all been observed in studies involving humans and in animal models. With regard to vasoconstriction, both endothelium dependent and endothelium independent vasoconstriction have been observed to be impaired in acute response experiments. Inflammation and oxidative stress, as well as acute rises in blood pressure, may result in rupture of an unstable atheromatous plaque. All the above mechanisms would result in an acute ischemic stroke and the pathophysiological evidence largely relates to adverse effects caused by fine and ultrafine particulate matter. A small number of epidemiological studies have also reported associations between increased exposure to air pollution and haemorrhagic stroke. A potential mechanism which could explain this link is an acute rise in blood pressure, which could precipitate rupture of a vulnerable blood vessel or a microaneurysm, resulting in intracerebral haemorrhage.

With regard to the chronic effects of air pollution exposure on stroke risk, the primary mechanism which could mediate this association is progression of atherosclerosis. Newby et al have identified and summarised the results of 12 epidemiological studies examining this potential mechanism (Newby et al., 2015). Most of these studies focussed on PM_{2.5} as the exposure of interest. The markers of sub-clinical atherosclerosis used in these studies included carotid intima-media thickness, coronary artery calcification, thoracic aortic calcification and abdominal aortic calcification. These epidemiological studies taken as a whole, along with animal studies identified by Newby et al, provide some evidence in support of this mechanism.

12. Implications for research and policy

There are a number of implications for research and policy. In terms of research, more accurate measures of exposure to air pollutants will be useful and may yield clearer evidence of association with stroke risk. Current evidence is largely based on measurements from outdoor monitoring stations and although this has significant limitations, it has nevertheless yielded evidence of association, particularly in studies examining acute exposure effects. Options for improved exposure assessment include (i) more complex models which take into account daily population movements, activities engaged in and concentrations of outdoor and indoor air pollutants at a fine spatial scale, (ii) personal monitors, and (iii) biomarkers of pollution exposure.

Research into associations with specific subtypes of stroke might contribute to a better understanding of the mechanisms underlying the link between air pollution and stroke. In addition to improved exposure assessment at the individual level, more accurate diagnosis

of stroke subtypes may yield clearer associations with stroke subtype leading to better understanding of the potential underlying mechanisms.

Further work is also needed to quantify the relative contributions of acute and chronic effects of air pollution exposure on stroke risk. This is an aspect which to date has received little attention, partly because of the complexity of statistical analysis required to tease out spatial and temporal effects of short-term from longer term spatial and temporal effects but also because of the detailed spatio-temporal pollution exposure assessment required to support this analysis.

Composition of particulate air pollutants is receiving considerable attention and improved measurement of elements within particles on a scale extensive enough to support epidemiological studies would be expected to yield clearer understanding of mechanisms underpinning the air pollution and stroke link in the long run.

In terms of policy, the importance of stroke as one of the key adverse outcomes associated with air pollution needs to be more widely recognised. As mentioned in the introduction, the WHO has estimated that stroke is the single largest contributor to mortality caused by both outdoor and indoor air pollution (WHO, 2014a) and wider recognition of this fact will highlight air pollution control as an important preventative measure in terms of reducing stroke risk. Whilst the WHO publication did not provide an estimate of the proportion of stroke deaths that were attributable to air pollution, another study estimated that 11% of stroke deaths in an urban area were attributable to outdoor air pollution (Maheswaran et al., 2005).

13. Conclusions

The evidence to date suggests that air pollution is a potentially significant cause of stroke. There is mounting evidence in relation to acute exposure effects. Evidence relating to chronic exposure is less clear and further studies are required. Nevertheless, there is sufficient evidence already to consider reduction in air pollution exposure as a preventative measure to reduce stroke risk globally.

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References

- Abercrombie GF. December fog in London and the emergency bed service. *Lancet* 1953;1:234-5.
- Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd: Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993, 24:35-41.
- Bamford J, Sandercock P, Dennis M, Burn J, Warlow C: Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991, 337:1521-1526.
- Donnan GA, Fisher M, Macleod M, Davis SM: Stroke. *Lancet* 2008;371:1612–1623.
- Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014;383:245-54.
- Glasser M, Greenburg L, Field F. Mortality and morbidity during a period of high levels of air pollution. *Arch Environ Health* 1967;15:684-94.
- House of Commons Environmental Audit Committee: Air Quality – Fifth report of session 2009-10.
<http://www.publications.parliament.uk/pa/cm200910/cmselect/cmenvaud/229/229i.pdf>
- Hu Z, Liebens J, Rao KR. Linking stroke mortality with air pollution, income, and greenness in northwest Florida: an ecological geographical study. *Int J Health Geogr* 2008;7:20.
- Johnson JY, Rowe BH, Villeneuve PJ. Ecological analysis of longterm exposure to ambient air pollution and the incidence of stroke in Edmonton, Alberta, Canada. *Stroke* 2010;41:1319–1325.
- Kloog I, Coull BA, Zanobetti A, Koutrakis P, Schwartz JD. Acute and chronic effects of particles on hospital admissions in New-England. *PLoS One* 2012;7:e34664.
- King's College London. London Air. <http://www.londonair.org.uk/london/asp/publicstats.asp> (accessed 30/12/2016)
- Last JM. A dictionary of epidemiology. Oxford: Oxford University Press, 1995.
- Ljungman PL, Mittleman MA. Ambient air pollution and stroke. *Stroke* 2014;45:3734-41.
- Logan WPD. Mortality in the London fog incident, 1952. *Lancet* 1953;1:336-8.
- Maheswaran R, Elliott P. Stroke mortality associated with living near main roads in England and Wales – a geographical study. *Stroke* 2003;34:2776-80.

Maheswaran R, Haining RP, Brindley P, Law J, Pearson T, Fryers PR, Wise S, Campbell MJ. Outdoor air pollution and stroke in Sheffield, United Kingdom – a small-area level geographical study. *Stroke* 2005;36:239-43.

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;41:869-77.

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;43:22-7.

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.

Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, Forastiere F, Franchini M, Franco OH, Graham I, Hoek G, Hoffmann B, Hoylaerts MF, Künzli N, Mills N, Pekkanen J, Peters A, Piepoli MF, Rajagopalan S, Storey RF; ESC Working Group on Thrombosis, European Association for Cardiovascular Prevention and Rehabilitation; ESC Heart Failure Association. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J* 2015;36:83-93b

Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064-89.

Scheers H, Jacobs L, Casas L, Nemery B, Nawrot TS. Long-Term Exposure to Particulate Matter Air Pollution Is a Risk Factor for Stroke: Meta-Analytical Evidence. *Stroke* 2015;46:3058-66.

Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, Langrish JP, Newby DE, Mills NL. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ* 2015;350:h1295.

United States Environmental Protection Agency. Air Trends.
<http://www3.epa.gov/airtrends/index.html> (accessed 20/12/2015)

Wang Y, Eliot MN, Wellenius GA. Short-term changes in ambient particulate matter and risk of stroke: a systematic review and meta-analysis. *J Am Heart Assoc* 2014;3:e000983.

Wilker EH, Mostofsky E, Lue SH, Gold D, Schwartz J, Wellenius GA, Mittleman MA. Residential proximity to high-traffic roadways and poststroke mortality. *J Stroke Cerebrovasc Dis* 2013;22:e366-72.

World Health Organisation. 7 million premature deaths annually linked to air pollution. 2014a. <http://www.who.int/mediacentre/news/releases/2014/air-pollution/en/> (accessed 22/12/2015)

World Health Organisation. Air quality deteriorating in many of the world's cities. 2014b. <http://www.who.int/mediacentre/news/releases/2014/air-quality/en/> (accessed 20/12/15)

Yang WS, Wang X, Deng Q, Fan WY, Wang WY. An evidence-based appraisal of global association between air pollution and risk of stroke. *Int J Cardiol* 2014;175:307-13.

Figure 1. Black smoke concentrations (annual means, in $\mu\text{g}/\text{m}^3$) from a background monitoring station in London, UK. 1962-1987.

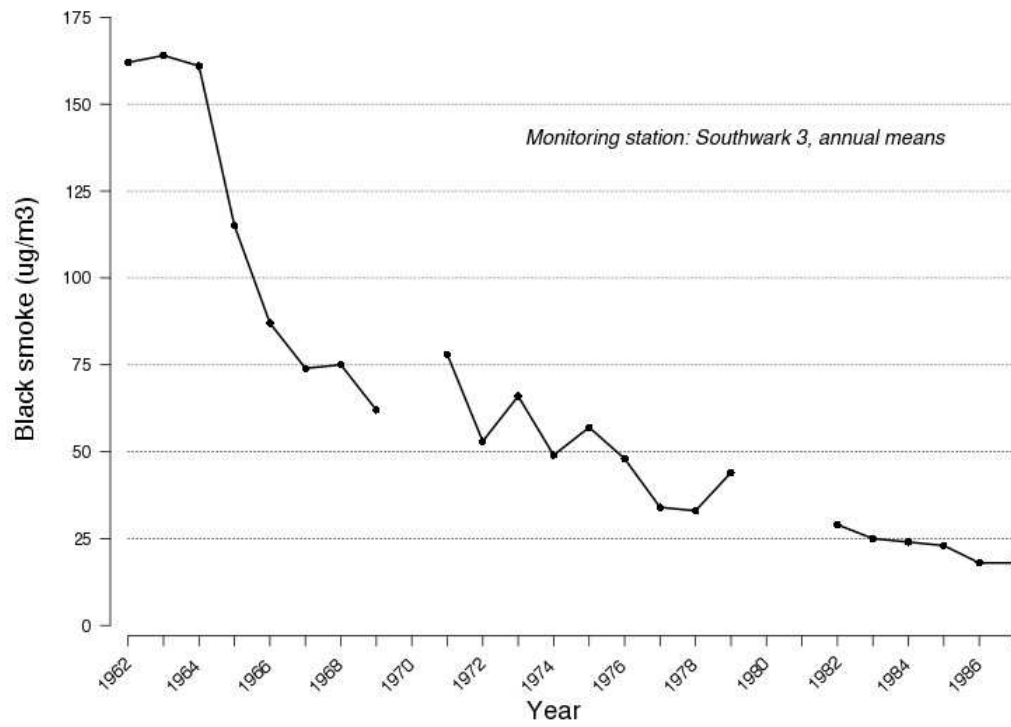


Figure 2. A conceptual framework linking air pollution exposure and stroke. Pathways are indicated by 1-4 and are described in more detail in the text.

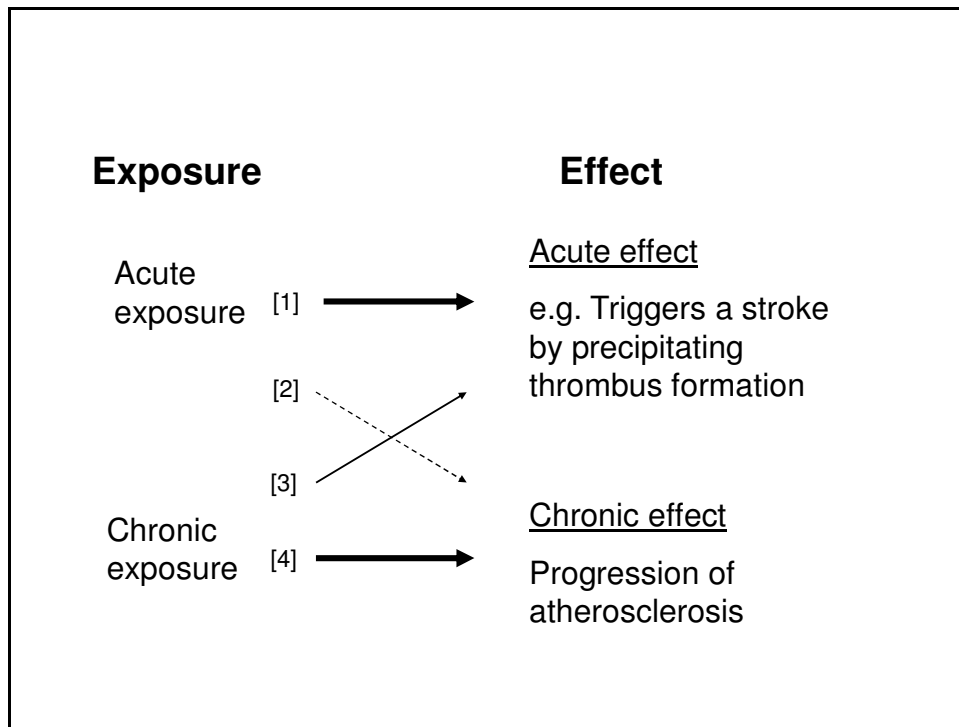


Figure 3. Hourly mean NO₂ concentrations (ppb) from a background monitoring station in London, UK. March 2006.

